Proposed Preferred Drug List

with

Prior Authorization Criteria

Proposal for TennCare

February 8, 2024

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Responsibilities of the TennCare Pharmacy Advisory Committee

Source: Tennessee Code/Title 71 Welfare/Chapter 5 Programs and Services for Poor Persons/Part 24 Tennessee TennCare Pharmacy Advisory Committee/71-5-2401 through 71-5-2404.

Make recommendations regarding a preferred drug list (PDL) to govern all state expenditures for prescription drugs for the TennCare program.
The TennCare Pharmacy Advisory Committee shall submit to the bureau of TennCare both specific and general recommendations for drugs to be included on any state PDL adopted by the bureau. In making its recommendations, the committee shall consider factors including, but not limited to, efficacy, the use of generic drugs and therapeutic equivalent drugs, and cost information related to each drug. The committee shall also submit recommendations to the bureau regarding computerized, voice, and written prior authorization, including prior authorization criteria and step therapy.
The state TennCare pharmacy advisory committee shall include evidence-based research in making its recommendations for drugs to be included on the PDL.
The TennCare bureau shall consider the recommendations of the state TennCare pharmacy advisory committee in amending or revising any PDL adopted by the bureau to apply to pharmacy expenditures within the TennCare program. The recommendations of the committee are advisory only and the bureau may adopt or amend a PDL regardless of whether it has received any recommendations from the committee. It isthe legislative intent that, insofar as practical, the TennCare bureau shall have the benefit of the committee's recommendations prior to implementing a PDL or portions thereof.

Keep minutes of all meetings including votes on all recommendations regarding drugs to be included on the state preferred drug list

The chair may request that other physicians, pharmacists, faculty members of institutions of higher learning, or medical experts who participate in various subspecialties act as consultants to the committee as needed.

PDL Decision Process

- The primary clinical decision that needs to be made is determining if the drugs within the therapeutic class of interest can be considered therapeutic alternatives.
- A **Therapeutic Alternative** is defined by the AMA as: "drug products with different chemical structures but which are of the same pharmacological and/or therapeutic class, and usually can be expected to have similar therapeutic effects and adverse reaction profiles when administered to patients in therapeutically equivalent doses"[1].
- The Committee should not feel obligated to decide if every drug within the therapeutic class is exactly equal to all other drugs within the class, nor should they feel obligated to decide if every drug within the therapeutic class works equally well in every special patient population or in every disease.
- In special situations (e.g., presence of comorbid conditions) and in special populations (e.g., pediatrics) use of a non- preferred drug might be the most appropriate therapy. These cases can be handled through prior authorization (PA). PA serves as a "safety valve" in that it facilitates use of the most appropriate agent regardless of PDLstatus.

[1] AMA Policy H-125.991 Drug Formularies and Therapeutic Interchange

LENGTH OF AUTHORIZATIONS: Dependent upon diagnosis and length of therapy needed to treat. (Most medications are used chronically, and thus would be approved for 1 year.)

- Is there any reason the patient cannot be changed to a medication not requiring prior approval within the same class?

  Acceptable reasons include:

  - **Allergy** to medications not requiring prior approval
  - **Contraindication** to or drug-to-drug interaction with medications not requiring prior approval
  - **History** of unacceptable/toxic side effects to medications not requiring prior approval

- The requested medication may be approved if both of the following are true:

  - If there has been a therapeutic failure of at least two medications within the same class not requiring prior approval (unless otherwise specified)
  - Approval of a branded product when a generic is available requires documentation of a serious adverse reaction from the generic via a FDA MedWatch form **OR** contraindication to an inactive ingredient in the AB-rated generic equivalent. Therapeutic Failure of an AB-rated generic equivalent may be considered for approval of branded products in the following high-risk medication classes: Anticonvulsants, Atypical Antipsychotics, HIV antivirals, Immunosuppressants, and Oncology Agents.

- The requested medication may be approved if the following is true:

  - An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or an FDA approved indication exists.

The information provided for each drug class is organized into the following sections, when applicable:

BACKGROUND:

1. General overview
2. Pharmacology
3. Therapeutic effect(s)
4. Adverse reactions
5. Outcome's data
6. Place in therapy according to current Treatment Guidelines

New Drug Reviews

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AIRSUPRA

New Drug Review

PDL Placement:

	Preferred	Non-Preferred
Beta Agonist-Corticosteroid Combination Products	ADVAIR HFA [QL] (fluticasone/salmeterol) ADVAIR DISKUS [QL] (fluticasone/salmeterol) DULERA [QL] (mometasone/formoterol) SYMBICORT [QL] (budesonide/formoterol)	AIRDUO RESPICLICK/DIGIHALER [PA, QL] (fluticasone/salmeterol) Airsupra [PA, QL] (albuterol/budesonide) BREO ELLIPTA [PA, QL] (fluticasone/vilanterol) budesonide/formoterol [PA, QL] fluticasone/vilanterol [PA, QL] fluticasone/salmeterol [PA, QL] WIXELA [PA, QL] (fluticasone/salmeterol)

Background

AIRSUPRA is a combination inhaler of albuterol (a beta-2 adrenergic agonist) and budesonide (a corticosteroid) indicated for as needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older. It is the first approved combination of an inhaled corticosteroid (ICS) and a short-acting beta-agonist (SABA). Additionally, AIRSUPRA is the first product containing an ICS to be approved as a reliever treatment rather than as a controller for asthma.

The 2023 GINA guidelines recommend ICS-formoterol reliever therapy is the preferred regimen for patients ≥ 12 years. ICS-formoterol reliever therapy is associated with significant risk reduction of severe asthma exacerbations compared to SABA reliever. SABA or ICS/SABA as reliever therapy is the alternative regimen per the GINA guidelines.

AIRSUPRA contains 180 mcg of albuterol and 160 mcg of budesonide administered as 2 puffs as needed for asthma symptoms. Each canister contains 120 inhalations, and no more than 6 doses (12 inhalations) in a 24-hour period is recommended. The most common adverse reactions included headache, oral candidiasis, cough, and dysphonia.

Class Recommendation

It is recommended that at least two combination LABA/ICS agents be available for use for patients with asthma and COPD, with one being budesonide-formoterol.

The above class has been previously presented in its entirety to the PAC Committee and is being provided for reference purposes only.

Prior Authorization criteria for AIRSUPRA

Interim Criteria:

- Agent will be used for the treatment of asthma in patients 18 years of age and older; **AND**
- Trial and failure, contraindication, or intolerance to preferred agents Symbicort and Dulera

Proposed Criteria:

Same as current

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- AIRSUPRA 2 inhalers per month

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Airsupra [package insert], Wilmington, DE: AstraZeneca Pharmaceuticals LP; January 2023
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention, 2023. www.ginasthma.org
- Food and Drug Administration (FDA). FDA news release: FDA approves drug combination treatment for adults with asthma. January 11, 2023. Food and Drug Administration Web site. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-combination-treatment-adults-asthma

AKEEGA

New: New Drug Review

PDL Placement:

	Preferred		Non-Preferred	
Oncology* Prostate Cancer Agents	abiraterone bicalutamide ELIGARD PA (leuprolide) EMCYT (estramustine) flutamide	leuprolide PA nilutamide	*Akeega PA, QL (niraparib/abiraterone)* CASODEX (bicalutamide) ERLEADA PA, QL (apalutamide) LUPRON DEPOT PA (leuprolide) NILANDRON (nilutamide)	NUBEQA PA, QL (darolutamide) ORGOVYX PA, QL (relugolix) XTANDI tablets PA (enzalutamide) YONSA PA (abiraterone acetate) ZYTIGA (abiraterone acetate)

* Table does not include all oncology agents. Oncology agents with the same indication as AKEEGA are included.

Background

AKEEGA (niraparib and abiraterone acetate) is the first dual action combination tablet approved for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated (BRCAm) metastatic castration-resistant prostate cancer (mCRPC). Niraparib is a poly ADP-ribose polymerase (PARP) enzyme inhibitor which play a role in DNA repair. Inhibiting PARP enzymatic activity results in DNA damage, apoptosis, and cell death. Niraparib is currently also available under the brand name ZEJULA indicated for ovarian cancer. Abiraterone is an androgen biosynthesis inhibitor which inhibits 17 α-hydroxylase/C17,20-lyase. Abiraterone is currently available as a generic and under the brand names ZYTIGA and YONSA for prostate cancer.

Prostate cancer is the second leading cause of cancer death among men in the United States. Approximately 10 to 15 % of patients with mCRPC have BRCA gene alterations. Patients with BRCA-mutation cancer have a more aggressive phenotype associated with poorer clinical outcomes and worse prognosis compared to prostate cancer cases without BRCA gene alterations.

AKEEGA is available as tablets containing 50 mg niraparib/500 mg abiraterone acetate or 100 mg niraparib/500 mg abiraterone acetate. The recommended dose of AKEEGA is 200mg niraparib/1000mg abiraterone acetate orally once daily in combination with 10mg prednisone daily until disease progression or unacceptable toxicity. Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.

The most common adverse reactions included decreased hemoglobin, decreased white blood cells, decreased platelets, decreased potassium, increased alkaline phosphatase, hypertension, musculoskeletal pain, fatigue, nausea, and edema.

Class Recommendation

Any new oncology agents with clinical efficacy or authoritative guidelines supporting their use will be available for use with prior authorization criteria until brought back to PAC for review.

The above class has been previously presented in its entirety to the PAC Committee and is being provided for reference purposes only.

Prior Authorization criteria for AKEEGA

Interim Criteria

- Diagnosis of metastatic castration-resistant prostate cancer (mCRPC); **AND**
- Patient has a deleterious or suspected deleterious BRCA-mutated (BRCAm) germline confirmed by an FDA approved test; **AND**
- Will be taken in combination with prednisone; **AND**
- ONE of the following:

- Patient will receive a gonadotropin-releasing hormone (GnRH)-analog (e.g., leuprolide, goserelin, triptorelin)
- Patient has had a bilateral orchiectomy

Proposed Criteria

Initial Criteria *(6- month duration)*

- Diagnosis of metastatic castration-resistant prostate cancer (mCRPC); **AND**
- Patient has a deleterious or suspected deleterious BRCA-mutated (BRCAm) germline confirmed by an FDA approved test; **AND**
- Will be taken in combination with prednisone; **AND**
- ONE of the following:
  - Patient will receive a gonadotropin-releasing hormone (GnRH)-analog (e.g., leuprolide, goserelin, triptorelin)
  - Patient has had a bilateral orchiectomy

Renewal Criteria

- *Patient continues to meet the initial criteria; **AND***
- *Tumor response with stabilization of disease or decrease in size of tumor or tumor spread; **AND***
- *Absence of unacceptable toxicity from the drug (e.g hepatotoxicity, fractures, hypertension)*

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- AKEEGA 2/day

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Akeega (niraparib and abiraterone acetate) [prescribing information]. Horsham, PA: Janssen Biotech, Inc; August 2023.
- Bicalutamide [prescribing information]. Pennington, NJ: Zydus Pharmaceuticals USA Inc; February 2014.
- Castro E, Romero-Laorden N, Del Pozo A, et al. PROREPAIR-B: A prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2019;37(6):490-503. doi:10.1200/JCO.18.00358.
- Cavanagh, H., & Rogers, K. M. (2015). The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers. Hereditary cancer in clinical practice, 13(1), 16. https://doi.org/10.1186/s13053-015-0038-x
- Eligard (leuprolide acetate) injectable suspension [prescribing information]. Fort Collins, CO: Tolmar Inc; January 2023.
- Erleada (apalutamide) [prescribing information]. Horsham, PA: Janssen Products LP; February 2023.
- Flutamide [prescribing information]. Chestnut Ridge, NY: Par Pharmaceutical; November 2016.
- Lupron (leuprolide acetate) [prescribing information]. North Chicago, IL: AbbVie Inc; March 2019.
- Messina, C., Cattrini, C., Soldato, D., et al (2020). BRCA mutations in prostate cancer: Prognostic and predictive Implications. *J Oncol.*, 2020, 4986365. https://doi.org/10.1155/2020/4986365
- Na, R., Zheng, S. L., Han, M., et al (2017). Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. European Urology, 71(5), 740–747. https://doi.org/10.1016/j.eururo.2016.11.033
- Nubeqa (darolutamide) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; October 2023.
- Orgovyx (relugolix) [prescribing information]. Brisbane, CA: Myovant Sciences Inc; March 2023.
- Scott RJ, Mehta A, Macedo GS, Borisov PS, Kanesvaran R, El Metnawy W. Genetic testing for homologous recombination repair (HRR) in metastatic castration-resistant prostate cancer (mCRPC): challenges and solutions. *Oncotarget*. 2021 Aug 3;12(16):1600-1614. doi: 10.18632/oncotarget.28015. PMID: 34381565; PMCID: PMC8351605. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8351605/
- Surveillance, Epidemiology, and End Results (SEER) program. Cancer stat facts. National Cancer Institute Web site. https://seer.cancer.gov/statfacts/. Accessed October 20, 2023.
- "U.S FDA Approves AKEEGA (Niraparib and Abiraterone Acetate), the First-And-Only Dual Action Tablet for the Treatment of Patients with BRCA-Positive Metastatic Castration-Resistant Prostate Cancer." Janssen Global Services, LLC. August 11, 2023. https://www.janssen.com/fda-approves-akeega-niraparib-and-abiraterone-acetate-first-and-only-dual-action-tablet
- Xtandi (enzalutamide) [prescribing information]. Northbrook, IL: Astellas Pharma US Inc; November 2023.
- Yonsa (abiraterone acetate) [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries Inc; March 2022.

ENTYVIO

New: New Drug Review

PDL Placement:

	Preferred	Non-Preferred	
Immunomodulators	ENBREL PA, QL (etanercept)	ACTEMRA PA, QL (tocilizumab)	SIMPONI PA, QL (golimumab)
	HUMIRA PA, QL (adalimumab)	AMJEVITA PA, QL (adalimumab)	SIMPONI PA, QL (golimumab)
	KINERET PA, QL (anakinra)	CIMZIA PA, QL (belimumab)	SKYRIZI PA, QL (risankizumab)
	ORENCIA PA, QL (abatacept)	COSENTYX PA, QL (secukinumab)	SOTYKTU PA, QL (deucravacitinib)
	OTEZLA PA, QL (apremilast)	*ENTYVIO PA, QL (vedolizumab)*	STELARA PA, QL (ustekinumab)
	OTEZLA PA, QL (apremilast)	KEVZARA PA, QL (sarilumab)	TREMFYA PA, QL (guselkumab)
	TALTZ PA, QL (ixekizumab)	SILIQ PA, QL (brodalumab)	

Background

ENTYVIO (vedolizumab) subcutaneous (SC) formulation has been FDA approved for the treatment of moderately to severely active ulcerative colitis (UC). ENTYVIO was previously available as an intravenous (IV) formulation with an additional indication for the treatment of moderately to severely active Crohn's disease (CD).

UC and CD are two of the most common forms of inflammatory bowel disease (IBD). Both UC and CD are chronic, relapsing, remitting, inflammatory conditions of the gastrointestinal tract. UC only involves the large intestine as opposed to CD, which can affect any part of the GI tract from mouth to anus. The 2020 American Gastroenterology Association and the 2019 American College of Gastroenterology guidelines both recommend infliximab, adalimumab, golimumab, tofacitinib, or vedolizumab for moderate to severe UC. ENTYVIO targets α4β7 integrin preventing leucocyte translocation from the blood into the inflamed gut tissue.

After the first two ENTYVIO IV doses administered at weeks 0 and 2, therapy may be switched to the SC formulation at week 6. Thereafter, the recommended dose is 108mg SC once every 2 weeks. Patients that are clinically stable beyond week 6 on the IV formulation may switch to the SC formulation. To do so, the first SC dose should be administered in place of the next scheduled IV infusion and then every two weeks thereafter. Therapy should be discontinued in patients who do not show evidence of therapeutic benefit by week 14.

The most common adverse reactions are nasopharyngitis, headache, arthralgia, nausea, pyrexia, fatigue, and injection site reactions.

Class Recommendation

It is recommended that at least two immunomodulators be available for use and at least one agent for each FDA-approved indication should be available. Additionally, due to the risk of significant adverse events associated with these agents, including an increased risk of potentially life-threatening infections, it is recommended that all agents in this class be subject to clinical criteria. In addition, to prevent misuse, all agents in the category should be subject to quantity limits.

The above class has been previously presented in its entirety to the PAC Committee and is being provided for reference purposes only.

Prior Authorization criteria for ENTYVIO SUBCUTANEOUS INJECTION

Interim Criteria

Initial Criteria: (4-month duration)

- Diagnosis of moderate to severe ulcerative colitis; **AND**
- Trial and failure, contraindication, or intolerance a TNF- inhibitor (e.g., Humira, Infliximab); **AND**
- Prescriber attests that patient has or will receive > 2 Intravenous doses of Entyvio prior to transitioning to subcutaneous therapy

Renewal Criteria:

- Diagnosis of moderate to severe ulcerative colitis; **AND**
- Patient is established on Entyvio subcutaneous therapy (supported by paid claims or chart notes); **AND**
- Disease response to therapy and tolerability compared to baseline (e.g., decreased UC disease activity index, endoscopic remission)

Note: Entyvio should be discontinued in patients who do not show evidence of therapeutic benefit by week 14. Entyvio SC formulation is not FDA approved for Crohn's Disease and will not be approved for that diagnosis.

Proposed Criteria

Initial Criteria: (4-month duration)

- Diagnosis of moderate to severe ulcerative colitis (UC); **AND**
- Trial and failure, contraindication, or intolerance a TNF- inhibitor (e.g., Humira, Infliximab); **AND**
- Prescriber attests that patient has or will receive ≥ 2 intravenous doses of Entyvio prior to transitioning to subcutaneous therapy

Renewal Criteria:

- Diagnosis of moderate to severe ulcerative colitis; **AND**
- Patient is established on Entyvio ~~subcutaneous~~ therapy (supported by paid claims or chart notes); **AND**
- Disease response to therapy and tolerability compared to baseline (e.g., decreased UC disease activity index)

Note: Entyvio should be discontinued in patients who do not show evidence of therapeutic benefit by week 14. Entyvio SC formulation is not FDA approved for Crohn's Disease and will not be approved for that diagnosis.

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- ENTYVIO 2 pens/28 days

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Baumgart DC, Carding SR. Lancet. 2007;369:1627-1640.
- Entyvio (vedolizumab) [prescribing information]. Lexington, MA: Takeda Pharmaceuticals USA Inc; September 2023.
- Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. Gastroenterology. 2020;158(5):1450-1461. doi: 10.1053/j.gastro.2020.01.006.
- Kobayashi T, Siegmund B, Le Berre C, et al. Nat Rev Dis Primers. 2020;6(74).
- Krugliak N, Torres J, Rubin DT. Gastroenterology. 2022;162:1396-1408.
- Ordas I, Eckmann L, Talamini M, et al. Lancet. 2012;380:1606-1619.
- Peppercorn MA, Cheifetz AS. Definitions, epidemiology, and risk factors in inflammatory bowel disease. UpToDate Web site. www.uptodate.com. Updated July 10, 2023. Accessed August 14, 2023.
- Rubin DT, Ananathakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol. 2019;114(3):384-413. doi: 10.14309/ajg.0000000000000152.
- Sands BE. Gastroenterology. 2004;126:1518-1532.
- Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Lancet. 2017; 389(10080):1741-1755.

INPEFA

New: New Drug Review

PDL Placement:

	Preferred	Non-Preferred
SGLT Inhibitors and Combinations	FARXIGA QL (dapagliflozin) GLYXAMBI QL (empagliflozin/linagliptin) INVOKAMET QL (canagliflozin/metformin) INVOKANA QL (canagliflozin) JARDIANCE QL (empagliflozin) SYNJARDY QL (empagliflozin/metformin) XIGDUO XR QL (dapagliflozin/metformin)	*INPEFA PA, QL (sotagliflozin)* INVOKAMET XR PA, QL (canagliflozin/metformin) QTERN PA, QL (dapagliflozin/saxagliptin) STEGLATRO PA, QL (ertugliflozin) SEGLUROMET PA, QL (ertugliflozin/metformin) STEGLUJAN PA, QL (ertugliflozin/sitagliptin) SYNJARDY XR PA, QL (empagliflozin/metformin) TRIJARDY XR PA, QL (empagliflozin/linagliptin/ metformin)

Background

INPEFA (sotagliflozin) is a sodium-glucose cotransporter 1 (SGLT1) and SGLT2 inhibitor indicated to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure (HF) or type 2 diabetes mellitus, chronic kidney disease (CKD), and other cardiovascular (CV) risk factors. Per the SCORED clinical trial that led INPEFA's FDA approval, CV risk factors included history of heart failure, obesity, dyslipidemia, hypertension, or elevated cardiac and inflammatory biomarkers.

The American Diabetes Association (ADA) recommends SGLT2 inhibitors with proven benefit in patients with HF, CKD, and established CVD or multiple risk factors for CVD. The ADA also list SGLT2 inhibitors as high efficacy agents for glycemic management. SGLT2 inhibitors are recommended as one of the four medication classes as guideline directed medical therapy for HF per the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) guideline. Lastly, the Kidney Disease Improving Global Outcomes (KDIGO) practice guideline recommends that patients with type 2 diabetes, CKD, and an eGFR ≥ 20 mL/min/1.73 m2 be treated with an SGLT2-I with cardiorenal protection regardless of glycemic status.

INPEFA is a once daily oral tablet, available in 200mg and 400mg tablets. Patients are initiated on the 200 mg then titrated up to 400mg as tolerated after at least 2 weeks. The most common adverse reactions are urinary tract infections, volume depletion, diarrhea, and hypoglycemia.

Class Recommendation

It is recommended that SGLT-2 inhibitors be available for use due to their guideline recommendations as a first-line agent demonstrated by their proven cardiovascular and renal benefits, risk reduction of heart failure, and high efficacy in achieving glycemic goals.

The above class has been previously presented in its entirety to the PAC Committee and is being provided for reference purposes only.

Prior Authorization criteria for INPEFA

Interim Criteria

- Requested medication is being used to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heat failure visit in adults with one of the following:
  - Heart Failure
  - Type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors; **AND**
- Trial and failure or intolerance to Farxiga

Proposed Criteria

- Requested medication is being used to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heat failure visit in adults with one of the following:
  - Heart Failure
  - Type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors; **AND**
- Trial and failure or intolerance to ~~Farxiga~~ *TWO preferred agents*

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- INPEFA 1/day

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Inpefa (sotagliflozin) [prescribing information]. The Woodlands, TX: Lexicon Pharmaceuticals, Inc; May 2023.
- "Lexicon Announces FDA Approval of INPEFA (Sotagliflozin) for Treatment of Heart Failure." Lexicon Pharmaceuticals, Inc., May 26, 2023. https://www.lexpharma.com/media-center/news/2023-05-26-lexicon-announces-fda-approval-of-inpefa-sotagliflozin-for-treatment-of-heart-failure, PDF download

JESDUVROQ

New: New Drug Review

PDL Placement:

	Preferred	Non-Preferred	
Hematopoietic Agents	Retacrit [PA] (epoetin alfa)	Aranesp [PA] (darbepoetin alfa)	*Jesduvroq [PA, QL] (daprodustat)*
		Epogen [PA] (epoetin alfa)	Procrit [PA] (epoetin alfa)

Background

JESDUVROQ (daprodustat) is the first oral treatment for anemia caused by chronic kidney disease for adults who have been receiving dialysis for at least four months. JESDUVROQ is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIFPHI). Inhibition of oxygen-sensing prolyl hydroxylase enzymes stabilizes hypoxia-inducible factors, which can lead to transcription of erythropoietin and other genes involved in the correction of anemia.

Anemia is a common complication estimated to affect approximately two-thirds of patients with CKD and up to 90% of those who are dialysis-dependent. Anemia may lead to a variety of signs and symptoms including fatigue, dyspnea, tachycardia, and decreases in cognitive function and mental acuity. It is associated with reduced quality of life as well as increased morbidity and mortality related to cardiovascular disease (CVD) and an increased risk of hospitalization. The Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends that CKD dialysis dependent patients utilize erythropoiesis-stimulating agents (ESAs) when hemoglobin is between 9.0 to 10.0 g/dL.

JESDUVROQ is not indicated for patients not on dialysis or as a substitute for transfusion in patients requiring immediate correction of anemia. JESDUVROQ has not been shown to improve quality of life, fatigue, or patient well-being. Prior to administering JESDUVROQ, other causes of anemia must be corrected and excluded, iron levels should be evaluated, and supplement as needed, and liver function testing must be completed. Initial dosing is dependent on if the patient has been receiving erythropoiesis-stimulating agents. The most common adverse reactions for JESDUVROQ include hypertension, thrombotic vascular events, and abdominal pain.

Class Recommendation

In order to ensure provider choice, it is recommended that at least one distinct erythropoietin agent be available for use. Due to the significant risks associated with use of the ESAs, it is recommended that all agents in the class be subject to clinical criteria.

The above class has been previously presented in its entirety to the PAC Committee and is being provided for reference purposes only.

Prior Authorization criteria for JESDUVROQ

Interim Criteria

Initial Criteria: (6-month duration)

- Diagnosis of anemia due to CKD; **AND**
- Patient h:as been receiving dialysis for ≥ 4 months; **AND**
- Recent documentation (within 30 days or request) of ALL the following:
  - Hemoglobin level <10 g/dL
  - Serum ferritin ≥ 100 ng/mL (mcg/L)
  - Transferrin saturation (TSAT) ≥ 20%; **AND**
- Trial and failure, contraindication, or intolerance to erythropoiesis-stimulating agents (ESAs); **AND**
- Prescriber attests to ALL of the following:
  - Will not use in combination with ESAs
  - Will not use in combination with strong CYP2C8 inhibitor such as gemfibrozil

- Patient does not have uncontrolled hypertension

Renewal Criteria:

- Patient is receiving dialysis for anemia due to CKD; **AND**
- Recent documentation (within 30 days or request) of ALL the following:
  - Hemoglobin level <11 g/dL
  - Serum ferritin ≥ 100 ng/mL (mcg/L)
  - Transferrin saturation (TSAT) ≥ 20%

Proposed Criteria

Initial Criteria: (6-month duration)

- Diagnosis of anemia due to CKD; **AND**
- Patient has been receiving dialysis for ≥ 4 months; **AND**
- Recent documentation (within 30 days or request) of ALL the following:
  - Hemoglobin level <10 g/dL
  - Serum ferritin ≥ 100 ng/mL (mcg/L)
  - Transferrin saturation (TSAT) ≥ 20%; **AND**
- Trial and failure, contraindication, or intolerance to erythropoiesis-stimulating agents (ESAs); **AND**
- Prescriber attests to ALL of the following:
  - Will not use in combination with ESAs
  - Will not use in combination with strong CYP2C8 inhibitor such as gemfibrozil
  - Patient does not have uncontrolled hypertension

Renewal Criteria:

- Patient is receiving dialysis for anemia due to CKD; **AND**
- *Submitted documentation demonstrating an increase hemoglobin from baseline;* ***AND***
- Recent documentation (within 30 days or request) of ALL the following:
  - ~~Hemoglobin level <11 g/dL~~
  - Serum ferritin ≥ 100 ng/mL (mcg/L)
  - Transferrin saturation (TSAT) ≥ 20%; **AND**
- *Prescriber attests to ALL of the following:*
  - *Will not use in combination with ESAs*
  - *Will not use in combination with strong CYP2C8 inhibitor such as gemfibrozil*
  - *Patient does not have uncontrolled hypertension*

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• JESDUVROQ 1mg, 2mg, 4mg	1/day
• JESDUVROQ 6mg	2/day
• JESDUVROQ 8mg	3/day

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Berns JS, Qunibi WY. Treatment of anemia in patients on dialysis. UpToDate Web site. Updated August 10, 2023. https://www.uptodate.com. Accessed October 26, 2023.
- "FDA Approves First Oral Treatment for Anemia Caused by Chronic Kidney Disease for Adults on Dialysis." FDA News Release. February 1, 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-treatment-anemia-caused-chronic-kidney-disease-adults-dialysis
- Jesduvroq (daprodustat) [prescribing information]. Durham, NC: GlaxoSmithKline; February 2023.
- Kidney Disease Improving Global Guidelines (KDIGO). Clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2(4):279-335.

MYALEPT

New: New Drug Review

PDL Placement:

	Preferred	Non-Preferred
Lipodystrophy Agents		Myalept [PA] (metreleptin)

Background

MYALEPT (metreleptin) is a leptin analog indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy (GL). GL is a rare condition characterized by deficiency of adipose tissue over the body without evidence of nutrition deprivation or a catabolic state. Due to the lack of adipose tissue, fat is stored in the liver and muscle contributing to severe metabolic abnormalities including diabetes, dyslipidemia, hepatic steatosis, polycystic ovarian syndrome, and acanthosis nigricans. The loss of adipose tissue is usually attributed to decreased leptin levels which plays a crucial role in energy homeostatic, appetite, and satiety.

MYALEPT replacement therapy adjunctive with diet is first line therapy for metabolic complications in patient with generalized lipodystrophy and for prevention of comorbidities in children. MYALEPT is administered as a subcutaneous injection once daily after the lyophilized cake is reconstituted with Bacteriostatic Water for Injection (BWFI) or preservative-free sterile Water for Injection (WFI). The dose is dependent on weight and gender specific with a maximum dose of 10mg/day.

MYALEPT is not indicated for use in patients with HIV-related lipodystrophy or in patients with metabolic disease without concurrent evidence of generalized lipodystrophy. The safety and effectiveness has not been established for use in liver disease or in the treatment of complications of partial lipodystrophy. Because of these risks associated with the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or metreleptin and the risk for lymphoma, metreleptin is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the MYALEPT REMS Program. MYALEPT is contraindicated in patients with general obesity not associated with congenital leptin deficiency and those with a hypersensitivity to metreleptin. The most common adverse reactions were headache, hypoglycemia, decreased weight, and abdominal pain.

Class Recommendation

No recommendation available. This is a new drug class and will be reviewed at a future PAC meeting.

Prior Authorization criteria for MYALEPT

Interim Criteria

Initial Criteria:

- Diagnosis of congenital or acquired lipodystrophy (documentation required)**; AND**
- Leptin deficiency confirmed by laboratory testing; **AND**
- Patient has complications of lipodystrophy (diabetes mellitus, hypertriglyceridemia); **AND**
- Requested agent will be used as adjunct to dietary management of lipodystrophy; **AND**
- Baseline glycemic index and triglycerides provided; **AND**
- Patient does NOT have HIV-related or partial lipodystrophy or metabolic disease without concurrent evidence of generalized lipodystrophy

Renewal Criteria:

- Patient continues to meet initial criteria; **AND**
- Improved from baseline metabolic control (improved glycemic control, decrease in triglycerides)

Proposed Criteria

Initial Criteria:

- Diagnosis of congenital or acquired lipodystrophy ~~(documentation required)~~**; AND**
- Leptin deficiency confirmed by laboratory testing; **AND**
- Patient has *one of the following* complications of lipodystrophy:
    - diabetes mellitus
    - hypertriglyceridemia
    - *hepatic steatosis*
    - *polycystic ovarian syndrome*
    - *acanthosis nigricans;* **AND**
- Requested agent will be used as adjunct to dietary management of lipodystrophy; **AND**
- *Documented* baseline ~~glycemic index, and~~ *HbA1C, fasting glucose*, triglycerides, and *liver enzymes* provided; **AND**
- Patient does NOT have HIV-related or partial lipodystrophy or metabolic disease without concurrent evidence of generalized lipodystrophy; **AND**
- *Prescriber is enrolled in the Myalept REMS program*

Renewal Criteria:

- ~~Patient continues to meet initial criteria; **AND**~~
- *Documented positive clinical response to therapy* ~~Improved from baseline metabolic control~~ (*e.g.,* improved glycemic control, decrease in triglycerides)

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- D. Araujo-Vilar, F. Santini. Diagnosis and treatment of lipodystrophy: a step-by-step approach. Journal of Endocrinological Investigation (2019) 42:61-73. December 6, 2017. https://doi.org/10.1007/s40618-018-0887-z
- Lexicomp. (n.d). Myalept: Drug information. UpToDate. Accessed December 15, 2023, from Metreleptin (Lexi-Drugs) - Lexicomp
- Myalept (metreleptin) [prescribing information]. Dublin, Ireland: Amryt Pharmaceuticals DAC; February 2022.
- Myalept REMS. Amryt Pharma. https://myaleptrems.com/
- Patni N, Garg A. Lipodystrophy for the Diabetologist-What to Look For. Curr Diab Rep. 2022 Sep;22(9):461-470. doi: 10.1007/s11892-022-01485-w. Epub 2022 Jul 11. PMID: 35821558; PMCID: PMC10704567.

OJJAARA

New: New Drug Review

PDL Placement:

	Preferred	Non-Preferred
Oncology* Myelofibrosis Agents	JAKAFI QL (ruxolitinib)	INREBIC PA, QL (fedratinib) OJJAARA PA, QL (momelotinib)

*Table does not include all oncology agents. Oncology agents with the same indication as OJJAARA are included.

Background

OJJAARA (momelotinib) is an oral agent approved for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF [post-polycythemia vera (PV) and post-essential thrombocythemia (ET)], in adults with anemia. MF is a blood cancer affecting approximately 25,000 patients in the United States. About 40% of patients have moderate to severe anemia at the time of diagnosis. It is a rare type of blood cancer characterized by the buildup of scar tissue called fibrosis in the bone marrow. As the scar tissue increases, the bone marrow cannot make enough healthy blood cells.

Secondary MF can develop in patients with PV and ET who progress to a fibrotic state known as post-PV and post-ET MF. PV is characterized by the overproduction of red blood cells (RBCs) or elevation which causing elevated hemoglobin or hematocrit (HCT) and hyper- viscosity. Post-PV MF develops in approximately 12 to 21% of patients with PV. ET is characterized by excessive, clonal platelet production with a majority of patients eventually developing thrombotic complications. The conversion rate of ET to post-ET MF after 10 to 20 years is less than 5%.

OJJAARA is an inhibitor of wild type Janus kinase 1 and 2 (JAK1/JAK2) and activin A receptor type 1 (ACVR1). These contribute to signaling of cytokines and growth factors that are important for hematopoiesis and immune function. JAK2 Mutations are present in most patients with PV (~96%), primary MF (~65%), and ET (~55%) and result in abnormal myeloproliferation. Inhibition of ACVR1 leads to a decrease in circulating hepcidin, which is elevated in MF, contributing to anemia.

The recommended dosage is 200 mg orally once daily, with reduced dosing for hepatic impairment and platelet count. The most common adverse events include thrombocytopenia, hemorrhage, bacterial infection, fatigue, dizziness, diarrhea, and nausea.

Class Recommendation

Any new oncology agents with clinical efficacy or authoritative guidelines supporting their use will be available for use with prior authorization criteria until brought back to PAC for review.

The above class has been previously presented in its entirety to the PAC Committee and is being provided for reference purposes only.

Prior Authorization criteria for OJJAARA

Interim Criteria

Initial Criteria:

- Patient has a diagnosis of primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis; **AND**
- Patient is considered intermediate-1, intermediate-2, or high-risk; **AND**
- Patient is anemic (e.g., hemoglobin (Hb) < 10 g/dL and/or hematocrit (Hct) < 30%); **AND**
- Patient's platelet count ≥ 50 x 109/L;

Renewal Criteria

- Patient's platelet count > 50 x 109 /L; **AND**
- Patient has positive clinical response to therapy (e.g., reduction in symptoms, decreased spleen size, decreased number of transfusion); **AND**
- Absence of unacceptable toxicity (e.g., thrombocytopenia, neutropenia, hepatotoxicity, major adverse cardiovascular events, thrombosis, and malignancies)

Proposed Criteria

Initial Criteria:

- Patient has a diagnosis of primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis; **AND**
- Patient is considered intermediate-1, intermediate-2, or high-risk; **AND**
- Patient is anemic (e.g., hemoglobin (Hb) < 10 g/dL and/or hematocrit (Hct) < 30%); ~~**AND**~~
- ~~Patient's platelet count ≥ 50 x 109/L;~~

Renewal Criteria:

- ~~Patient's platelet count > 50 x 109 /L; **AND**~~
- Patient has positive clinical response to therapy (e.g., reduction in symptoms, decreased spleen size, decreased number of transfusion); **AND**
- Absence of unacceptable toxicity (e.g., thrombocytopenia, neutropenia, hepatotoxicity, major adverse cardiovascular events, thrombosis, and malignancies)

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• OJJAARA	1/day

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- "Ojjaara (momelotinib) approved in the US as the first and only treatment indicated for myelofibrosis patients with anemia". GSK. September 15, 2023. https://www.gsk.com/en-gb/media/press-releases/ojjaara-momelotinib-approved-in-the-us-as-the-first-and-only-treatment-indicated-for-myelofibrosis-patients-with-anaemia/
- Ojjaara (momelotinib) [prescribing information]. Durham, NC: GlaxoSmithKline; September 2023.
- Tefferi A. Clinical manifestations and diagnosis of primary myelofibrosis. UpToDate Web site. Updated September 13, 2022(c). www.uptodate.com. Accessed November 4, 2023.
- Tefferi A. Primary myelofibrosis: 2021 update on diagnosis, risk-stratification and management. Am J Hematol. 2021:96:145-162
- Tefferi A. Prognosis and treatment of essential thrombocythemia. UpToDate Web site. Updated May 24, 2022(b). www.uptodate.com. Accessed November 4, 2023.
- Tefferi A. Prognosis and treatment of polycythemia vera and secondary polycythemia. UpToDate Web site. Updated November 29, 2022(d). www.uptodate.com. Accessed November 4, 2023.

SKYCLARYS

New: New Drug Review

PDL Placement:

	Preferred	Non-Preferred
Friedreich's ataxia		SKYCLARYS (omaveloxolone) PA, QL

Background

SKYCLARYS (omaveloxolone) is the first product FDA-approved for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older. Friedreich's ataxia is a rate, genetic, neurodegenerative condition caused by mutations in the frataxin (FXN) gene which cause transcriptional repression of frataxin expression. Frataxin is a mitochondrial protein that plays an important role in homeostasis. Frataxin reduction manifests as mitochondrial dysfunction with a decreased production of adenosine triphosphate (ATP), increased oxidative stress, suppression of nuclear factor erythroid 2-related factor (Nrf2), and ultimate cell damage.

Typical symptoms include progressive loss of coordination, muscle weakness, fatigue, dysphagia, cardiomyopathy, diabetes mellitus, and foot deformity. Patients typically require a wheelchair in their 20s. The prevalence of FA is estimated to be approximately 5,000 people in the United States.

The exact mechanism of action in these patients is unknown; however, SKYCLARYS has been shown to activate the nuclear factor erythroid 2-related factor 2 activator (Nrf2), which is involved in the cellular response to oxidative stress. The recommended dosage of SKYCLARYS is 150mg (3 capsules) taken orally once daily on an empty stomach, at least 1 hour before eating. The most common adverse reactions are elevated liver enzymes (AST/ALT), headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain.

Class Recommendation

No recommendation available. This is a new drug class and will be reviewed at a future PAC meeting.

Prior Authorization criteria for SKYCLARYS

Interim Criteria

Initial Criteria

- Patient is ≥ 16 years old; **AND**
- Patient has diagnosis of Friedreich's ataxia (FA); **AND**
- Patient has documentation of genetic testing confirming frataxin (FXN) gene mutation; **AND**
- Prescribed by, or in consultation with, a neurologist, geneticist, or cardiologist

Renewal Criteria

- Patient has positive clinical response to therapy (e.g., improvement in speech or swallowing, increased upper/lower limb coordination, improved upright stabilization)

Proposed Criteria

Initial Criteria

- Patient is ≥ 16 years old; **AND**
- Patient has diagnosis of Friedreich's ataxia (FA); **AND**
- Patient has documentation of genetic testing confirming frataxin (FXN) gene mutation; **AND**
- Prescribed by, or in consultation with, a neurologist, geneticist, or cardiologist

Renewal Criteria

- Patient has *disease stabilization or* positive clinical response to therapy (e.g., improvement in speech or swallowing, increased upper/lower limb coordination, improved upright stabilization)

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- SKYCLARYS 3/day

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Corben LA, Lynch D, Pandolfo M, et al. Consensus clinical management guidelines for Friedreich ataxia. Orphanet J Rare Dis. 2014;9:184.
- Corben LA, Collins V, Milne S, et al. Clinical management guidelines for Friedreich ataxia: best practice in rare diseases. Orphanet J Rare Dis. 2022 Nov 12;17(1):415.
- Lynch DR, Chin MP, Boesch S, et al. Efficacy of omaveloxolone in Friedreich's ataxia: delayed-start analysis of the moxie extension. Mov Disord. 2023;38(2):313-320.
- Profeta V, McIntyre K, Wells M, Park C, Lynch DR. Omaveloxolone: an activator of Nrf2 for the treatment of Friedreich ataxia. Expert Opin Investig Drugs. 2023;32(1):5-16.
- Skyclarys (omaveloxolone) [prescribing information]. Plano, TX: Reata Pharmaceuticals Inc; February 2023.

SOHONOS

New: New Drug Review

PDL Placement:

	Preferred	Non-Preferred
Fibrodysplasia ossificans progressive (FOP)		SOHONOS (palovarotene) [PA]

Background

SOHONOS (palovarotene) capsule is the first FDA approved medication for fibrodysplasia ossificans progressive (FOP). FOP is a rare severely disabling genetic bone disorder in which skeletal muscle and connective tissue are gradually replaced by bone a process known as heterotopic ossification (HO). HO is irreversible causing deformities and decreased mobility. Patient with FOP also experience flare-ups which may be precipitated by soft tissue injury, intramuscular injections, surgical incisions, falls, muscular stretching, or viral illness. During flare-ups there is rapid spread of HO lesions along muscle planes into adjacent tissue. The flare-up occurrence, duration, and severity is unpredictable. It is estimated that FOP affects an estimated 400 people in the U.S.

HO is driven by a gain-of-function mutation in the bone morphogenetic protein (BMP) type I receptor, activin A receptor type I/activin-like kinase 2 (ACVR1/ALK2). Approximately 97% of patients with FOP have the ACVR1/ALK2 mutation. SOHONOS is a retinoic acid receptor (RAR) agonist, with selectivity at the gamma subtype of RAR. Binding to the RAR decreases the BMP/ALK2 downstream signaling pathway preventing HO and allows for normal muscle tissue repair or regeneration.

The recommended dosage of SOHONOS for adults and pediatric patients 14 years and older, is 5mg orally once daily, with an increase in dose during a flare up. During a flare up, the dose may be increased up to 20mg once daily for 4 weeks, followed by 10mg once daily for 8 weeks, for a total of 12 weeks. For pediatric patients under 14 years, the dosing is adjusted for weight and dosing ranges from 2.5 to 5mg daily. Before treatment, a negative pregnancy test in females of reproductive potential must be obtained. The most common adverse reactions (incidence ≥ 10%) are dry skin, lip dry, arthralgia, pruritis, pain in extremity, rash, alopecia.

Class Recommendation

No recommendation available. This is a new drug class and will be reviewed at a future PAC meeting.

Prior Authorization criteria for SOHONOS

Interim Criteria:

- Diagnosis of fibrodysplasia ossificans progressive (FOP); **AND**
- One of the following:
  - Female aged ≥ 8 years of age
  - Male aged ≥ 10 years of age; **AND**
- Diagnosis of FOP confirmed by one of the following:
  - Mutation in the ALK2/ACVR1 gene
  - Classic FOP clinical features such as malformation of big toe and progressive heterotopic endochondral ossification in ribbons, sheets, and plates
  - Radiographic bone scans detecting heterotopic ossification (HO); **AND**
- Prescriber attests to all of the following:
  - Patient is not pregnant
  - Female patients of reproductive potential will be counseled to use effective contraception during treatment with therapy and for at least 1 month after last dose
  - For pediatric patients, premature epiphyseal closure has not occurred

Proposed Criteria:

Same as current

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- International Fibrodysplasia Ossificans Progressiva Association (IFOPA). IFOPA Web site. https://www.ifopa.org. Accessed October 19, 2023.
- Kaplan FS, Mukaddam MA, Baujat G, et al. The International Clinical Council on FOP (ICC) & Consultants. The medical management of fibrodysplasia ossificans progressiva: Current treatment considerations. May 2022. IFOPA Web site. https://www.iccfop.org/dvlp/wp-content/uploads/2022/05/guidelines-updated-May-2022.pdf. Accessed October 12, 2023.
- "US FDA approves Ipsen's Sohonos (palovarotene) capsules, the first and only treatment for people with fibrodysplasia ossificans progressiva." Ipsen Pharmaceuticals, Inc., August 16, 2023. https://www.ipsen.com/press-releases/us-fda-approves-ipsens-sohonostm-palovarotene-capsules-the-first-and-only-treatment-for-people-with-fibrodysplasia-ossificans-progressiva/, PDF download
- Sohonos (palovarotene) [prescribing information]. Cambridge, MA: Ipsen Biopharmaceuticals Inc; August 2023.
- Tis J. Fibrodysplasia ossificans progressiva. UpToDate Web site. Updated October 3, 2022. https://www.uptodate.com. Accessed October 20, 2023

VANFLYTA

New: New Drug Review

PDL Placement:

	Preferred	Non-Preferred
Oncology* Acute Myeloid Leukemia	RYDAPT (midostaurin)	*VANFLYTA (quizartinib)* *XOSPATA (gilteritinib)*

*Table does not include all oncology agents. Oncology agents with the same indication as VANFLYTA are included.

Background

VANFLYTA (quizartinib) is the first FLT3 inhibitor specifically for FLT3-ITD-positive acute myeloid leukemia (AML). AML is one of the most common forms of leukemia in adults. 30% of newly diagnosed patients with AML have a FLT3 gene mutation and approximately 20-25% of these are FLT3-ITD mutations, which drive cancer growth and contribute to increased risk of relapse and shorter overall survival. VANFLYTA is indicated for newly diagnosed AML and may be used in the induction, consolidation, and maintenance phases of AML. VANFLYTA is not approved as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (HSCT), as improvement in overall survival has not been demonstrated in this setting.

The standard of care for newly diagnosed FLT3-ITD positive AML includes treatment with induction and consolidation chemotherapy in combination with a FLT3 inhibitor. A typical treatment course of VANFLYTA consists of up to 2 cycles in combination with induction of cytarabine and anthracycline, up to 4 cycles in combination with high dose cytarabine consolidation, and up to 36 cycles as maintenance therapy. VANFLYTA maintenance therapy should be initiated following consolidation chemotherapy upon blood count recovery of absolute neutrophil count > 500/mm3 and platelet count > 50,000/mm3.

VANFLYTA is administered orally, and the dose depends on the phase of therapy. VANFLYTA is contraindicated in patients with severe hypokalemia, severe hypomagnesemia, long QT syndrome, and in patients with a history of ventricular arrhythmias or torsade's de pointes. The REMS program mitigates the serious risk of arrhythmias and cardiac arrest associated with VANFLYTA. The most common (>20%) adverse reactions are laboratory abnormalities which include decreased lymphocytes, potassium, albumin, phosphorous, calcium, and magnesium.

Class Recommendation

Any new oncology agents with clinical efficacy or authoritative guidelines supporting their use will be available for use with prior authorization criteria until brought back to PAC for review.

The above class has been previously presented in its entirety to the PAC Committee and is being provided for reference purposes only.

Prior Authorization criteria for VANFLYTA

Interim Criteria

Initial Criteria:

- Patient has newly diagnosis acute myeloid leukemia (AML); **AND**
- AML is FLT3 internal tandem duplication (ITD)-positive as detected by an FDA-approved test; **AND**
- Vanflyta will be used in combination with cytarabine and anthracycline induction and high dose cytarabine consolidation therapy followed by maintenance monotherapy therapy; **AND**
- Vanflyta will not be used as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (HSCT); **AND**
- Patient and prescriber are enrolled in the Vanflyta REMS program

Renewal Criteria:

- Patient continues to meet initial criteria; **AND**
- Patient demonstrates disease stabilization or improvement as evidenced by a complete response (CR) (e.g., morphologic, cytogenetic, or molecular complete response), complete hematologic response, or a partial response by CBC, bone marrow cytogenic analysis, quantitative PCR, or fluorescence in situ hybridization (FISH)

Proposed Criteria:

Same as current

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• VANFLYTA	2/day

COMITEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Food and Drug Administration. Vanflyta multi-disciplinary review. Review (fda.gov). July 19, 2023. Accessed August 20, 2023.
- National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology – Acute Myeloid Leukemia. v4.2023a. July 11, 2023. aml.pdf (nccn.org). Accessed August 10, 2023.
- "VANFLYTA First FLT3 Inhibitor Approved in the U.S. Specifically for Patients with Newly Diagnosed FLT3-ITD Positive AML." Daiichi Sankyo, Inc. July 20, 2023. https://www.daiichisankyo.com/files/news/pressrelease/pdf/202307/20230720_E.pdf
- Vanflyta (quizartinib) [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo Inc; July 2023.

STANDARD DRUG CLASS REVIEWS

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ANTIBIOTICS: AGENTS FOR DIARRHEA

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred	
Agents for Diarrhea	vancomycin caps PA *vancomycin solution PA, QL*	AEMCOLO PA, QL (rifamycin) FIRVANQ PA, QL (vancomycin solution)	VANCOCIN caps PA (vancomycin caps)

Last Review Date: February 2022

Recent Significant Changes

- No significant changes since last review

Background

Table 1. Medications Included Within Class Review

Drug	Generic Availability
AEMCOLO (rifamycin)	-
FIRVANQ (vancomycin solution)	✔
VANCOCIN (vancomycin capsules)	✔

Table 2. Food and Drug Administration Approved Indications

Indication	AEMCOLO (rifamycin)	FIRVANQ (vancomycin)	VANCOCIN (vancomycin)
Travelers' diarrhea caused by noninvasive strains of *Escherichia coli* (*E. coli*)	✔		
Treatment of *Clostridium difficile*-associated diarrhea		✔	✔
Treatment of enterocolitis caused by *Staphylococcus aureus*		✔	✔

Clostridioides difficile infection

Clostridioides difficile infection (CDI) colonizes the human intestinal tract after the normal gut flora has been disrupted (frequently in association with antibiotic therapy) and is the cause of antibiotic-associated colitis including pseudomembranous colitis. Patients with suspected or proven CDI should be placed on contact precautions, and health care workers should wash hands before and after patient contact. An important initial step in the treatment of CDI is discontinuation of the inciting antibiotic agent(s) as soon as possible. Treatment with concomitant antibiotics (ie, antibiotics other than those given to treat CDI) is associated with prolongation of diarrhea, increased likelihood of treatment failure, and increased risk of recurrent CDI. Supportive care with attention to correction of fluid losses and electrolyte imbalances is also important.

CDI can be differentiated based on disease severity and placed into two categories, nonfulminant disease and fulminant colitis. Nonfulminant disease can be further classified into (1) Non-severe CDI – White blood cell count ≤15,000 cells/mL and serum creatinine <1.5 mg/dL, or (2) Severe CDI – White blood cell count >15,000 cells/mL and/or serum creatinine ≥1.5 mg/dL. Fulminant colitis (previously referred to as severe, complicated CDI) is defined as hypotension or shock, ileus, or megacolon.

Treatment for CDI should be started only for patients with a positive diagnostic test and symptoms including acute diarrhea (≥ 3 loose stools in 24 hours) with no obvious alternative explanation. For patients with an initial episode of CDI, regimens include either fidaxomicin or oral vancomycin; however, the Infectious Disease Society of America (IDSA) Guideline recommended fidaxomicin rather than oral vancomycin. For recurrent CDI episodes, fidaxomicin is recommended with oral vancomycin as an alternative. Fulminant CDI should be treated with vancomycin orally or through nasogastric tube.

Travelers' Diarrhea

Travelers' diarrhea (TD) is the most common illness in persons traveling from resource-rich to resource-limited regions of the world. Among travelers to such areas, 30% - 70% develop diarrhea. Episodes of TD are usually benign and self-limited, but symptoms may result in health care visits for some travelers. There is growing recognition that TD and its self-treatment abroad are associated with the acquisition of organisms harboring antibiotic resistance. Bacterial and viral TD generally present symptoms within 6-72 hours which can range from mild cramps and urgent loose stools to severe abdominal pain, bloody diarrhea, fever, and vomiting. Untreated, bacterial diarrhea can last 3 - 7 days. Fluid replacement is the most essential component of therapy. If symptoms persist 10 - 14 days after returning, patients should seek medical advice. For serious infection, choice of empiric antibiotic therapy should be azithromycin or fluoroquinolones depending on local susceptibility patterns, travel history, and patient risk factors.

Safety Information

To reduce the development of drug-resistant bacteria and maintain the effectiveness of vancomycin oral products and other antibacterial drugs, the medications discussed should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. Oral vancomycin should be reserved for *Clostridium difficile*-associated diarrhea or enterocolitis caused by *Staphylococcus aureus*. Orally administered vancomycin is not effective for treatment of other types of infections. Aemcolo has not been shown to be effective in patients with diarrhea complicated by fever and/or bloody stools due to pathogens other than *E. coli*. Aemcolo should be discontinued if diarrhea worsens or persists for more than 48 hours. The most common adverse events (AEs) associated with Aemcolo are headache and constipation. The most common AEs for Firvanq and Vancocin are nausea, abdominal pain, and hypokalemia. Additionally, Firvanq and Vancocin have been associated with nephrotoxicity and ototoxicity.

Clinical Rationale

Oral vancomycin is not systemically absorbed and thereby has limited use for the treatment of Clostridium difficile-associated diarrhea or enterocolitis caused by Staphylococcus aureus.

Recommendation

~~Due to concerns regarding the emergence of resistance, it is recommended that oral vancomycin be subject to clinical criteria to ensure appropriate use.~~ *It is recommended that vancomycin be available for use. Aemcolo should be subjected to prior authorization criteria to ensure appropriate use.*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for vancomycin caps

Current Criteria:

- Diagnosis of enterocolitis caused by methicillin-resistant Staphylococcus aureus; **OR**
- Diagnosis of pseudomembranous colitis caused by C. difficile

Note: Individuals started on vancomycin oral therapy in the hospital for the above diagnoses will be approved for this agent following hospital discharge in order to allow for completion of the course of therapy.

Proposed Criteria:

Remove PA Criteria

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for VANCOCIN CAPS

Current Criteria:

- Diagnosis of enterocolitis caused by methicillin-resistant Staphylococcus aureus; **OR**
- Diagnosis of pseudomembranous colitis caused by C. difficile

Note: Individuals started on vancomycin oral therapy in the hospital for the above diagnoses will be approved for this agent following hospital discharge in order to allow for completion of the course of therapy.

Proposed Criteria:

- ~~Diagnosis of enterocolitis caused by methicillin-resistant Staphylococcus aureus; **OR**~~
- ~~Diagnosis of pseudomembranous colitis caused by C. difficile~~

~~**Note**: Individuals started on vancomycin oral therapy in the hospital for the above diagnoses will be approved for this agent following hospital discharge in order to allow for completion of the course of therapy.~~

- *Trial and failure, contraindication, or intolerance generic vancomycin capsules*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for vancomycin solution

Current Criteria:

- Diagnosis of one of the following:
  - Enterocolitis caused by methicillin-resistant Staphylococcus aureus
  - Pseudomembranous colitis caused by C. difficile; **AND**
- If patient is > 12 years of age, patient is unable to swallow solid dosage forms

Proposed Criteria:

- ~~Diagnosis of one of the following:~~
  - ~~Enterocolitis caused by methicillin-resistant Staphylococcus aureus~~
  - ~~Pseudomembranous colitis caused by C. difficile; **AND**~~
- ~~If patient is > 12 years of age,~~ Patient is unable to swallow solid dosage forms

Note: *PA not required for patients less than 12 years of age*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for FIRVANQ

Current Criteria:

- Diagnosis of one of the following:
  - Enterocolitis caused by methicillin-resistant Staphylococcus aureus
  - Pseudomembranous colitis caused by C. difficile; **AND**
- If patient is > 12 years of age, patient is unable to swallow solid dosage forms

Proposed Criteria:

- ~~Diagnosis of one of the following:~~
  - ~~Enterocolitis caused by methicillin-resistant Staphylococcus aureus~~
  - ~~Pseudomembranous colitis caused by C. difficile; **AND**~~
- ~~If patient is > 12 years of age,~~ Patient is unable to swallow solid dosage forms; **AND**
- *Trial and failure, contraindication, or intolerance generic vancomycin solution*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for AEMCOLO

Current Criteria:

- Patient is being treated for traveler's diarrhea; **AND**
- Trial and failure, contraindication, intolerance, drug-drug interaction or resistance to a fluoroquinolone or azithromycin

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• AEMCOLO	~~4/day;~~ *12 tab/RX; max 24 tab/year*
• FIRVANQ	2,000mg/day
• vancomycin solution	2,000mg/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Aemcolo (rifamycin) [prescribing information]. Raleigh, NC; RedHill Biopharma Inc: February 2021.
- Connor B. Travelers' Diarrhea: CDC Yellow Book 2024. https://wwwnc.cdc.gov/travel/yellowbook/2024/preparing/travelers-diarrhea#table209
- Drekonja DM, Butler M, MacDonald R, et al. Comparative effectiveness of Clostridium difficile treatments: a systematic review. Ann Intern Med 2011; 155:839.
- Firvanq (vancomycin hydrochloride) [prescribing information]. Wilmington, MA: Azurity Pharmaceuticals; January 2021.
- Hill DR. Health problems in a large cohort of Americans traveling to developing countries. J Travel Med 2000; 7:259.
- Hu MY, Katchar K, Kyne L, et al. Prospective derivation and validation of a clinical prediction rule for recurrent Clostridium difficile infection. Gastroenterology 2009; 136:1206.
- Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clin Infect Dis 2021; 73:e1029.
- Kantele A, Lääveri T, Mero S, et al. Antimicrobials increase travelers' risk of colonization by extended-spectrum betalactamase-producing Enterobacteriaceae. Clin Infect Dis 2015; 60:837.
- Kelly CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. Am J Gastroenterol 2021; 116:1124.
- Kelly CP, LaMont JT. Clostridium difficile--more difficult than ever. N Engl J Med 2008; 359:1932.
- McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018; 66:e1.
- Mellon G, Turbett SE, Worby C, et al. Acquisition of Antibiotic-Resistant Bacteria by U.S. International Travelers. N Engl J Med 2020; 382:1372.
- Mullane KM, Miller MA, Weiss K, et al. Efficacy of fidaxomicin versus vancomycin as therapy for Clostridium difficile infection in individuals taking concomitant antibiotics for other concurrent infections. Clin Infect Dis 2011; 53:440.
- Nelson RL, Suda KJ, Evans CT. Antibiotic treatment for Clostridium difficile-associated diarrhoea in adults. Cochrane Database Syst Rev 2017; 3:CD004610.
- Riddle MS, Connor BA, Beeching NJ, et al. Guidelines for the prevention and treatment of travelers' diarrhea: a graded expert panel report. J Travel Med 2017; 24:S57.
- Steffen R, Hill DR, DuPont HL. Traveler's diarrhea: a clinical review. JAMA 2015; 313:71.
- Stoney RJ, Han PV, Barnett ED, et al. Travelers' Diarrhea and Other Gastrointestinal Symptoms Among Boston-Area International Travelers. Am J Trop Med Hyg 2017; 96:1388.
- Vancocin (vancomycin hydrochloride) [prescribing information]. Baudette, MN: ANI Pharmaceuticals Inc; December 2021.
- Worby CJ, Earl AM, Turbett SE, et al. Acquisition and Long-term Carriage of Multidrug-Resistant Organisms in US International Travelers. Open Forum Infect Dis 2020; 7:ofaa543.

ANTIBIOTICS: ORAL ANTI-TUBERCULOSIS

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred		Non-Preferred	
Anti-Tuberculosis	ethambutol isoniazid pyrazinamide rifabutin PA	rifampin	cycloserine MYAMBUTOL (ethambutol) MYCOBUTIN PA (rifabutin) PRIFTIN (rifapentine)	RIFADIN (rifampin) SIRTURO PA (bedaquiline) TRECATOR (ethionamide)

Last Review Date: February 2022

Recent Significant Changes

- World Health Organization (WHO) updated Guidelines on Tuberculosis (TB): Drug-Resistant Tuberculosis Treatment update (2022)
- Discontinued Drugs:
  - RIFAMATE, 2022
  - RIFATER, 2022
  - PASER, 2022

Background

Mycobacterium tuberculosis causes tuberculosis (TB) and is a leading infectious cause of death in adults worldwide. More than 1.7 billion people (approximately 22 percent of the world population) are estimated to be infected with *M. tuberculosis*. The global incidence of TB peaked around 2003 and appears to be declining slowly. According to the World Health Organization (WHO), in 2021, 10.6 million individuals became ill with TB and 1.6 million died. The human host serves as a natural reservoir for *M. tuberculosis*. The risk factors for TB include impaired immunity and increased exposure to infectious persons.

First-line agents for treatment of susceptible TB disease consist of isoniazid, a rifamycin (rifampin or [less frequently] either rifapentine or rifabutin), pyrazinamide, and ethambutol; in addition, moxifloxacin is a first-line agent when administered in combination with isoniazid, rifapentine, and pyrazinamide. Presence of drug resistance, contraindication, or intolerance to first-line agents may warrant substitution with one or more second-line agents. Examples of second line agents include bedaquiline, cycloserine, ethambutol, and ethionamide. Compared to first-line agents, second-line agents show decreased activity against *M. tuberculosis*, relative lack of clinical data, an unfavorable pharmacokinetic profile, and increased adverse events.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
cycloserine	✔
isoniazid	✔
MYAMBUTOL (ethambutol)	✔
MYCOBUTIN (rifabutin)	✔
PRIFTIN (rifapentine)	-
pyrazinamide	✔
RIFADIN (rifampin)	✔
SIRTURO (bedaquiline)	-
TRECATOR (ethionamide)	-

Table 2. Food and Drug Administration Approved Indications

	cycloserine	isoniazid	ethambutol	rifabutin	PRIFTIN	pyrazinamide	rifampin	SIRTURO	TRECATOR
Pulmonary multi-drug resistant tuberculosis (MDR-TB)								✔	
Pulmonary and extrapulmonary TB when primary medications are not adequate	✔								
All forms of TB in which organisms are susceptible		✔							
Pulmonary tuberculosis			✔						
Prevention of disseminated Mycobacterium avium complex (MAC) disease in patients with advanced HIV infection				✔					
Treatment of active pulmonary tuberculosis (TB)					✔				
In combination with other antituberculosis agents in the treatment of clinical tuberculosis						✔	✔		
Active tuberculosis in patients with M. tuberculosis resistant to isoniazid or rifampin, or when there is intolerance on the part of the patient to other drugs									✔

For latent tuberculosis infection (LTBI), the National Tuberculosis Controllers Association (NTCA) and Centers for Disease Control and Prevention (CDC) recommend three preferred rifamycin-based regimens and two alternative monotherapy regimens with daily isoniazid. For treatment of an active TB infection, combination therapy is required. Monotherapy should never be used for tuberculosis. First-line agents include isoniazid, rifampin, rifabutin, rifapentine, pyrazinamide, and ethambutol. Basic TB treatment regimen examples include an intensive phase of two months, followed by a continuation phase of either 4 or 7 months. Examples of regimens:

- Daily isoniazid/rifampin/pyrazinamide/ethambutol for 8 weeks followed by daily isoniazid/rifampin for 18 weeks (preferred regimen)
- Daily isoniazid/rifampin/pyrazinamide/ethambutol for 2 weeks, then three-times-weekly for 6 weeks, followed by three-times-weekly isoniazid/rifampin for 18 weeks (alternative regimen)
- Three-times-weekly isoniazid/rifampin/pyrazinamide/ethambutol for 8 weeks, followed by three-times-weekly isoniazid/rifampin for 18 weeks (alternative regimen)

Available second-line agents include injectable aminoglycosides (amikacin, kanamycin, streptomycin), injectable polypeptides, fluoroquinolones (levofloxacin, moxifloxacin, ofloxacin, gatifloxacin), para-aminosalicylic acid, cycloserine, ethionamide, and linezolid. Multi-drug-resistant TB (MDR-TB) is a TB disease in which the organisms are resistant to more than one anti-TB agent and at least isoniazid and rifampin. Treatment for MDR-TB is complicated and requires close consultation and management to prevent inappropriate treatment. Combinations of first and second-line agents are used at high doses. In addition, bedaquiline may be used for MDR-TB infections.

Isoniazid has a boxed warning for associated severe and sometimes fatal hepatitis. Myambutol is contraindicated in patients with known optic neuritis and in those who are unable to report visual side effect effects or changes. *Clostridium difficile* associated diarrhea (CDAD) has been reported with nearly all antibacterial agents. Priftin has a warning for discoloration of bodily fluids (e.g., permanently staining contact lenses or dentures (red/orange)) and should be avoided in patients with porphyria. Reports from the Centers for Disease Control and Prevention of the US showed high rates of hospitalization and death from liver injury following the combined use of pyrazinamide and rifampin for the treatment of latent tuberculosis because of a higher potential hepatotoxicity. Rifadin is contraindicated in combination with ritonavir-boosted saquinavir, atazanavir, darunavir, fosamprenavir, tipranavir, or praziquantel. Sirturo has a warning for QT prolongation.

The most common adverse events (AEs) associated with the agents discussed are as followed:

- Cycloserine: skin rash, nervous system symptoms (e.g., fatigue, headache, tremor, confusion) related to dosage, and elevated serum transaminase
- Isoniazid: peripheral neuropathy, hepatic reactions (e.g., elevated serum transaminase, jaundice)
- Myambutol: optic neuropathy, decreased visual acuity, dermatitis and skin reactions, nausea/vomiting, gastrointestinal upset, fever, malaise, dizziness, headache
- Mycobutin: rash, gastrointestinal intolerance, neutropenia
- Priftin: anemia, lymphopenia, hemoptysis neutropenia, cough, thrombocytosis, increased sweating, increased ALT, increased AST, back pain, rash, anorexia, arthralgia, increased blood urea, headache
- Pyrazinamide: arthralgia, hepatotoxicity
- Rifadin: blood and lymphatic system disorders, endocrine disorders, visual disturbances, gastrointestinal intolerance, hepatobiliary disorders, immunological reactions, pulmonary disorders
- Sirturo: nausea, arthralgia, and headache
- Trecator: gastrointestinal intolerance, psychotic disturbances, drowsiness, dizziness, restlessness, headache, postural hypotension, hepatic disturbances, hypersensitivity reactions, hypoglycemia, hypothyroidism, gynecomastia, impotence

Clinical Rationale

First-line agents for treatment of tuberculosis consist of isoniazid, rifampin (or rifapentine or rifabutin in certain situations), pyrazinamide, and ethambutol. Presence of drug resistance or intolerance to first-line agents warrants use of second-line agents.

Recommendation

It recommended that at least isoniazid, rifampin, pyrazinamide, rifapentine, and ethambutol be available for use ~~with the combination products subject to clinical criteria~~. Additionally, rifabutin should be available for MAC treatment and prophylaxis ~~subject to clinical criteria~~.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for rifabutin

Current Criteria:

- Prophylaxis against MAC in patients with contraindication, or intolerance to clarithromycin AND azithromycin; **OR**
- Treatment of disseminated MAC in combination with a macrolide and ethambutol

Proposed Criteria:

Remove PA

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for Mycobutin

Current Criteria:

- One of the following:
  - Prophylaxis against MAC in patients with contraindication, or intolerance to clarithromycin AND azithromycin
  - Treatment of disseminated MAC in combination with a macrolide and ethambutol; **AND**
- Approval requires a trial and failure, contraindication, or intolerance of 2 preferred agents (must include rifabutin)

Proposed Criteria:

- ~~One of the following:~~
  - ~~Prophylaxis against MAC in patients with contraindication, or intolerance to clarithromycin AND azithromycin~~
  - ~~Treatment of disseminated MAC in combination with a macrolide and ethambutol; **AND**~~
- ~~Approval requires a trial and failure, contraindication, or intolerance of 2 preferred agents (must include rifabutin)~~
- *Trial and failure of preferred rifabutin*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for SIRTURO

Current Criteria:

Criteria: (9-month approval duration)

- Patient is ≥ 5 years of age and weighs ≥ 15 kg; **AND**
- Patient has a diagnosis of pulmonary multi-drug resistant tuberculosis (MDR-TB); **AND**
- Sirturo is prescribed as part of a combination regimen with at least 3 other drugs to which the patient's MDR-TB isolate has been shown to be susceptible; **AND**
- Prescribed by, or in consultation with, an infectious disease specialist; **AND**
- Prescriber attests all of the following have been obtained prior to treatment:
  - ECG
  - Liver enzymes
  - Electrolytes; **AND**
- Sirturo will not be approved for the following:
  - Latent infection due to Mycobacterium tuberculosis
  - Drug-sensitive tuberculosis
  - Extra-pulmonary tuberculosis
  - Infections caused by non-tuberculous mycobacteria

Proposed Criteria:

Criteria: (9-month approval duration)

- Patient is ≥ 5 years of age and weighs ≥ 15 kg; **AND**
- Patient has a diagnosis of pulmonary multi-drug resistant tuberculosis (MDR-TB); **AND**
- Prescribed as part of a combination regimen with at least 3 other drugs to which the patient's MDR-TB isolate has been shown to be susceptible; **AND**
- Sirturo is prescribed by, or in consultation with, an infectious disease specialist; **AND**
- ~~Prescriber attests all of the following have been obtained prior to treatment:~~
  - ~~ECG~~
  - ~~Liver enzymes~~
  - ~~Electrolytes; **AND**~~
- ~~Sirturo will not be approved for the following:~~
  - ~~Latent infection due to Mycobacterium tuberculosis~~
  - ~~Drug-sensitive tuberculosis~~
  - ~~Extra-pulmonary tuberculosis~~
  - ~~Infections caused by non-tuberculous mycobacteria~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Adigun R, Singh R. Tuberculosis. [Updated 2023 Jul 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441916/
- Carr W, Kurbatova E, Starks A, et al. Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis - United States, 2022. MMWR Morb Mortal Wkly Rep 2022; 71:285.
- Cycloserine capsules [prescribing information]. Princeton, NJ: Dr Reddy's Laboratories Inc; February 2023.
- Ethambutol tablet [prescribing information]. Baltimore, MD: Lupin Pharmaceuticals Inc; February 2016.
- Isoniazid oral solution [prescribing information]. Farmville, NC: CMP Pharma; March 2018.
- Isoniazid tablets [prescribing information]. North Wales, PA: Teva Pharmaceuticals; July 2016.
- Mycobutin capsules (rifabutin) [prescribing information]. New York, NY: Pharmacia & Upjohn Co LLC; September 2021.
- Nahid P, Mase SR, Migliori GB, et al. Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. Am J Respir Crit Care Med 2019; 200:e93.
- Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis 2016; 63:e147.
- Paser (aminosalicylic acid) [prescribing information]. Princeton, NJ: Jacobus Pharmaceutical Company Inc; June 2010.
- Peloquin CA. Pharmacology of the antimycobacterial drugs. Med Clin North Am 1993; 77:1253.
- Priftin (rifapentine) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis US LLC; July 2021.
- Pyrazinamide (tablets, USP 500 mg) [prescribing information]. New Castle, DE: Marlex Pharmaceuticals Inc; March 2022.
- Rifadin capsules (rifampin) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis US LLC; August 2023.
- Rifampin capsules [prescribing information]. Congers, NY: Chartwell RX, LLC; May 2023.
- Rifamate (rifampin/isoniazid) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; August 2019.
- Rifater (rifampin/isoniazid/pyrazinamide) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis US LLC; February 2023.
- Sirturo (bedaquiline) [prescribing information]. Horsham, PA: Janssen Products LP; October 2023.
- Testing and Treatment of Latent Tuberculosis Infection in the United States: Clinical Recommendations. National Tuberculosis Controllers Association. https://www.tbcontrollers.org/resources/tb-infection/clinical-recommendations/ (Accessed January 2, 2024).
- Treatment for TB Disease. Centers for Disease Control and Prevention. https://www.cdc.gov/tb/topic/treatment/tbdisease.htm
- Trecator (ethionamide) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals Inc; July 2023.
- World Health Organization. WHO 2019 consolidated guidelines on drug-resistant tuberculosis treatment. https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1 (Accessed on March 28, 2019).
- World Health Organization. Global Tuberculosis Report 2022. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022 (Accessed on May 04, 2023).

ANTIBIOTICS: OXAZOLIDINONES

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
Oxazolidinones	linezolid tabs PA, QL linezolid suspension PA, QL	SIVEXTRO PA, QL (tedizolid) ZYVOX suspension PA, QL (linezolid) ZYVOX tabs PA, QL (linezolid)

Last Review Date: February 2022

Recent Significant Changes

- No significant updates since last review.

Background

The oxazolidinones represent a novel class of synthetic antibiotics. Due to the increased resistance of many common gram-positive pathogens (eg, *Staphylococcus aureus, Enterococcus species, and Streptococcus pneumoniae*), the oxazolidinone class was discovered to have a unique mechanism of inhibiting protein synthesis by binding at the P site at the ribosomal 50S subunit. Resistance to other protein synthesis inhibitors does not affect oxazolidinone activity; its use is generally reserved for infections that are resistant to other antibiotics.

Zyvox (linezolid) was the first-in-class, synthetic, oxazolidinone antibiotic approved in 2000 for the treatment of various gram-positive bacterial infections. Linezolid carries activity against resistant gram-positive bacteria including methicillin-resistant *S. aureus* (MRSA), penicillin-resistant pneumococci, macrolide-resistant streptococci, and vancomycin-resistant Enterococci. In addition to the antibacterial properties, linezolid is a reversible non-selective monoamine oxidase inhibitor (MAOI). As a result, co-administration with certain antidepressants may precipitate serotonin syndrome. Sivextro (tedizolid) is an oxazolidinone prodrug approved by the FDA in 2014 for the treatment of gram-positive skin and skin structure infections in adult and pediatric patients 12 years and older. Tedizolid has shown to have ≥ 4-fold greater activity (compared to linezolid) against gram-positive species including *staphylococci, enterococci,* and *streptococci*, including drug-resistant strains such as MRSA, vancomycin-resistant Enterococci (VRE) and linezolid-resistant phenotypes. Tedizolid has oral bioavailability nearing 91%, with high penetration into plasma, muscle, adipose and lung tissues.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
SIVEXTRO (tedizolid)	-
ZYVOX (linezolid)	✔

Table 2. Food and Drug Administration Approved Indications

Indication	SIVEXTRO (tedizolid)	ZYVOX (linezolid)
ABSSSI† caused by S. aureus (including MSSA and MRSA), S. pyogenes, S. agalactiae, S. anginosus group (ie, S. anginosus, S. intermedius, and S. constellatus), and E. faecalis. Note: Should be used only to treat ABSSSI that are proven or strongly suspected to be caused by susceptible bacteria.	✔	-
Nosocomial pneumonia caused by S. aureus (including MSSA and MRSA) or S. pneumoniae.	-	✔

Indication	SIVEXTRO (tedizolid)	ZYVOX (linezolid)
ABSSSI† caused by gram-positive organisms including S. aureus (including MSSA and MRSA), S. pyogenes, S. agalactiae, S. anginosus group (including S. anginosus, S. intermedius, S. constellatus), and E. faecalis.	-	✔
CAP caused by S. pneumoniae, including cases with concurrent bacteremia or S. aureus (MSSA only).	-	✔
Uncomplicated SSTI caused by S. aureus (MSSA only) or S. pyogenes.	-	✔
VRE infections, including cases with concurrent bacteremia	-	✔

Abbreviations: ABSSSI = acute bacterial skin and skin structure infections; CAP = community acquired pneumonia; MRSA = methicillin-resistant *S. Aureus*; MSSA = methicillin-susceptible *S. Aureus*. SSTI = skin and skin structure infections;

The 2020 Surgical Infection Society guideline on the management of complicated SSTIs recommends considering empiric coverage of MRSA, especially in purulent infections. Oral therapy for suspected or confirmed MRSA SSTIs include linezolid, trimethoprim-sulfamethoxazole (TMP-SMX), and doxycycline or minocycline. Alternatives include tedizolid, delafloxacin and omadacycline. Empiric oral therapies that can be used to treat outpatient community-associated (CA)-MRSA SSTIs include TMP-SMX, doxycycline or minocycline, and linezolid. The guideline noted that linezolid is an effective alternative but not superior to other agents. This guideline was updated prior to the FDA approval of tedizolid, thus no recommendations for place in therapy were included.

The 2011 IDSA guidelines for the treatment of MRSA infections recommends, for a cutaneous abscess, incision and drainage is the primary treatment. Empirical coverage for CA-MRSA is recommended in patients who do not respond to b-lactam therapy and may be considered in those with systemic toxicity. For empiric coverage of CA-MRSA in outpatients with SSTIs, oral antibiotic options include clindamycin, SMX/TMP, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both b-hemolytic Streptococci and CA-MRSA is desired, options include clindamycin alone, SMX/TMP or a tetracycline in combination with a b-lactam (eg, amoxicillin), or linezolid alone.

Linezolid is contraindicated in use with MAOIs within 2 weeks. There are warnings for myelosuppression, peripheral and optic neuropathy, serotonin syndrome, *Clostridioides difficile*-associated diarrhea, hypoglycemia, hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and phenylketonuria (PKU). The most common adverse events associated with linezolid are diarrhea, vomiting, headache, nausea, and anemia. Tedizolid should be used with caution in patients with neutropenia and those with *C. difficile*-associated diarrhea. Tedizolid's most common adverse events are nausea, headache, diarrhea, vomiting, and dizziness.

Clinical Rationale

The oxazolidinones represent a novel class of synthetic antibiotics for various gram-positive infections, including drug-resistant isolates. Linezolid is FDA-approved for several indications including ABSSSIs, CAP, nosocomial pneumonia, and uncomplicated SSTIs. Tedizolid carries an indication for ABSSSIs only.

Recommendation

It is recommended *that linezolid be available for use* ~~oxazolidinones be subject to prior authorization criteria~~.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for linezolid tablets, ZYVOX TABLETS

Current Criteria:

- Diagnosis of ONE of the following:
  - Vancomycin Resistant Enterococcus faecalis infections

- Healthcare-associated Methicillin-Resistant Staph Aureus (MRSA) infections or community-acquired MRSA with polyresistance

Please note the following:

- The patient must have culture documentation of diagnoses
- Individuals started on therapy in the hospital will be approved for this agent following hospital discharge in order to allow for completion of the course of therapy.

Proposed Criteria:

- ~~Diagnosis of~~ *Treatment is for* ONE of the following:
  - Vancomycin Resistant Enterococcus faecalis infections
  - ~~Healthcare-associated Methicillin-Resistant Staph Aureus (MRSA) infections or community-acquired MRSA with polyresistance~~
  - *Community-acquired pneumonia (CAP) caused by S. pneumoniae or S. aureus (MSSA)*
  - *Nosocomial pneumonia caused by S. pneumoniae or S. aureus (including MSSA and MRSA)*
  - *Complicated skin and skin structure infections (SSSI) caused by S. aureus (MSSA and MRSA), S. pyogenes, or S. agalactiae.*
  - *Uncomplicated SSTI caused by S. aureus (MSSA only) or S. pyogenes*
  - *Patient is continuing therapy from an inpatient hospital stay (to facilitate completion of therapy);* ***AND***
- *If request if for Zyvox tablets, trial and failure of preferred linezolid tablets*

~~**Please note the following:**~~

- ~~The patient must have culture documentation of diagnoses~~
- ~~Individuals started on therapy in the hospital will be approved for this agent following hospital discharge in order to allow for completion of the course of therapy.~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for linezolid suspension, ZYVOX SUSPENSION

Current Criteria:

- Culture documentation of ONE of the following diagnoses:
  - Vancomycin Resistant Enterococcus faecium infections
  - Vancomycin Resistant Enterococcus faecalis infections
  - Healthcare-associated Methicillin-Resistant Staph Aureus (MRSA) infections or community-acquired MRSA with polyresistance; **AND**
- One of the following:
  - Patient is less than 12 years of age
  - Patient is unable to swallow oral dosage forms; **AND**
- Clinically valid reason why the preferred Zyvox suspension cannot be used

Note: Individuals started on therapy in the hospital will be approved for the agent following discharge in order to allow for completion of the course of therapy

Proposed Criteria:

- ~~Culture documentation of ONE of the following diagnoses:~~
  - ~~Vancomycin Resistant Enterococcus faecium infections~~
  - ~~Vancomycin Resistant Enterococcus faecalis infections~~
  - ~~Healthcare-associated Methicillin-Resistant Staph Aureus (MRSA) infections or community-acquired MRSA with polyresistance; **AND**~~
- ~~Clinically valid reason why the preferred Zyvox suspension cannot be used~~
- One of the following:
  - Patient is less than 12 years of age

- Patient is unable to swallow oral dosage forms
- *Patient is continuing therapy from an inpatient hospital stay (to facilitate completion of therapy)*: ***AND***

- *If request is for Zyvox suspension, trial and failure of preferred linezolid suspension*

~~**Note**: Individuals started on therapy in the hospital will be approved for the agent following discharge in order to allow for completion of the course of therapy~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for SIVEXTRO

Current Criteria:

- Diagnosis of acute bacterial skin and skin structure infection; **AND**
- Culture documenting one of the following susceptible gram-positive cocci as causative organism:
  - Enterococcus faecalis
  - Staphylococcus aureus (MRSA)
  - Staphylococcus aureus (MSSA)
  - Streptococcus agalactiae (group B streptococci)
  - Streptococcus anginosus
  - Streptococcus constellatus
  - Streptococcus intermedius
  - Streptococcus pyogenes (group A beta-hemolytic streptococci); **AND**
- Patient must be resistant to or have a contraindication, or intolerance, to all other treatment options

Note: Individuals started on therapy in the hospital will be approved for the agent following discharge in order to allow for completion of the course of therapy

Proposed Criteria: *(2-week approval duration)*

- One of the following:
  - Diagnosis of acute bacterial skin and skin structure infection; **AND**
    - ~~Culture documenting one of the following susceptible gram-positive cocci as causative organism:~~
      - ~~Enterococcus faecalis~~
      - ~~Staphylococcus aureus (MRSA)~~
      - ~~Staphylococcus aureus (MSSA)~~
      - ~~Streptococcus agalactiae (group B streptococci)~~
      - ~~Streptococcus anginosus~~
      - ~~Streptococcus constellatus~~
      - ~~Streptococcus intermedius~~
      - ~~Streptococcus pyogenes (group A beta-hemolytic streptococci);~~ ~~**AND**~~
    - Patient must be resistant to or have a contraindication, or intolerance, to all other treatment options
  - *Patient is continuing therapy from an inpatient hospital stay (to facilitate completion of therapy)*

~~**Note**: Individuals started on therapy in the hospital will be approved for the agent following discharge in order to allow for completion of the course of therapy~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• ZYVOX (linezolid) tablets	2/day
• ZYVOX (linezolid) suspension	60 mL/day
• SIVEXTRO	1/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Bai AD, McKenna S, Wise H. Association of linezolid with risk of serotonin syndrome in patients receiving antidepressants. JAMA Netw Open. 2022;5(12):e2247426.
- Bozdogan B, Appelbaum PC. Oxazolidinones: activity, mode of action, and mechanism of resistance. Int J Antimicrob Agents. 2004;23(2):113-119.
- Diekema DJ, Jones RN. Oxazolidinones: a review. Drugs. 2000;59(1):7-16.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed September 18, 2023.
- infections. Surg Infect (Larchmt).2021;22(4):383-399.
- FDA Drug Safety Communication. Updated information about the drug interaction between linezolid (Zyvox) and serotonergic psychiatric medications. US Food and Drug Administration. October 20, 2011. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-updated-information-about-drug-interaction-between-linezolid-zyvox-and. Accessed November 9, 2023.
- FDA Guidance Document. Acute bacterial skin and skin structure infections: developing drugs for treatment. Updated April 21, 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acute-bacterial-skin-and-skin-structure-infections-developing-drugs-treatment. Accessed November 9, 2023.
- Flanagan SD, Bien PA, Munoz KA. Pharmacokinetics of tedizolid following oral administration: single and multiple dose, effect of food, and comparison of two solid forms of the prodrug. Pharmacotherapy. 2013; 34(3): 240–250.
- Food and Drug Administration (FDA). Zyvox medical review [part 3]. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21130_Zyvox_medr_P3.pdf. April 21, 2000. Accessed November 15, 2023.
- Linezolid powder for suspension [prescribing information]. Eatontown, NJ: West-Ward Pharmaceuticals Corp; September 2020.
- Linezolid tablet [prescribing information]. Pulaski, TN: AvKARE Inc; January 2016.
- Liu C, Bayer A, Cosgrove SE, et al; for the Infectious Diseases Society of America (IDSA). Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011;52(3):e18-55.
- Micromedex 2.0 [database on the Internet]. Greenwood Village, CO: Truven Health Analytics; 2023. http://www.micromedexsolutions.com/home/dispatch. Accessed November 15, 2023.
- Moellering RC. Linezolid: The First Oxazolidinone Antimicrobial. Ann Intern Med. 2003;138(2):135-142.
- Sivextro (tedizolid) tablet [prescribing information]. Rahway, NJ: Merck Sharp & Dohme LLC; March 2023.
- William A. Bower, MD ; Yon Yu, PharmD ; Marissa K. Person, MSPH ; Corinne M. Parker, PharmD ; Jordan L. Kennedy, MSPH ; David Sue, PhD ; Elisabeth M. Hesse, MD ; Rachel
- Cook, MS ; John Bradley, MD ; Jürgen B. Bulitta, PhD ; Adolf W. Karchmer, MD ; Robert M. Ward, MD ; Shana Godfred Cato, DO ; Kevin Chatham Stephens, MD ; Katherine A.
- Hendricks, MD (VIEW AUTHOR AFFILIATIONS)
- Zhanel GG, Love R, Adam H, et al. Tedizolid: a novel oxazolidinone with potent activity against multidrug-resistant gram-positive pathogens. Drugs. 2015;75(3):253-270.
- Zyvox (linezolid) [prescribing information]. New York, NY: Pharmacia and Upjohn; August 2023.

ANTIBIOTICS: QUINOLONES, ORAL

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred	
Oral Quinolones	ciprofloxacin tabs levofloxacin tabs	BAXDELA [PA, QL] (delafloxacin) CIPRO tabs and susp [PA] (ciprofloxacin) ciprofloxacin susp [PA]	levofloxacin soln [PA] moxifloxacin ofloxacin tabs

Last Review Date: February 2022

Recent Significant Changes

- Infectious Disease Society of America (IDSA) Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Background

The fluoroquinolones are broad-spectrum antibiotics that have potent activity against aerobic, enteric gram-negative bacilli (rods) and many common respiratory pathogens. Some of the fluoroquinolones are also active against *Pseudomonas* spp, selected gram-positive organisms, anaerobes, and mycobacteria. Ciprofloxacin has the greatest activity against aerobic, enteric gram-negative bacilli and *Pseudomonas aeruginosa*, while levofloxacin and delafloxacin have reduced, but still adequate activity. Moxifloxacin is not generally used to treat infections caused by *P. aeruginosa, Providencia* spp., *Proteus* spp, and *Serratia marcescens* as it has significantly less activity compared to ciprofloxacin. Levofloxacin and moxifloxacin are active against most respiratory pathogens including *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*, and intracellular or cell wall-deficient bacteria (ie, *Legionella* spp, *Mycoplasma* spp, and *Chlamydia pneumoniae*).

Ciprofloxacin has limited to no activity against gram-positive organisms (eg, *S. pneumoniae*); thus, it may not be appropriate for empiric therapy of respiratory tract infections. However, ciprofloxacin does have potent activity against aerobic gram-negative respiratory pathogens (eg, *H. influenzae, M. catarrhalis*). Levofloxacin, moxifloxacin, and delafloxacin are active against certain gram-positive organisms including *Staphylococcus aureus*, some streptococci, and some strains of coagulase-negative staphylococci. Delafloxacin is the only fluroquinolone with activity against methicillin-resistant *S. aureus* (MRSA). Moxifloxacin is the only fluoroquinolone with sufficient activity against anaerobic bacteria. Moxifloxacin and levofloxacin have greater potency against *Mycobacterium tuberculosis* compared to other fluoroquinolones. They are considered second-line treatment when there is resistance or intolerance to first-line agents.

The fluoroquinolones are commonly used to treat a variety of infections including urinary tract infections, sinusitis, lower respiratory tract infections, intra-abdominal infections, infectious diarrhea, skin and skin structure infections, sexually transmitted diseases, community-acquired bacterial pneumonia (CABP), bacterial prostatitis, and typhoid. There is also considerable off-label data for use in neutropenic patients and for treatment of tuberculosis and mycobacterial infections in patients with human immunodeficiency virus (HIV). While relatively uncommon illnesses, the United States government recognizes *Yersinia Pestis* (causing various forms of the plague) and *Bacillus anthracis* (causing anthrax) as potential bioterrorism weapons, and as a result, mandates evidenced-based guidelines on appropriate treatment measures. Fluoroquinolones are considered first-line antimicrobial treatment and prophylaxis of plague infections (bubonic, pharyngeal, pneumonic septicemic) caused by *Y. Pestis*.

Ciprofloxacin, delafloxacin, levofloxacin, and moxifloxacin are available as IV and oral formulations. The first-generation agents (e.g., nalidixic acid, cinoxacin) and the third-generation agents (gatifloxacin, grepafloxacin, sparfloxacin) are no longer available. Ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin are available in otic and/or ophthalmic formulations. However, only the oral formulations will be included in this review.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
BAXDELA (delafloxacin) tablets	-
CIPRO (ciprofloxacin) powder for oral suspension	-
CIPRO (ciprofloxacin) tablets	✔
levofloxacin tablets, oral solution	✔
moxifloxacin tablets	✔
ofloxacin	✔

Table 2. Food and Drug Administration Approved Indications

Indication	delafloxacin	ciprofloxacin	levofloxacin	moxifloxacin	ofloxacin
Acute bacterial sinusitis caused by *S. pneumoniae, H. influenzae*, or *M. catarrhalis*.		✔	✔	✔	
Acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae* or *H. influenzae*.					✔
Acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae, H. influenzae, H. parainfluenzae, K. pneumoniae,* methicillin-susceptible *S. aureus* (MSSA), *M. catarrhalis*.			✔	✔	
Community acquired pneumonia caused by *S. pneumoniae* or *H. influenzae*.					✔
Community acquired pneumonia caused *by S. pneumoniae*, H. influenzae, M. catarrhalis*, MSSA, *K. pneumoniae, M. pneumoniae*, or *C. pneumoniae*.			✔	✔	
Community acquired pneumonia caused by *S. pneumoniae*, MSSA, *H. influenzae*, *H. parainfluenzae, Escherichia coli, P. aeruginosa, M. pneumoniae, C. pneumonia, Legionella pneumophilia, K. pneumoniae.*	✔				
Lower respiratory tract infections caused by *E. coli, K. pneumoniae, Enterobacter cloacae, P. mirabilis, P. aeruginosa, H. influenzae, H. parainfluenzae*, or *S. pneumoniae.*		✔			
Uncomplicated skin and skin structure infections caused by MSSA or *S. pyogenes*.			✔	✔	
Uncomplicated skin and skin structure infections caused by MSSA, *S. pyogenes*, or *P. mirabilis*.					✔
Complicated skin and skin structure infections caused by MSSA, *E. coli, K. pneumoniae*, or *E. cloacae*.				✔	
Complicated skin and skin structure infections caused by MSSA, *S. pyogenes, E. faecalis*, or *P. mirabilis*.			✔		
Skin and skin structure infections caused by *E. coli, K. pneumoniae, E. cloacae, P. aeruginosa*, MSSA and MRSA, *S. haemolyticus, S. lugdunensis, S. agalactiae, S. anginosus* group, *S. pyogenes*, and *E. faecalis*	✔				
Skin and skin structure infections caused by *E. coli, K. pneumoniae, E. cloacae, P. mirabilis, P. vulgaris, P. stuartii, M. morganii, C. freundii, P. aeruginosa*, MSSA, methicillin-susceptible *S. epidermidis*, or *S. pyogenes.*		✔			
Bone and joint infections caused by *E. cloacae, S. marcescens*, or *P. aeruginosa*.		✔			
Complicated intra-abdominal infections caused by *E. coli, Bacteroides fragilis, S. anginosus, S. constellatus, E. faecalis, P. mirabilis, Clostridium perfringens, B. thetaiotaomicron*, or *Peptostreptococcus* spp.				✔	
Complicated intra-abdominal infections (used in combination with metronidazole) caused by *E. coli, P. aeruginosa, P. mirabilis, K. pneumoniae*, or *B. fragilis*.		✔			
Uncomplicated urinary tract infection caused by *E. coli, K. pneumoniae*, or *S. saprophyticus*.			✔		
Complicated urinary tract infection caused *by E. coli, P. mirabilis, K. pneumoniae*, *E. faecalis, E. cloacae*, or *P. aeruginosa*.			✔		
Complicated urinary tract infection caused by *E. coli, P. mirabilis, K. pneumoniae*, *P. aeruginosa*, or *Citrobacter koseri*.					✔
Acute uncomplicated pyelonephritis caused by *E. coli*.			✔		

Indication	delafloxacin	ciprofloxacin	levofloxacin	moxifloxacin	ofloxacin
Urinary tract infection caused by *E. coli, K. pneumoniae, E. cloacae, S. marcescens, P. mirabilis, P. rettgeri, M. morganii, C. koseri, C. freundii, P.* aeruginosa, methicillin-susceptible *S. epidermidis, S. saprophyticus*, or *E. faecalis*.		✔			
Acute uncomplicated cystitis in females caused by *E. coli* or *S. saprophyticus*.		✔			
Acute uncomplicated cystitis caused by *C. koseri, E. aerogenes, E. coli, K. pneumoniae, P. mirabilis*, or *P. aeruginosa*.					✔
Chronic bacterial prostatitis caused by *E. coli* or *P. mirabilis*.		✔			
Chronic bacterial prostatitis caused by *E. coli, E. faecalis* or methicillin-susceptible *S. epidermidis*.			✔		
Prostatitis caused by *E. coli*.					✔
Infectious diarrhea caused by *E. coli* (enterotoxigenic isolates), *Campylobacter jejuni, S. boydii, S. dysenteriae, S. flexneri* or *S. sonnei*.		✔			
Typhoid fever (enteric fever) caused by *S. typhi*.		✔			
Uncomplicated cervical and urethral gonorrhea caused by *N. gonorrhoeae.*		✔			✔
Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *B. anthracis.*		✔	✔		
Plague caused by *Y. pestis* (treatment and prophylaxis).		✔	✔	✔	
Urethritis and cervicitis caused by *C. trachomatis*					✔

Treatment guidelines for the treatment of urinary tract infections, skin and soft tissue infections, vertebral osteomyelitis, intra-abdominal infections, and Mycobacterium avium complex disease recommend fluoroquinolones as alternative agents. Geographic resistance patterns are an important consideration for treatment. Recent recommendations from Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) recommend selection of empiric antimicrobial regimens for outpatient treatment of CABP are based on the presence of patient comorbidities. The following recommendations are made for outpatient treatments. Patients with no comorbidities or risk factors for MRSA or *P. aeruginosa* require amoxicillin or doxycycline or macrolide. For patients with comorbidities (ie, chronic heart, lung, liver or renal disease, diabetes mellitus, alcoholism, malignancy or asplenia): (1) Combination therapy with amoxicillin/clavulanate or cephalosporin AND macrolide or doxycycline, OR; (2) Monotherapy with respiratory fluoroquinolone (levofloxacin or moxifloxacin). For initial empiric therapy of severe CABP, the 2019 guidelines suggest stronger evidence for β-lactam/macrolide combination.

Best practice advice from the American College of Physicians on appropriate use of short-course antibiotics for common infections recommends the following. For patients with CABP, antibiotic recommendations for empirical therapy should cover common pathogens, such as *S. pneumoniae, H. influenzae, M. pneumoniae,* MSSA, and atypical pathogens, such as *Legionella* spp. These can include amoxicillin, doxycycline or macrolides for healthy adults or a β-lactams plus macrolide or respiratory fluoroquinolone in patients with comorbidities for a minimum of 5 days. For patients with uncomplicated pyelonephritis, a short course therapy with either fluoroquinolones (5 to 7 days) or trimethoprim-sulfamethoxazole (TMP-SMZ) (14 days) would be appropriate based on antibiotic susceptibility.

In July 2023, IDSA published guidance on the treatment of antimicrobial resistant gram-negative infections, such as AmpC B-lactamase producing Enterobacterales, carbapenem-resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* infections. Oral step-down therapy with TMP-SMZ or fluoroquinolones can be considered for bloodstream infections caused by AmpC B-lactamase producing Enterobacterales. Levofloxacin is considered a treatment option for mild *S. maltophilia* infections and for severe infections, but use of levofloxacin should only be considered in combination with a second active agent such as TMP-SMZ, minocycline, tigecycline, or cefiderocol.

Fluoroquinolones may be considered first-line therapy for bacterial prostatitis, inhalational and cutaneous anthrax, plague, and some types of infectious diarrhea. The 2021 CDC recommendations for the treatment and prophylaxis of plague indicate that FDA-approved antimicrobials for treatment and prophylaxis of plague include streptomycin, ciprofloxacin, levofloxacin, moxifloxacin, and doxycycline. Although gentamicin, chloramphenicol, and TMP-SMZ are not FDA approved for plague, they are effective based on clinical experience and animal data.

Due to the potentially permanent serious adverse events involving the tendons, muscles, joints, nerves, and CNS, the FDA published a safety communication, which recommends reserving the use of fluoroquinolones in acute bacterial sinusitis, acute bacterial bronchitis, and uncomplicated urinary tract infections for patients with no alternative treatment options. The risk for fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart, or lung transplants. Patients with prior CNS disorders are at risk for developing seizures even with the first dose. A safety alert released by the FDA in 2017 stated that after review, it did not find that use of fluoroquinolones resulted in detached retina, aortic aneurysm, or aortic dissection. However, in 2018, the FDA published a safety communication that warned about the increased risk of aortic dissection with fluoroquinolone use. People at risk for this rare, but serious adverse event include those with hypertension or a history of blockages or aneurysms of the aorta or other blood vessels, patients with certain genetic disorders that involve blood vessel changes, and the elderly.

In 2018, the FDA required that package inserts of all fluoroquinolones elaborate on the risks of hypoglycemia (eg, potential to cause coma) and describe psychiatric adverse events such as disturbances in attention, disorientation, agitation, nervousness, memory impairment, and delirium.

Fluoroquinolones may cause QT interval prolongation, anaphylactic reactions, phototoxicity, Clostridioides difficile diarrhea, and blood glucose disturbances (both hypoglycemia and hyperglycemia). In 2 systematic reviews and meta-analyses, the use of fluoroquinolones was found to potentially increase the risk of serious arrhythmias and cardiovascular death. The most common adverse events with fluoroquinolones include gastrointestinal and CNS toxicities. Rash is frequently observed with fluoroquinolones.

Clinical Rationale

Fluoroquinolones are highly effective antibiotics with many advantageous pharmacokinetic properties including high oral bioavailability, large volume of distribution, and broad-spectrum antimicrobial activity

Recommendation

It is recommended that at least two quinolones be available for use~~; one of which should be a third-generation respiratory quinolone~~.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for BAXDELA

Current Criteria:

- Patient age ≥ 18 years of age; **AND**
- Diagnosis of ONE of the following:
  - Acute bacterial skin and skin structure infection (ABSSSI) that is proven or strongly suspected to be caused by bacteria susceptible to delafloxacin
  - Community-Acquired Bacterial Pneumonia (CABP); **AND**
- Patient has no hypersensitivity to delafloxacin, any of its components, or any of the fluoroquinolone class of antibacterial drugs; **AND**
- Patient does not have end stage renal disease (ESRD) (eGFR < 15 mL/min/1.73 m2); **AND**
- Patient has no history of myasthenia gravis; AND

- Delafloxacin is not ordered to treat the same infection for which it or another fluoroquinolone has already been used and treatment was insufficient (e.g., incomplete infection resolution/treatment failure); **AND**
- Patient has a clinically valid reason why preferred agents FDA-approved for CABP or ABSSSI cannot be used (should not be approved if patient has failed another fluoroquinolone) [lab documentation is required for resistance to preferred PDL agents]

NOTE: Individuals started on therapy in the hospital will be approved for this agent following hospital discharge to allow for completion of the course of therapy.

Proposed Criteria:

- Patient age ≥ 18 years of age; **AND**
- ~~Diagnosis of~~ ONE of the following:
  - *Diagnosis of* acute bacterial skin and skin structure infection (ABSSSI) ~~that is proven or strongly suspected to be caused by bacteria susceptible to delafloxacin~~; ***AND***
    - *Trial and failure to, contraindication, or resistance to ONE preferred standard of care agents for ABSSSI (e.g., linezolid, clindamycin, doxycycline, SMX-TMP, vancomycin, cephalosporin, a preferred fluoroquinolone)*
  - Diagnosis of community-acquired bacterial pneumonia (CABP); **AND**
    - *Trial and failure to, contraindication, or resistance to TWO preferred standard of care agents for CABP (e.g., macrolide, doxycycline, a preferred fluoroquinolone, beta-lactam, linezolid)*
  - *Patient is continuing therapy from an inpatient hospital stay (to facilitate completion of therapy)*
- ~~Patient has no hypersensitivity to delafloxacin, any of its components, or any of the fluoroquinolone class of antibacterial drugs; AND~~
- ~~Patient does not have end stage renal disease (ESRD) (eGFR < 15 mL/min/1.73 m2); AND~~
- ~~Patient has no history of myasthenia gravis; AND~~
- ~~Delafloxacin is not ordered to treat the same infection for which it or another fluoroquinolone has already been used and treatment was insufficient (e.g., incomplete infection resolution/treatment failure); AND~~
- ~~Patient has a clinically valid reason why preferred agents FDA-approved for CABP or ABSSSI cannot be used (should not be approved if patient has failed another fluoroquinolone) [lab documentation is required for resistance to preferred PDL agents]~~

~~**NOTE:** Individuals started on therapy in the hospital will be approved for this agent following hospital discharge to allow for completion of the course of therapy.~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for ciprofloxacin suspension, CIPRO SUSPENSION, levofloxacin solution

Current Criteria:

- Patient is unable to swallow solid dosage forms

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• BAXDELA	2/day; Max 14-day supply
• ciprofloxacin ER	1/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Baxdela (delafloxacin) [prescribing information]. Lincolnshire, IL: Melinta Therapeutics LLC; June 2021.
- Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults. Clin Infect Dis. 2015;61(6):e26-e46.
- Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the HIV Medicine Association of the Infectious Diseases Society of America (IDSA). Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV- Exposed and HIV-infected children. Updated September 14, 2023b. https://clinicalinfo.hiv.gov/en/guidelines/pediatric-opportunistic-infection/whats-new. Accessed November 23, 2023.
- Centers for Disease Control and Prevention (CDC). Plague: Resources for Clinicians. Updated February 25, 2022. http://www.cdc.gov/plague/healthcare/clinicians.html. Accessed November 23, 2023.
- Centers for Disease Control and Prevention (CDC). Sexually transmitted infections treatment guidelines, 2021. https://www.cdc.gov/std/treatment-guidelines/toc.htm. Accessed November 23, 2023.
- Cipro tablet and oral suspension (ciprofloxacin) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; November 2021.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2023. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 23, 2023.
- Duane TM, Huston JM, Collom M, et al. Surgical Infection Society 2020 updated guidelines on the management of complicated skin and soft tissue infections. Surg Infect (Larchmt). 2021;22(4):383-399. doi:10.1089/sur.2020.436
- Food and Drug Administration (FDA) Drug Safety Communication. FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients [press release]. December 21, 2018[b]. https://www.fda.gov/Drugs/DrugSafety/ucm628753.htm. Accessed November 23, 2023.
- Food and Drug Administration (FDA) Drug Safety Communication. Fluoroquinolone antibiotics: FDA requires labeling changes due to low blood sugar levels and mental health side effects. July 10, 2018[a]. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm612995.htm. Accessed November 23, 2023.
- Food and Drug Administration (FDA) Drug Safety Communication. Fluoroquinolone antibacterial drugs for systemic use: drug safety communication – warnings updated due to disabling side effects. [press release]. May 10, 2017 Accessed November 23, 2023.
- Hendricks KA, Wright ME, Shadomy SV, et al. Centers for Disease Control and Prevention expert panel meetings on prevention and treatment of anthrax in adults. Emerg Infect Dis [serial on the Internet]. 2014 Feb. https://wwwnc.cdc.gov/eid/article/20/2/13-0687_article.
- Hooper DC. Fluoroquinolones. UpToDate Web site. Updated May 15, 2023. www.uptodate.com. Accessed November 23, 2023.
- Infectious Diseases Society of America. IDSA 2023 guidance on the treatment of antimicrobial-resistant gram-negative infections. July 18, 2023. https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed November 23, 2023.
- Lee RA, Centor RM, Humphrey LL, et al. Appropriate use of short-course antibiotics in common infections: best practice advice from the American College of Physicians. Ann Intern Med. 2021;174(6):822-827.
- Levofloxacin oral solution [prescribing information]. Gurnee, IL: Akorn Operating Company LLC; November 2022.
- Levofloxacin tablets [prescribing information]. Princeton, NJ: Macleods Pharma USA Inc; February 2023.
- Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45-e67.
- Moxifloxacin tablet [prescribing information]. Berlin, CT: Breckenridge Pharmaceutical Inc; January 2021.
- Nelson CA, Meaney-Delman D, Fleck-Derderian S, Cooley KM, Yu PA, Mead PS; Contributors. Antimicrobial treatment and prophylaxis of plague: recommendations for naturally acquired infections and bioterrorism response. MMWR Recomm Rep. 2021;70(3):1-27.
- Ofloxacin tablets [prescribing information]. Canton, MS: Larken Laboratories Inc; August 2020.
- Sartelli M, Coccolini F, Kluger Y, et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. World J Emerg Surg. 2021;16(1)L49: doi: 10.1186/s13017-021-00387-8.
- Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. Clin Infect Dis. 2017;65(12):e45-e80.
- St Cyr S, Barbee L, Workowski KA, et al. Update to CDC's treatment guidelines for gonococcal infection, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(50):1911-1916. doi:10.15585/mmwr.mm6950a6.

ANTIBIOTICS: TETRACYCLINES

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred	
Tetracyclines	doxycycline hyclate 50 & 100mg QL doxycycline monohydrate 50 & 100mg caps QL minocycline caps tetracycline caps	demeclocycline PA DORYX QL (doxycycline) doxycycline hyclate DR tabs QL doxycycline hyclate 20mg tabs PA, QL doxycycline monohydrate 75mg & 150mg caps QL doxycycline monohydrate susp PA doxycycline monohydrate tabs QL doxycycline monohydrate 40mg caps QL MINOCIN (minocycline cap) minocycline ER PA, QL	minocycline tabs MINOLIRA PA, QL (minocycline ER tab) NUZYRA PA, QL (omadacycline) ORACEA QL (doxycycline monohydrate DR cap) SOLODYN PA, QL (minocycline ER tab) TARGADOX QL (doxycycline hyclate tab) VIBRAMYCIN QL (doxycycline monohydrate) XIMINO PA, QL (minocycline, ER cap)

Last Review Date: February 2022

Recent Significant Changes

- Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2023)

Background

The tetracycline class of antibiotics, discovered in the 1940s, has been widely used for its broad-spectrum bacteriostatic activity. The tetracyclines are useful in treating aerobic gram-positive, gram-negative bacteria, and atypical pathogens (eg, *Rickettsia* species [spp], *Borrelia* spp, *Treponema* spp, *Chlamydia* spp). The tetracyclines have a number of indications, some of which include acne, rosacea, sexually transmitted diseases, acute bacterial skin and skin structure infections (ABSSSIs), urinary tract infections, respiratory tract infections, and various other infections (see Table 2 for the labelled indications for the individual agents). The antimicrobial activity is generally similar between the tetracyclines, although some differences in the relative degree of activity against certain pathogens do exist among the various agents.

Tetracyclines function by binding reversibly to the 30S ribosomal subunit at a position that blocks the binding of the aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex. Protein synthesis is ultimately inhibited, leading to a bacteriostatic effect. With regard to resistance, once resistance develops to one of the drugs in this class, it is typically conferred to all tetracyclines. However, there are differences in resistance among species of bacteria. Doxycycline and minocycline are the most frequently prescribed drugs in this class. Newer generation oral tetracyclines approved by the Food and Drug Administration (FDA) include Nuzyra (omadacycline). Omadacycline was approved for community-acquired bacterial pneumonia (CABP) and ABSSSIs (including cellulitis, wound infection, and major cutaneous abscess).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
demeclocycline HCl tablets	✔
doxycycline hyclate tablets	✔
DORYX (doxycycline hyclate) delayed-release tablets	✔
DORYX MPC (doxycycline hyclate) delayed-release tablets	-
minocycline HCl extended-release tablets	✔
minocycline HCl capsules, tablets	✔
MINOLIRA (minocycline HCl) extended-release tablets	-
NUZYRA (omadacycline) tablets, injection	-

Drug	Generic Availability
ORACEA (doxycycline monohydrate) delayed-release capsules	✔
SOLODYN (minocycline HCl) extended-release tablets	✔
TARGADOX (doxycycline hyclate) tablets	✔
tetracycline HCl capsule	✔
VIBRAMYCIN (doxycycline monohydrate) suspension	✔
VIBRAMYCIN (doxycycline hyclate) capsules	✔
XIMINO (minocycline HCl) extended-release capsules	✔

Table 2. Food and Drug Administration Approved Indications

Indication	Demeclocycline	Doxycycline	Minocycline	Omadacycline	Tetracycline
Gonococcal infections, uncomplicated	✔	✔	✔		
Listeriosis	✔		✔		
Syphilis	✔	✔	✔		✔
Vincent's infection	✔	✔	✔		✔
Yaws	✔	✔	✔		✔
Treatment of asymptomatic meningococcal carriers			✔		
Acne	✔	✔	✔		✔
Rosacea		✔			
Skin and soft tissue infections	✔		✔	✔	✔
Acute intestinal amebiasis	✔	✔	✔		✔
Cholera	✔	✔	✔		✔
Chancroid	✔	✔	✔		✔
Urinary tract infections	✔	✔	✔		✔
Conjunctivitis (inclusion)	✔	✔	✔		✔
Trachoma	✔	✔	✔		✔
Anthrax	✔	✔	✔		✔
Psittacosis	✔	✔	✔		✔
Respiratory tract infection	✔	✔	✔		✔
CABP				✔	
Disease caused by rickettsiae	✔	✔	✔		✔
Q fever	✔	✔	✔		✔
Rickettsialpox	✔	✔	✔		✔
Rocky Mountain spotted fever	✔	✔	✔		✔
Typhus	✔	✔	✔		✔
Endocervical infections		✔	✔		✔
Granuloma inguinale	✔	✔	✔		✔
Lymphogranuloma venereum	✔	✔	✔		✔
Nongonococcal urethritis	✔	✔	✔		
Rectal infections		✔	✔		✔
Urethritis, uncomplicated	✔	✔	✔		✔
Malaria prophylaxis		✔			
Periodontitis		✔			
Plague	✔	✔	✔		✔
Relapsing fever	✔	✔	✔		✔
Tularemia	✔	✔	✔		✔

There are some limitations of use to these agents. Oracea has not been evaluated in the treatment or prevention of infections. It should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease. Oracea has not been evaluated for the treatment of the erythematous, telangiectatic, or ocular components of rosacea. Ximino did not demonstrate any effect on non-inflammatory acne lesions. Safety of Ximino has not been established beyond 12 weeks of use. This formulation of minocycline has not been evaluated in the treatment of infections.

Community-Acquired Bacterial Pneumonia (CABP)

CABP is an acute infection of the pulmonary parenchyma in patients who have acquired the infection in the community. CABP is a common and potentially serious illness. It is associated with considerable morbidity and mortality, particularly in older adults and those with major comorbidities. *Streptococcus pneumoniae* is the most commonly identified bacterial cause of CABP worldwide. Other common pathogens include *Haemophilus influenzae*; atypical bacteria *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* spp.; and oropharyngeal aerobes and anaerobes (in the setting of aspiration). Viruses are also common causes of CABP.

Treatment recommendations from the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) recommend selection of empiric antimicrobial regimens for outpatient treatment of CABP are based on the presence of patient comorbidities. Routine blood cultures are no longer recommended at the time of diagnosis for outpatient or inpatient CABP. However, 2 specific situations in which sputum gram stain and culture are recommended include in hospitalized patients with severe CABP or when strong risk factors for MRSA and *Pseudomonas (P) aeruginosa* are identified. In patients with no comorbidities or risk factors for MRSA or *P. aeruginosa*, amoxicillin or doxycycline or macrolide are recommended. In patients with comorbidities, recommendations include: 1) Combination therapy with amoxicillin/clavulanate or cephalosporin AND macrolide or doxycycline, OR 2) Monotherapy with respiratory fluoroquinolone (levofloxacin and moxifloxacin).

The 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommends the use of empirical treatment with aminopenicillin with clavulanic acid, a macrolide, or a tetracycline for acute respiratory infections with a high probability of bacterial cause (presence of increased sputum purulence in addition to increased dyspnea and/or increased sputum volume), in patients with chronic obstructive lung disease (COPD).

Acute bacterial skin and skin structure infection (ABSSSI)

The IDSA practice guidelines for the diagnosis and management of skin and soft tissue infections recommend for mild purulent skin and soft tissue infections (SSTIs) infection (inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles), incision and drainage treatment. In moderate infections (ie, purulent infection with systemic signs of infection), the decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of SIRS. Empiric treatment options include sulfamethoxazole/trimethoprim (SMX/TMP) and doxycycline.

The IDSA guidelines for the treatment of MRSA infections recommends for outpatients with purulent cellulitis, empiric therapy for community acquired MRSA (CA-MRSA) is recommended pending culture results. Empiric therapy for infection due to b-hemolytic streptococci is likely to be unnecessary. For outpatients with nonpurulent cellulitis, empiric therapy for infection due to b-hemolytic streptococci is recommended. Empiric coverage for CA-MRSA is recommended in patients who do not respond to b-lactam therapy and may be considered in those with systemic toxicity. For empiric coverage of CA-MRSA in outpatients with SSTI, oral antibiotic options include clindamycin, SMX/TMP, a tetracycline, and linezolid.

Acne

The American Academy of Dermatology published guidelines for the management of acne vulgaris in 2015. Systemic antibiotics are recommended in the management of moderate and severe acne, and forms of inflammatory acne that are resistant to topical treatments. Doxycycline and minocycline are considered more effective than tetracycline, but neither agent is considered superior over the other. Oral erythromycin and azithromycin can be effective; however, their use should be limited to patients who cannot use tetracyclines (eg, pregnant women or children < 8 years of age). Of note, erythromycin should be used carefully, due to the

increased risk of bacterial resistance. Systemic antibiotic use should be limited to the shortest possible duration, usually 3 months, in order to minimize the risk of bacterial resistance. Monotherapy with systemic antibiotics is not recommended. Concomitant topical therapy (eg, benzoyl peroxide and/or retinoid) should be used with systemic antibiotics, as well as maintenance after completion of systemic antibiotic therapy.

Sexually Transmitted diseases (STDs)
The Centers for Disease Control (CDC) published treatment guidelines for the management of STDs in 2021. The recommendations are listed below. For granuloma inguinale infections, although azithromycin is recommended, doxycycline, erythromycin, or SMX/TMP may be used as an alternative. For lymphogranuloma venereum infections, doxycycline for 21 days is recommended. In syphilis infections, penicillin G is the preferred treatment but alternative agents in patients who are allergic to penicillin may include doxycycline, tetracycline, or ceftriaxone (for neurosyphilis). For both urethritis and cervicitis, doxycycline is the recommended treatment with azithromycin as an alternative regimen. For patients with chlamydia, doxycycline is recommended with azithromycin recommended in pregnant patients. Epididymitis is treated with ceftriaxone plus doxycycline. Proctitis is treated with ceftriaxone plus doxycycline.

For pelvic inflammatory disease the recommended therapies include 1) ceftriaxone plus metronidazole plus doxycycline; 2) cefotetan plus doxycycline; 3) cefoxitin plus doxycycline. Alternative parenteral regimens are ampicillin/sulbactam plus doxycycline (oral or IV) or clindamycin plus gentamicin. Outpatient oral therapy may be considered in patients with mild to moderate disease. Recommended regimens include ceftriaxone plus doxycycline with metronidazole, cefoxitin and probenecid plus doxycycline with metronidazole, or another parenteral third generation cephalosporin plus doxycycline with metronidazole.

Safety Information
The tetracyclines are contraindicated in patients hypersensitive to tetracyclines. Some warnings and precautions include tooth discoloration, enamel hypoplasia, inhibition of bone growth during the second and third trimester of pregnancy, infancy, and childhood up to the age of 8 years, *C. difficile*-associated diarrhea, and photosensitivity. Tetracyclines are generally considered safe; the most common adverse effects associated with this class are gastrointestinal in nature. Key drug interactions with the tetracycline class include antacids and iron preparations, methoxyflurane, anticoagulants, retinoids, and urinary alkalinizers and zinc salts.

Clinical Rationale

The tetracyclines are broad-spectrum bacteriostatic antibiotics with activity against many aerobic gram-positive and gram-negative bacteria and atypical pathogens. Within the class, no major clinically significant differences exist among the various agents; however, doxycycline and minocycline appear to be the most highly utilized. Newer generation oral tetracycline omadacycline should be reserved for its FDA approved indications.

Recommendation

It is recommended that at doxycycline and at least 1 other tetracyclines are available for use. Demeclocycline should be available for patients with SIADH.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for doxycycline monohydrate suspension

Current Criteria:

- Patient is ≤ 12 years and has a diagnosis of a tick-borne disease; **OR**
- Patient is unable to swallow solid dosage forms

Proposed Criteria:

- ~~Patient is ≤ 12 years and has a diagnosis of a tick-borne disease; **OR**~~
- Patient is unable to swallow solid dosage forms

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for NUZYRA

Current Criteria:

Criteria: (approval duration: 14 days)

- Patient is ≥ 18 years of age; **AND**
- Diagnosis of one of the following:
  - Community-acquired bacterial pneumonia (CABP) caused or suspected by one of the following susceptible organisms: *Streptococcus pneumoniae, Staphylococcus aureus [methicillin-susceptible isolates; MSSA], Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, or Chlamydophila pneumoniae*
  - Acute bacterial skin and skin structure infections (ABSSSI) caused or suspected by one of the following susceptible organisms: *S. aureus [methicillin-susceptible and -resistant isolates], Staphylococcus lugdunensis, Streptococcus pyogenes, Streptococcus anginosus group [includes S. anginosus, S. intermedius, and S. constellatus], Enterococcus faecalis, Enterobacter cloacae, and K. pneumoniae;* **AND**
- If patient is female and of childbearing potential, it has been confirmed the patient is NOT pregnant; **AND**
- Patient meets one of the following conditions:
  - If C & S report is available, patient has tried and failed, or has a contraindication or intolerance, of TWO preferred antibiotic agents susceptible to the isolated pathogen
  - If provider is unable to provide a C & S report, patient has tried and failed, or has a contraindication or intolerance, of TWO preferred antibiotics indicated for the member's diagnosis; **AND**
- Patient dosing follows FDA-approved dosing instructions

NOTE: Individuals started on therapy in the hospital will be approved for this agent following hospital discharge to allow for completion of the course of therapy.

Proposed Criteria:

Criteria: (approval duration: 14 days)

- Patient is ≥ 18 years of age; **AND**
- ~~Diagnosis of~~ one of the following:
  - *Diagnosis of* Community-acquired bacterial pneumonia (CABP) ~~caused or suspected by one of the following susceptible organisms: Streptococcus pneumoniae, Staphylococcus aureus [methicillin-susceptible isolates; MSSA], Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, or Chlamydophila pneumoniae~~; AND
    - *Trial and failure to, contraindication, or resistance to TWO preferred standard of care agents for CABP (e.g., macrolide, doxycycline, a preferred fluoroquinolone, beta-lactam, linezolid)*
  - *Diagnosis of* Acute bacterial skin and skin structure infections (ABSSSI) ~~caused or suspected by one of the following susceptible organisms: S. aureus [methicillin-susceptible and -resistant isolates], Staphylococcus lugdunensis, Streptococcus pyogenes, Streptococcus anginosus group [includes S. anginosus, S. intermedius, and S. constellatus], Enterococcus faecalis, Enterobacter cloacae, and K. pneumoniae~~; **AND**
    - *Trial and failure to, contraindication, or resistance to ONE preferred standard of care agents for ABSSSI (e.g., linezolid, clindamycin, doxycycline, SMX-TMP, vancomycin, cephalosporin, a preferred fluoroquinolone)*
  - *Patient is continuing therapy from an inpatient hospital stay (to facilitate completion of therapy)*

- ~~If patient is female and of childbearing potential, it has been confirmed the patient is NOT pregnant; **AND**~~
- ~~Patient meets one of the following conditions:~~
  - ~~If C & S report is available, patient has tried and failed, or has a contraindication or intolerance, of TWO preferred antibiotic agents susceptible to the isolated pathogen~~
  - ~~If provider is unable to provide a C & S report, patient has tried and failed, or has a contraindication or intolerance, of TWO preferred antibiotics indicated for the member's diagnosis; **AND**~~
- ~~Patient dosing follows FDA-approved dosing instructions~~

~~**NOTE:** Individuals started on therapy in the hospital will be approved for this agent following hospital discharge to allow for completion of the course of therapy.~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for demeclocycline

Current Criteria:

- Trial and failure of 2 preferred agents; **OR**
- Treatment is for syndrome of inappropriate antidiuretic hormone secretion (SAIDH)

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for doxycycline hyclate 20mg

Current Criteria:

- Agent is used as an adjunct to scaling and root planting to promote attachment level gain and to reduce pocket depth for adult periodontitis

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for minocycline ER, Minolira ER, Solodyn, Ximino

Current Criteria:

- Patient is ≤ 21 years old; **AND**
- Diagnosis of non-nodular moderate to severe acne vulgaris with inflammatory lesions; **AND**
- Patient requires long-term therapy with an oral tetracycline; **AND**
- Trial and failure, contraindication, or intolerance of TWO of the following topical agents:
  - Metronidazole (Metrogel®)
  - Azelaic acid (Azelex®, Finacea®)
  - Erythromycin (A/T/S® solution, gel)
  - Clindamycin (Cleocin T®)
  - Topical keratolytic agents (such as benzoyl peroxide, salicylic acid preparations); **AND**
- Clinically valid reason why the preferred minocycline capsules cannot be used

Proposed Criteria:
Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for ORACEA

Current Criteria:
- Diagnosis of inflammatory lesions (papules and pustules) of rosacea; **AND**
- Patient is < 21 years of age; **AND**
- Patient requires long-term therapy (greater than 3 months) with an oral antibiotic; **AND**
- Trial and failure, contraindication, or intolerance to ONE of the following topical agents:
  - Metronidazole (e.g., MetroGel®, MetroCream®)
  - Azelaic Acid (e.g., Azelex®, Finacea®)
  - Erythromycin gel or solution

Proposed Criteria:
Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• DORYX, VIBRAMYCIN (doxycycline) 50mg	3/day
• DORYX, VIBRAMYCIN (doxycycline)- all other strengths	2/day
• MINOLIRA ER, SOLODYN, XIMINO (minocycline ER)	1/day
• NUZYRA	3/day; Max 14-day supply
• ORACEA	2/DAY
• TARGADOX	3/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. CDC Web site. https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf . Updated 2021. Accessed September 17, 2023.
- Doryx (doxycycline hyclate) [prescribing information]. Greenville, NC: Mayne Pharma; July 2022.
- Doxycycline capsules [prescribing information]. Congers, NY: Chartwell RX LLC; February 2022.
- Doxycycline hyclate capsules, suspension, tablets, USP [prescribing information]. Congers, NY: Chartwell Rx LLC; February 2022.
- Doxycycline hyclate delayed-release tablets [prescribing information]. Greenville, NC: Mayne Pharma; February 2020.
- Doxycycline hyclate tablets, USP [prescribing information]. Congers, NY: Chartwell RX LLC; February 2023.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed September 17, 2023.
- File T. Epidemiology, pathogenesis, and microbiology of community-acquired pneumonia in adults. UpToDate Web site. www.uptodate.com. Updated March 3, 2023. Accessed September 17, 2023.
- File T. Treatment of community-acquired pneumonia in adults in the outpatient setting. UpToDate Web site. www.uptodate.com. Updated April 15, 2022. Accessed September 17, 2023.
- Food and Drug Administration. Multi-discipline review: Nuzyra. 2019. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209816Orig1s000,209817Orig1s000TOC.cfm. Accessed September 17, 2023.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2023. https://goldcopd.org/2023-gold-report-2/. Accessed October 21, 2023.
- Liu C, Bayer A, Cosgrove SE, et al; for the Infectious Diseases Society of America (IDSA). Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011;52(3):e18-55.
- May DB. Tetracyclines. UpToDate Web site. www.uptodate.com. Updated June 20, 2022. Accessed September 17, 2023.
- Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. Am J Respir Crit Care Med. 2019:200(7);e45-e67

- Minocin (minocycline) oral suspension [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; November 2018.
- Minocin (minocycline) pellet-filled capsules [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; January 2019.
- Minocycline capsules [prescribing information]. Basking Ridge, NJ: Torrent Pharma Inc; January 2019.
- Minocycline extended-release tablets [prescribing information]. Baltimore, MD: Lupin Pharmaceuticals, Inc; December 2018.
- Minocycline film-coated tablets [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc; May 2018.
- Minocycline hydrochloride [prescribing information]. Basking Ridge, NJ: Torrent Pharma; July 2015.
- Minocycline hydrochloride capsules [prescribing information]. Basking Ridge, NJ: Torrent Pharma Inc; January 2018.
- Minocycline hydrochloride tablets [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries Inc; May 2018.
- Minocycline oral suspension [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; November 2018.
- Minolira (minocycline) extended-released tablets [prescribing information]. Charleston, SC: EPI Health, LLC; June 2018.
- Nelson ML, Levy SB. The history of tetracyclines. Ann N Y Acad Sci. 2011;1241:17-32.
- Nuzyra (omadacycline) injection and tablets [prescribing information]. Boston, MA: Paratek Pharmaceuticals Inc; May 2021.
- Oracea (doxycycline) [prescribing information]. Fort Worth, TX: Galderma Laboratories LP; December 2021.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed September 17, 2023.
- Solodyn (minocycline) [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals; September 2017.
- Stevens DL, Bisno AL, Chambers HF, et al; for the Infectious Diseases Society of America (IDSA). Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(2):147-159.
- Targadox (doxycycline) [prescribing information]. Scottsdale, AZ: Journey Medical Corporation; January 2019.
- Vibramycin (doxycycline oral) [prescribing information]. New York; NY: Pfizer; received August 2017.
- Vibramycin Hyclate Capsules (doxycycline hyclate) [prescribing information]. New York; NY: Pfizer Labs; December 2019.
- Vibramycin Monohydrate for Oral Suspension (doxycycline monohydrate) [prescribing information]. New York; NY: Pfizer Labs; December 2019.
- Ximino (minocycline) [prescribing information]. New Brunswick, NJ: Ohm Laboratories Inc; November 2019.
- Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74:945-973.

ANTIFUNGALS, ORAL

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred	
Oral Antifungals	clotrimazole troches fluconazole tabs and susp PA griseofulvin microsize griseofulvin susp griseofulvin ultramicrosize nystatin SPORANOX caps ~~PA,~~ QL (itraconazole) SPORANOX soln PA, QL (itraconazole) terbinafine tabs ~~PA,~~ QL	ANCOBON PA (flucytosine) BREXAFEMME PA, QL (ibrexafungerp) CRESEMBA PA (isavuconazonium sulfate) DIFLUCAN susp PA (fluconazole) DIFLUCAN tabs QL (fluconazole) flucytosine PA itraconazole caps PA, QL itraconazole soln PA, QL ketoconazole PA	NOXAFIL PA (posaconazole) ORAVIG PA, QL (miconazole) posaconazole PA TOLSURA PA, QL (itraconazole) Vfend PA (voriconazole) Vivjoa QL, PA (oteseconazole) voriconazole PA

Last Review Date: February 2022

Recent Significant Changes

- Centers for Disease Control and Prevention (CDC). Sexually transmitted infections treatment guidelines, 2021: vulvovaginal candidiasis (VVC). Last reviewed July 22

Background

The oral antifungals class includes agents for the treatment of many different fungal infections, including aspergillosis, blastomycosis, histoplasmosis, candidiasis, onychomycosis, and ringworm infections. The agents are often used in persons living with human immunodeficiency virus (HIV) and neutropenia due to hematopoietic stem cell transplants, or after aggressive chemotherapy and radiation.

Clotrimazole, nystatin suspension, and Oravig (miconazole) are not absorbed systemically and are only used for oropharyngeal candidiasis treatment. Cresemba (isavuconazonium sulfate), Diflucan (fluconazole), Vfend (voriconazole), and Noxafil (posaconazole) are available as oral and intravenous (IV) formulations. Ketoconazole, terbinafine, and nystatin are available as oral and topical preparations. Brexafemme (ibrexafungerp), Vivjoa (oteseconazole), Sporanox and Tolsura (itraconazole) are only available as oral formulations. Clotrimazole and miconazole are available as oral, topical, and vaginal formulations. Only the oral formulations will be discussed in this review.

The use of ketoconazole for the treatment of skin and nail fungal infections should be limited due to the risk of severe liver injuries and adrenal gland problems and advised that it can lead to harmful drug interactions with other medications. Ketoconazole should be used for the treatment of certain fungal infections, known as endemic mycoses, only when alternative antifungal therapies are not available or tolerated.

In 2019, the CDC released a report on antibiotic resistance threats in the United States. Among the various organisms within the report were 3 fungi – *Candida auris* (urgent threat), drug-resistant *Candida* spp (serious threat), and azole-resistant *Aspergillus fumigatus* (watch list). The inclusion of these fungi underscores the importance of appropriate use of antibiotics including antifungal agents.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
ANCOBON (flucytosine) capsule	✔
BREXAFEMME (ibrexafungerp) tablet	-
clotrimazole troche	✔
CRESEMBA (isavuconazonium sulfate) capsule	-
DIFLUCAN (fluconazole) oral suspension, tablet	✔

Drug	Generic Availability
griseofulvin microsize oral suspension, tablet	✔
griseofulvin ultramicrosize tablet	✔
ketoconazole tablet	✔
NOXAFIL (posaconazole) delayed-release tablet, oral suspension	✔
NOXAFIL (posaconazole) oral packet	-
nystatin oral suspension, tablet	✔
ORAVIG (miconazole) tablet	-
SPORANOX (itraconazole) capsule, oral solution	✔
terbinafine tablet	✔
TOLSURA (itraconazole) capsule	-
VFEND (voriconazole) oral suspension	✔
VIVJOA (oteseconazole) capsule	-

Table 2. Food and Drug Administration Approved Indications

Indication	BREXAFEMME	clotrimazole	fluconazole	flucytosine	griseofulvin	CRESEMBA	itraconazole	ketoconazole	posaconazole	nystatin	ORAVIG	VIVJOA	voriconazole
Oropharyngeal candidiasis		✔							✔	✔	✔		
Oropharyngeal and esophageal candidiasis			✔				✔						
Esophageal candidiasis													✔
Non-esophageal mucous membrane gastrointestinal candidiasis										✔			
Prophylactically to reduce the incidence of oropharyngeal candidiasis in patients immunocompromised by conditions that include chemotherapy, radiotherapy, solid tumors, or renal transplantation		✔											
Serious infections caused by susceptible strains of Candida and/or Cryptococcus				✔									
Vaginal candidiasis			✔										
Reduce the incidence of recurrent vulvovaginal candidiasis in women with a history of recurrent infection who are not of reproductive potential												✔	
Treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis	✔												
Reduction in the incidence of recurrent vulvovaginal candidiasis in adult and post-menarchal pediatric females	✔												
Cryptococcal meningitis			✔										
Prophylactically to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy			✔										
Treatment of the following ringworm infections: tinea corporis (ringworm of the body), tinea pedis (athlete's foot), tinea cruris (ringworm of the groin and thigh), tinea barbae (barber's itch), tinea capitis (ringworm of the scalp), and tinea unguium (onychomycosis, ringworm of the nails), caused by ≥ 1 of fungi.					✔								

Indication	BREXAFEMME	clotrimazole	fluconazole	flucytosine	griseofulvin	CRESEMBA	itraconazole	ketoconazole	posaconazole	nystatin	ORAVIG	VIVJOA	voriconazole
Onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)							✓						
Treatment of the following systemic infections in patients who have failed or are intolerant to other therapies: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis								✓					
Prophylaxis of invasive Aspergillus and Candida infections in patients who are at high risk due to being severely immunocompromised									✓				
Blastomycosis, pulmonary and extrapulmonary							✓						
Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, nonmeningeal histoplasmosis							✓						
Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy							✓						
Invasive aspergillosis						✓			✓				✓
Invasive mucormycosis						✓							
Candidemia in non-neutropenic patients and in the following infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds													✓
Serious fungal infections caused by Scedosporium apiospermum (asexual form of Pseudallescheria boydii) and Fusarium spp including Fusarium solani, in patient's intolerant of, or refractory to, other therapy													✓

Multiple treatment guidelines address the role of the systemic antifungals. Due to changing resistance patterns, guidelines should be frequently referenced. There are various clinical considerations required to select an agent for the treatment of a fungal infection, including the severity and type of fungal infection, activity against yeast, mold, and dimorphic fungi; susceptibility/resistance; bioavailability and tissue penetration of the drug, individual patient characteristics, drug interactions, and tolerance. Treatment of a fungal infection may require initial treatment with IV therapy with a transition to oral therapy, while differences in the bioavailability between oral formulations (ie, tablet vs liquid formulations) have been noted in the literature. The choice of the formulation is dependent upon the clinical situation, and oral formulations are generally not interchangeable. Antifungal therapies are often used for prophylaxis and treatment of fungal infections in patients with HIV and those with cancer at intermediate to high risk of infection. Agents are recommended at various levels from first line to alternative therapies.

For vulvovaginal candidiasis, intravaginal azole therapy (including over the counter clotrimazole, miconazole, and tioconazole and prescription butoconazole and terconazole) or oral fluconazole are recommended for the treatment of uncomplicated vulvovaginal candidiasis. No evidence exists to show the superiority of any one topical regimen, and oral and topical azole antifungal formulations have been shown to achieve entirely equivalent results (responses range from 80% to 90%). Nonpregnant patients with complicated vulvovaginal candidiasis require more aggressive treatment to achieve relief of symptoms. Oral fluconazole has been shown to be an effective treatment for complicated infections due to *C. albicans*. Treatment for vulvovaginal candidiasis due to non-*albicans* Candida may include intravaginal boric acid or nystatin intravaginal suppositories. Only topical azole therapies are recommended for use among pregnant women. Current guidelines were published before the FDA approval of ibrexafungerp and oteseconazole.

Table 3: Contraindications

Drug	Contraindications
ANCOBON (flucytosine)	Known complete dihydropyrimidine dehydrogenase (DPD) enzyme deficiency
BREXAFEMME (ibrexafungerp)	Pregnancy
CRESEMBA (isavuconazonium sulfate)	Familial short QT syndrome
griseofulvin	Porphyria, hepatocellular failure, women who are/may become pregnant
itraconazole	Treatment of onychomycosis in patients with evidence of ventricular dysfunction, or in women who intend to become pregnant
ketoconazole	Acute or chronic liver disease
NOXAFIL (posaconazole) suspension	Known or suspected hereditary fructose intolerance
ORAVIG (miconazole)	Hypersensitivity to milk protein concentrate
terbinafine	Chronic or acute hepatic disease
VIVJOA (oteseconazole)	Pregnancy, females of reproductive potential, lactation

Table 4. Boxed Warnings

Drug	Boxed Warnings
flucytosine	Use with extreme caution in patients with impaired renal function; close monitoring of hematologic, renal, and hepatic status of all patients is essential
ketoconazole	Should only be used to treat serious systemic fungal infections when other effective antifungal therapy is not available or tolerated, and the potential benefits are considered to outweigh the potential risks; serious hepatotoxicity including death or need for liver transplantation have occurred; coadministration of the following drugs is contraindicated: dofetilide, quinidine, pimozide, cisapride, methadone, disopyramide, dronedarone, and ranolazine due to potential QT prolongation ventricular dysrhythmias
itraconazole	Should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction; Coadministration of methadone, disopyramide, dofetilide, dronedarone, quinidine, isavuconazonium sulfate, ergot alkaloids, irinotecan, lurasidone, oral midazolam, pimozide, triazolam, felodipine, nisoldipine, ivabradine, ranolazine, eplerenone, cisapride, naloxegol, lomitapide, lovastatin, simvastatin, avanafil, ticagrelor and, in subjects with renal or hepatic impairment, colchicine, fesoterodine, eliglustat, and solifenacin is contraindicated

Clinical Rationale

The oral class of antifungals includes a variety of different agents used to treat many different fungal infections, including aspergillosis, blastomycosis, histoplasmosis, candidiasis, mucormycosis, onychomycosis, ringworm infections, and others. There are various clinical considerations required to select an agent for the treatment of a fungal infection, including the severity and type of fungal infection, activity against yeast, mold, and dimorphic fungi; susceptibility/resistance; bioavailability and tissue penetration of the drug, individual patient characteristics, drug interactions, and tolerance.

Recommendation

Due to the relative safety and efficacy of fluconazole and griseofulvin in the treatment of fungal infections, it is recommended these agents should be available. ~~Ketoconazole, itraconazole, posaconazole and voriconazole are all effective for their respective FDA-approved indications; however, these agents are associated with significant adverse events and/or have very specific FDA-approved indications; therefore, these agents should be subject to clinical criteria~~. ~~Due to the emergence of resistance, flucytosine is only indicated to be given in combination with amphotericin B; therefore, this agent should be subject to clinical criteria.~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for terbinafine tablets

Current Criteria:

- ONE of the following:
  - Diagnosis of tinea capitis and patient is ≥ 4 years of age;
  - Diagnosis of onychomycosis (tinea unguium) and patient is ≥ 2 years of age; **AND**
    - Patient has positive diagnostic microbiological or histological test confirming onychomycosis (e.g., KOH preparation, fungal culture, or nail biopsy); **AND**
- Patient does not have active or chronic liver disease

Proposed Criteria:

Remove PA

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for BREXAFEMME

Current Criteria:

- Diagnosis of vulvovaginal candidiasis; **AND**
- One of the following:
  - Patient is ≥ 18 years of age
  - Patient is a post-menarchal female; **AND**
- Patient is not pregnant; **AND**
- Trial and failure, contraindication, or intolerance of 1 preferred oral agent (fluconazole tablets) and 1 preferred topical agent (miconazole-3 kit or terconazole)

Proposed Criteria:

- Diagnosis of vulvovaginal candidiasis; **AND**
- One of the following:
  - Patient is ≥ 18 years of age
  - Patient is a post-menarchal female; **AND**
- Patient is not pregnant; **AND**
- Trial and failure, contraindication, or intolerance of 1 preferred oral agent (fluconazole tablets) ~~and~~ *OR* 1 preferred topical agent (miconazole-3 kit or terconazole)

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for SPORANOX capsules

Current Criteria:

- Itraconazole is unrestricted for Blastomycosis, Histoplasmosis, Aspergillosis (in patients intolerant or refractory to amphotericin B therapy), Cryptococcosis, Coccidiomycosis, febrile neutropenia, oropharyngeal/esophageal candidiasis, Candida krusei infections, and any other systemic fungal infection.
- Also, unrestricted for prevention of histoplasmosis or any other invasive fungal infection (including cryptococcosis, coccidiomycosis) in HIV or immunocompromised patients.
- For diagnosis of onychomycosis, ALL the following:
  - Patient has positive diagnostic microbiological or histological test confirming onychomycosis (e.g., KOH preparation, fungal culture, or nail biopsy); **AND**
  - Trial and failure, contraindication, or intolerance to terbinafine

Proposed Criteria:

Remove PA

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for itraconazole capsules

Current Criteria:

- Itraconazole is unrestricted for Blastomycosis, Histoplasmosis, Aspergillosis (in patients intolerant or refractory to amphotericin B therapy), Cryptococcosis, Coccidiomycosis, febrile neutropenia, oropharyngeal/esophageal candidiasis, Candida krusei infections, and any other systemic fungal infection.
- Also, unrestricted for prevention of histoplasmosis or any other invasive fungal infection (including cryptococcosis, coccidiomycosis) in HIV or immunocompromised patients.
- For diagnosis of onychomycosis, ALL the following:
  - Patient has positive diagnostic microbiological or histological test confirming onychomycosis (e.g., KOH preparation, fungal culture, or nail biopsy); **AND**
  - Trial and failure, contraindication, or intolerance to terbinafine

Proposed Criteria:

- ~~Itraconazole is unrestricted for Blastomycosis, Histoplasmosis, Aspergillosis (in patients intolerant or refractory to amphotericin B therapy), Cryptococcosis, Coccidiomycosis, febrile neutropenia, oropharyngeal/esophageal candidiasis, Candida krusei infections, and any other systemic fungal infection.~~
- ~~Also, unrestricted for prevention of histoplasmosis or any other invasive fungal infection (including cryptococcosis, coccidiomycosis) in HIV or immunocompromised patients.~~
- ~~For diagnosis of onychomycosis, ALL the following:~~
  - ~~Patient has positive diagnostic microbiological or histological test confirming onychomycosis (e.g., KOH preparation, fungal culture, or nail biopsy);~~ ~~**AND**~~
  - ~~Trial and failure, contraindication, or intolerance to terbinafine~~
- *Trial and failure of preferred Sporanox capsules*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for SPORANOX solution, itraconazole solution

Current Criteria:

- Itraconazole is unrestricted for Blastomycosis, Histoplasmosis, Aspergillosis (in patients intolerant or refractory to amphotericin B therapy), Cryptococcosis, Coccidiomycosis, febrile neutropenia, oropharyngeal/esophageal candidiasis, Candida krusei infections, and any other systemic fungal infection.
- Also, unrestricted for prevention of histoplasmosis or any other invasive fungal infection (including cryptococcosis, coccidiomycosis) in HIV or immunocompromised patients.
- For diagnosis of onychomycosis, ALL the following:
  - Patient has positive diagnostic microbiological or histological test confirming onychomycosis (e.g., KOH preparation, fungal culture, or nail biopsy); **AND**
  - Trial and failure, contraindication, or intolerance to terbinafine

Proposed Criteria:

- ~~Itraconazole is unrestricted for Blastomycosis, Histoplasmosis, Aspergillosis (in patients intolerant or refractory to amphotericin B therapy), Cryptococcosis, Coccidiomycosis, febrile neutropenia, oropharyngeal/esophageal candidiasis, Candida krusei infections, and any other systemic fungal infection.~~

- ~~Also, unrestricted for prevention of histoplasmosis or any other invasive fungal infection (including cryptococcosis, coccidiomycosis) in HIV or immunocompromised patients.~~
- ~~For diagnosis of onychomycosis, ALL the following:~~
  - ~~Patient has positive diagnostic microbiological or histological test confirming onychomycosis (e.g., KOH preparation, fungal culture, or nail biopsy);~~ ~~**AND**~~
  - ~~Trial and failure, contraindication, or intolerance to terbinafine~~
- *Patient is unable to swallow solid dosage forms*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for ketoconazole

Current Criteria:

- Treatment of blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis or paracoccidioidomycosis, **AND**
- Trial and failure, contraindication, intolerance, refractory or resistant to ALL other antifungals

Note: If started as an inpatient hospital regimen and this is a continuation of therapy, then the drug is approvable

Proposed Criteria:

- ~~Treatment of blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis or paracoccidioidomycosis,~~ ~~**AND**~~
- ~~Trial and failure, contraindication, intolerance, refractory or resistant to ALL other antifungals~~

~~**Note:** If started as an inpatient hospital regimen and this is a continuation of therapy, then the drug is approvable~~

- *Trial and failure, contraindication, or intolerance to TWO preferred agents;* ***OR***
- *Patient is continuing therapy from an inpatient hospital stay (to facilitate completion of therapy)*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for TOLSURA

Current Criteria:

- Diagnosis of ONE of the following:
  - Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy
  - Blastomycosis, pulmonary and extrapulmonary
  - Histoplasmosis, including chronic cavitary pulmonary disease, disseminated, or nonmeningeal; **AND**
- Clinically valid reason why the patient cannot use the other itraconazole products

Note: Will not be approved for treatment of onychomycosis.

Proposed Criteria:

- Diagnosis of ONE of the following:
  - Aspergillosis (pulmonary and extrapulmonary),~~ in patients who are intolerant of or who are refractory to amphotericin B therapy~~; **AND**
  - Blastomycosis, pulmonary and extrapulmonary
  - Histoplasmosis, including chronic cavitary pulmonary disease, disseminated, or nonmeningeal; **AND**
- Clinically valid reason why the patient cannot use ~~the other~~ itraconazole ~~products~~ *capsules or solution*

~~**Note:** Will not be approved for treatment of onychomycosis~~.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for VFEND, voriconazole

Current Criteria:

- Treatment is for ONE of the following:
  - Invasive aspergillosis
  - Serious fungal infections caused by S. apiospermum and Fusarium species including F. solani
  - Part of standard anti-fungal regimen in febrile neutropenic patients
  - Other fungal infections that are refractory or resistant to other oral triazole agents (i.e., fluconazole, ketoconazole, itraconazole)

  Note: If started as an inpatient hospital regimen and this is a continuation of therapy, then the drug is approvable

Proposed Criteria:

- Treatment is for ONE of the following:
  - *Candidemia (in non-neutropenic patients);*
  - *Esophageal candidiasis*
  - Invasive aspergillosis
  - Serious fungal infections caused by S. apiospermum and Fusarium species including F. solani
  - Part of standard anti-fungal regimen in febrile neutropenic patients
  - Other fungal infections that are refractory or resistant to other oral triazole agents (i.e., fluconazole, ketoconazole, itraconazole); ***OR***
- *Patient is continuing therapy from an inpatient hospital stay (to facilitate completion of therapy)*

  ~~**Note:** If started as an inpatient hospital regimen and this is a continuation of therapy, then the drug is approvable~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for DIFLUCAN SUSPENSION

Current Criteria:

- Patient is unable to swallow solid dosage forms

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for flucytosine, ANCOBON

Current Criteria:

- Diagnosis of systemic candidiasis or cryptococcosis

Note: If started as an inpatient hospital regimen and this is a continuation of therapy, then the drug is approvable

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for CRESEMBA ORAL

Current Criteria:

- Patient is ≥ 18 years of age; **AND**
- Diagnosis of one of the following:
  - Invasive aspergillosis; **AND**
    - Trial and failure, contraindication, or intolerance to voriconazole OR posaconazole; OR
  - Invasive mucormycosis; **AND**
- A fungal culture and relevant laboratory study (including histopathology) has been obtained to isolate and identify the causative organism(s)

Note: If started as an inpatient hospital regimen and this is a continuation of therapy, then the drug is approvable

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for fluconazole suspension

Current Criteria:

- Patient is unable to swallow solid dosage forms

Note: PA not required for patients < 21 years of age

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for NOXAFIL, posaconazole

Current Criteria:

- ONE of the following:
  - As indicated for the prophylaxis of invasive aspergillus and/or candida in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD), recipients with hematologic malignancies (leukemia, lymphoma, myelodysplastic syndromes) with prolonged neutropenia from chemotherapy, or recipients with AIDS.
  - Treatment of Fusariosis disease
  - Treatment of Zygomycetes disease
  - Treatment of other fungal infections or molds that are refractory or resistant to, or in patient who have a contraindication, or intolerance to itraconazole or voriconazole

Note: If started as an inpatient hospital regimen and this is a continuation of therapy, then the drug is approvable

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for ORAVIG

Current Criteria:

- Patient is 18 years of age or older; **AND**
- Patient has a diagnosis of oropharyngeal candidiasis; **AND**
- Patient has a contraindication, allergic reaction, or drug-drug interaction to clotrimazole troche and nystatin suspension

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for VIVJOA

Current Criteria:

- Diagnosis of recurrent vulvovaginal candidiasis (RVCC); **AND**
- Provider attests patient is NOT of reproductive potential; **AND**
- The member has experienced ≥ 3 episodes of VVC in less than one year; **AND**
- Failure of a maintenance course of oral fluconazole defined as 100-mg, 150-mg, or 200-mg taken weekly for 6 months

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• fluconazole tablets, 150mg	4/28 days
• terbinafine tablets	84/year
• BREXAFEMME	4 tabs/Rx
• DIFLUCAN tablets, 150mg	4/28 days
• itraconazole capsules	4/day
• itraconazole solution	40 mL/day
• ORAVIG	1/day
• SPORANOX tablets/capsules	4/day
• SPORANOX solution	40 mL/day
• TOLSURA	4/day
• VFEND	18/84 days

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. Vaginitis in nonpregnant patients: ACOG Practice Bulletin, Number 215. Obstet Gynecol. 2020;135(1):e1-e17. doi: 10.1097/AOG.0000000000003604.
- Ancobon (flucytosine) [prescribing information]. Bridgewater, NJ: Bausch Health US LLC; February 2022.

- Brexafemme (ibrexafungerp) [prescribing information]. Jersey City, NJ: Scynexis Inc; November 2022.
- Centers for Disease Control and Prevention (CDC). Biggest threats and data: 2019 AR threats report. Last reviewed November 23, 2021a. https://www.cdc.gov/drugresistance/biggest-threats.html#auris. Accessed November 15, 2023.
- Centers for Disease Control and Prevention (CDC). Information for healthcare professionals about histoplasmosis. Last reviewed August 4, 2023. https://www.cdc.gov/fungal/diseases/histoplasmosis/health-professionals.html. Accessed November 15, 2023.
- Centers for Disease Control and Prevention (CDC). Information for healthcare professionals about mucormycosis. Last reviewed May 27, 2020. https://www.cdc.gov/fungal/diseases/mucormycosis/health-professionals.html. Accessed November 15, 2023.
- Centers for Disease Control and Prevention (CDC). Sexually transmitted infections treatment guidelines, 2021: vulvovaginal candidiasis (VVC). Last reviewed July 22, 2021b. https://www.cdc.gov/std/treatment-guidelines/candidiasis.htm. Accessed November 15, 2023.
- Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America (CDC/NIH/IDSA); Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the CDC/NIH/IDSA. Updated September 25, 2023. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines. Accessed November 15, 2023.
- Clotrimazole Troche lozenges (clotrimazole oral) [prescribing information]. Eatontown, NJ: West-Ward Pharmaceuticals Corp; April 2016.
- Cresemba (isavuconazonium) [prescribing information]. Northbrook, IL: Astellas Pharma US Inc; November 2022.
- Diflucan (fluconazole) oral suspension, tablets [prescribing information]. New York, NY: Roerig, Division of Pfizer Inc; January 2023.
- Drugs@FDA [database on the Internet]. Rockville, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2023. http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 15, 2023.
- Food and Drug Administration (US) Drug Safety Communication. NIZORAL (ketoconazole) oral tablets: Drug Safety Communication—Prescribing for unapproved uses including skin and nail infections continues; linked to patient death. 2016. https://www.fda.gov/Drugs/DrugSafety/ucm500597.htm. Accessed November 15, 2023.
- Galgiani JN, Ampel NM, Blair JE, et al. 2016 IDSA clinical practice guideline for the treatment of coccidioidomycosis. Clin Infect Dis. 2016;63(6):e112-e146.
- Griseofulvin oral suspension [prescribing information]. Parsippany, NJ: Actavis Pharma Inc; April 2020.
- Griseofulvin tablet (microsize) [prescribing information]. Princeton, NJ: Sandoz Inc.; December 2016.
- Griseofulvin tablet (ultramicrosize) [prescribing information]. Congers, NY: Chartwell Pharmaceuticals, LLC; November 2020.
- Itraconazole oral solution [package insert], Upper Saddle River, NJ: Dash Pharmaceuticals; August 2023.
- Ketoconazole [prescribing information]. East Brunswick, NJ: Strides Pharma Inc; May 2023.
- Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Disease Society of America. Clin Infect Dis. 2009;49(1):1-45.
- Micromedex [database on the Internet]. Greenwood Village, CO: Truven Health Analytics; 2023. http://www.micromedexsolutions.com/home/dispatch. Accessed November 15, 2023.
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: prevention and treatment of cancer-related infections. Version 1.2023 – June 28, 2023. NCCN Web site. https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed November 15, 2023.
- National Institutes of Health, Centers for Disease Control and Prevention, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics (NIH/CDC/IDSA/PIDS/AAP). Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the NIH/CDC/IDSA/PIDS/AAP. Updated September 14, 2023. https://clinicalinfo.hiv.gov/en/guidelines/pediatric-opportunistic-infection/whats-new. Accessed November 15, 2023.
- Noxafil [package insert], Rahway, NJ: Merck and Co, Inc.; October 2023.
- Noxafil (posaconazole) [prescribing information]. Rahway, NJ: Merck Sharp & Dohme LLC; September 2022.
- Nystatin oral suspension [prescribing information]. Greenville, SC: PAI Pharmaceutical Associates Inc; January 2020.
- Nystatin tablets [prescribing information]. East Brunswick, NJ: Avet Pharmaceuticals Inc; June 2020.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2023. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed November 15, 2023.
- Oravig (miconazole) [prescribing information]. Marietta, GA: Galt Pharmaceuticals LLC; June 2021.
- Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1-50.
- Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63(4):e1-60.
- Sporanox (itraconazole) capsules [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals Inc; October 2023.
- Sporanox (itraconazole) oral solution [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals Inc; October 2023.
- Stevens DL, Bisno AL, Chambers HF. Practice Guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(2):e10-52.
- Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol. 2018a;36(14):1443-1453. doi:10.1200/JCO.2017.77.6211.
- Terbinafine [prescribing information]. Princeton, NJ: OrchidPharma Inc; January 2022.
- Tolsura (itraconazole) [prescribing information]. Greenville, NC: Mayne Pharma; April 2022.
- Vfend (voriconazole) [prescribing information]. New York, NY: Roerig, Division of Pfizer Inc; October 2022.
- Vivjoa (oteseconazole) [prescribing information]. Durham, NC: Mycovia Pharmaceuticals Inc; April 2022.

ANTI-INFECTIVES: ANTIPROTOZOAL AGENTS, ORAL

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred	
Oral Antiprotozoal Agents	atovaquone PA dapsone tabs metronidazole tabs	benznidazole PA, QL DARAPRIM (pyrimethamine) PA FLAGYL (metronidazole) LAMPIT PA (nifurtimox) LIKMEZ PA (metronidazole) MEPRON PA (atovaquone)	metronidazole caps nitazoxanide tabs PA pyrimethamine PA Solosec (secnidazole) PA, QL sulfadiazine PA tinidazole

Last Review Date: February 2022

Recent Significant Changes

- Intestinal Parasitic Infections in 2023. Gastroenterology Research, 2023
- The following agents have been moved to this PDL class:
  - SOLOSEC and tinidazole (from the "Anti-Infectives: Nitroimidazoles" class)
  - Sulfadiazine (from the "Antibiotics: Sulfonamides, Folate Agonist" class)

Background

Antiprotozoal agents are a class of drugs used to treat infections caused by protozoa. Protozoa are unicellular, non-phototrophic, eukaryotic microorganisms lacking cell walls. This group comprises over 65,000 species. Most protozoa cause a number of diseases in animals and humans. In the cyst stage of the life cycle, protozoa are most dormant and resistant to environmental stress factors. Cysts are often the mode of infection in disease causing protozoa.

There are four distinct groups of protozoan parasites: the amebae, the flagellates, the ciliates, and the sporozoa. Antiprotozoal agents work in the following ways by destroying protozoa or inhibiting their growth and ability to reproduce, damaging the protozoal DNA to limit the spread of infection, or by inhibiting a fundamental pathway of energy metabolism (inhibition of parasite dehydrogenase activity) in the protozoa, thus making them unable to grow and reproduce.

Nitroimidazole antimicrobials include benznidazole, Flagyl (metronidazole), Solosec (secnidazole), and tinidazole. Mepron (atovaquone) is a quinone antimicrobial. Daraprim (pyrimethamine) is used for the treatment of toxoplasmosis. Lampit (nifurtimox) is a synthetic nitrofuran compound and nitazoxanide is a nitrothiazolyl-salicylamide derivative. Antiprotozoal agents are used to treat conditions such as giardiasis, pneumocystis pneumonia, amebiasis, and toxoplasmosis.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
benznidazole	--
Daraprim (pyrimethamine)	✔
FLAGYL (metronidazole) tabs, caps	✔
LAMPIT (nifurtimox)	--
LIKMEZ (metronidazole) suspension	--
MEPRON (atovaquone)	✔
nitazoxanide	--
tinidazole	--

Table 2. FDA Approved Indications

Indication	atovaquone	benznidazole	pyrimethamine	metronidazole	nifurtimox	nitazoxanide	tinidazole
Diarrhea caused by Giardia lamblia or Cryptosporidium parvum						✔	
Treatment of Chagas disease, caused by Trypanosoma cruzi		✔			✔		
Symptomatic and asymptomatic trichomoniasis (T. vaginalis infection) and treatment of asymptomatic sexual partners				✔			✔
Acute intestinal amebiasis and amebic liver abscess				✔			✔
Treatment of serious infections caused by susceptible anaerobic bacteria				✔			
Treatment or prevention of Pneumocystis jirovecii PCP in patients who cannot tolerate trimethoprim-sulfamethoxazole (TMP-SMX)	✔						
Treatment of mild-to-moderate PCP in adults and adolescents aged 13 years and older who cannot tolerate TMP-SMX	✔						
Treatment of giardiasis in patients 3 years of age and older							✔
Treatment of toxoplasmosis when used in combination with a sulfonamide			✔				

Giardiasis

Giardia duodenalis (also known as *G. lamblia* or *G. intestinalis*) can cause sporadic or epidemic diarrheal illness. Giardiasis is a cause of waterborne and foodborne disease, daycare center outbreaks, and illness in international travelers. It is especially common in areas with poor sanitary conditions and limited water-treatment facilities.

Transmission occurs via three routes: waterborne, foodborne, or fecal-oral transmission. Giardiasis is a cause of diarrheal illness among hikers in wilderness areas who drink water that has not been adequately filtered, treated, or boiled. Transmission of giardiasis can also occur via ingestion of raw or undercooked food contaminated with cysts or via food that is contaminated after cooking. Person-to-person transmission can occur in settings in which there is fecal incontinence and poor hygiene, such as childcare centers. Symptoms of acute giardiasis include diarrhea, malaise, abdominal cramps, and weight loss.

Metronidazole and tinidazole are potent agents against giardiasis. The usual dose of metronidazole is 500 to 750 mg/day for 5 to 10 days (efficacy 88%) or a single dose of 2 to 2.4 g (efficacy 48%). The usual dose of tinidazole is 300 mg/day for 7 days (median efficacy 87%) or a single dose of 1 to 2 g (efficacy 92%).

Pneumocystis Pneumonia

Pneumocystis pneumonia (PCP) is caused by *Pneumocystis jirovecii*. Before the widespread use of PCP prophylaxis and antiretroviral therapy (ART), PCP occurred in 70% to 80% of patients with AIDS. Approximately 90% of PCP cases occurred in patients with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3. The incidence of PCP has declined substantially with widespread use of PCP prophylaxis and ART. Most cases of PCP now occur in patients who are unaware of their HIV infection or are not receiving ongoing care for HIV and in those with advanced immunosuppression. In patients with HIV, the most common manifestations of PCP are subacute onset of dyspnea, fever, non-productive cough, and chest discomfort that worsens within days to weeks.

Patients with HIV with CD4 counts <200 cells/mm3 should receive chemoprophylaxis against PCP. Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic agent for PCP. For patients who cannot tolerate TMP-SMX, alternative prophylactic regimens include dapsone, dapsone plus pyrimethamine plus leucovorin, aerosolized pentamidine administered with the Respirgard II nebulizer, and atovaquone.

Amebiasis

Amebiasis is a colonic infection caused by *Entamoeba histolytica*. It is the second most common parasitic disease worldwide. Although amebiasis is widely distributed worldwide, it is more common in tropical and developing countries with poor sanitation. In resource-rich countries, amebiasis is generally seen in migrants from and travelers to endemic areas. Clinical amebiasis generally has a subacute onset, usually over one to three weeks. Symptoms range from mild diarrhea to severe dysentery, producing abdominal pain, diarrhea, and bloody stools. Amebic colitis has been recognized in asymptomatic patients as well.

Nitroimidazoles are the main line of amoebic colitis or extra-intestinal amebiasis treatment: metronidazole 500 to 750 mg three times daily for 5 to 10 days or tinidazole 2 g daily for 3 days. In a Cochrane database systemic review, tinidazole was found to be more effective in reducing clinical failure and associated with fewer side effects than metronidazole. Amoebic liver abscess is treated by a course of nitroimidazole followed by a course of luminal amebicide.

Chagas Disease

Chagas disease (American trypanosomiasis) is caused by the parasite *Trypanosoma cruzi* which is transmitted to animals and people by insect vectors. This disease is found only in the Americas (mainly, in rural areas of Latin America where poverty is widespread). Antiparasitic treatment is indicated for all cases of acute or reactivated Chagas disease and for chronic *T. cruzi* infection in children up to age 18. Congenital infections are considered acute disease. Treatment is strongly recommended for adults up to 50 years old with chronic infection who do not already have advanced cardiomyopathy. For adults older than 50 years with chronic *T. cruzi* infection, the decision to treat with antiparasitic drugs should be individualized, weighing the potential benefits and risks for the patient. Physicians should consider factors such as the patient's age, clinical status, preference, and overall health. The two drugs used to treat infection with *T. cruzi* are nifurtimox and benznidazole.

Toxoplasmosis

Toxoplasmosis is caused by *Toxoplasma gondii*. Immunocompetent persons with primary infection are usually asymptomatic. However, some patients with toxoplasmosis present with cervical and/or generalized lymphadenopathy, cerebral encephalitis, and ocular toxoplasmosis. Transmission of infection often occurs through the ingestion of tissue cysts via improperly cooked/raw meat, or ingestion of oocysts via contaminated food and water. After initial infection, latent infection will persist for the life of the host. Immunocompromised individuals can have reactivation of latent infection.

Therapeutic treatment is indicated in immunocompetent individuals with severe or prolonged symptoms as well as all immunocompromised patients. In cases of suspected *T. gondii* infection, empirical therapy based on presumptive diagnosis is preferred rather than waiting for test results. The combination of pyrimethamine and sulfadiazine is the preferred regimen for treatment. Initial therapy should be continued for 6 weeks and be followed by chronic maintenance therapy.

Table 3. Adverse Reactions

Drug	Adverse Reactions
atovaquone	diarrhea, rash, headache, nausea, fever, vomiting
nitazoxanide	abdominal pain, diarrhea, vomiting, headache
benznidazole	abdominal pain, rash, vomiting, neutropenia, urticaria, pruritus, eosinophilia, decreased appetite
metronidazole	central nervous system reactions, metallic taste, pruritis, QT prolongation, renal and hepatic reactions
nifurtimox	vomiting, abdominal pain, headache, decreased appetite, nausea, pyrexia, rash
tinidazole	metallic taste, nausea, weakness, dyspepsia, cramps, epigastric discomfort, vomiting, anorexia, headache, dizziness, constipation

Benznidazole and metronidazole should not be used within two weeks of therapy with disulfiram. Patients need avoid alcoholic beverage consumption during and for at least three days after therapy with benznidazole and metronidazole. Metronidazole has a boxed warning for its carcinogenic potential and unnecessary use should be avoided. Tinidazole is contraindicated in the first trimester of pregnancy and in nursing mothers.

Clinical Rationale

Antiprotozoals are used to treat a variety of protozoal diseases, including amebiasis, giardiasis, trichomoniasis, toxoplasmosis, trypanosomiasis, and babesiosis. This drug class also includes agents used to treat Pneumocystis pneumonia. Antiprotozoal drugs are the preferred treatment for such diseases.

Recommendation

It is recommended that atovaquone be subject to clinical criteria to ensure its use as a second-line agent. Additionally, metronidazole tablets should be available for use.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for benznidazole

Current Criteria:

- Diagnosis of American trypanosomiasis (Chagas disease); **AND**
- Patient must not be pregnant or breastfeeding; **AND**
- Female patients of reproductive potential should use effective contraception during treatment and for at least 1 week after treatment; **AND**
- Males undergoing treatment with female partners of reproductive age should use effective contraception during treatment and 1 week after treatment due to male mediated teratogenicity; **AND**
- Alcohol consumption will be avoided while on therapy

Proposed Criteria:

- Diagnosis of American trypanosomiasis (Chagas disease) caused by *Trypanosoma cruzi*; **AND**
- ~~Patient must not be pregnant or breastfeeding; **AND**~~
- ~~Female patients of reproductive potential should use effective contraception during treatment and for at least 1 week after treatment; **AND**~~
- ~~Males undergoing treatment with female partners of reproductive age should use effective contraception during treatment and 1 week after treatment due to male mediated teratogenicity; **AND**~~
- ~~Alcohol consumption will be avoided while on therapy~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for LAMPIT

Criteria: (60-day approval duration)

- Diagnosis of Chagas disease caused by *Trypanosoma cruzi*; **AND**
- Patient is < 18 years of age and weights ≥2.5 kg; **AND**
- Prescribed by, or in consultation with, an infectious disease specialist; **AND**
- Female patients should use effective contraception during treatment and ≥ 1 week after treatment; **AND**
- Males undergoing treatment with female partners of reproductive age should use effective contraception during treatment and 1 week after treatment due to male mediated teratogenicity; **AND**
- Provider will counsel patient against the use of alcohol consumption while on therapies

Proposed Criteria:

Criteria: (60-day approval duration)

- Diagnosis of *American trypanosomiasis* (Chagas disease) caused by *Trypanosoma cruzi*; **AND**
- ~~Patient is < 18 years of age and weights ≥2.5 kg; **AND**~~
- ~~Prescribed by, or in consultation with, an infectious disease specialist; **AND**~~
- ~~Female patients should use effective contraception during treatment and ≥ 1 week after treatment; **AND**~~

- ~~Males undergoing treatment with female partners of reproductive age should use effective contraception during treatment and 1 week after treatment due to male mediated teratogenicity;~~ ~~**AND**~~
- ~~Provider will counsel patient against the use of alcohol consumption while on therapies~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for MEPRON, atovaquone

Current Criteria:

- Treatment is for prophylaxis of *Pneumocystis* pneumonia (PCP) or *Toxoplasmosis gondii* encephalitis; **AND**
- Trial and failure, contraindication, intolerance, or drug-drug interaction to sulfamethoxazole/trimethoprim

Proposed Criteria:

- ~~Treatment is for prophylaxis of *Pneumocystis* pneumonia (PCP) or *Toxoplasmosis gondii* encephalitis;~~ ~~**AND**~~
- *One of the following:*
  - *Treatment is for Pneumocystis pneumonia (PCP) prevention or treatment;* ***AND***
    - Trial and failure, contraindication, intolerance to sulfamethoxazole/trimethoprim
  - *Diagnosis of Toxoplasmosis gondii encephalitis;* ***AND***
    - Trial and failure, contraindication, intolerance to sulfamethoxazole/trimethoprim
  - *Diagnosis of Babesiosis;* ***AND***
- *If request is for Mepron, trial and failure of preferred atovaquone*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for SOLOSEC

Current Criteria:

- Patient is 12 years of age or older; **AND**
- One of the following:
  - Diagnosis of bacterial vaginosis supported by one of the following; **AND**
    - One of the following to support the diagnosis:
      - Off-white/gray vaginal discharge
      - Vaginal pH ≥ 4.7
      - Clue cells ≥ 20% on microscopy
      - Positive 10% KOH whiff test
      - Nugent score ≥ 4 on gram stain; **AND**
    - Patient has tried and failed CDC recommended course of clindamycin therapy unless there is a clinically valid reason why the preferred treatment course cannot be used; **OR**
  - Diagnosis of trichomoniasis caused by *Trichomonas vaginalis*; **AND**
  - Patient has tried and failed CDC recommended course of metronidazole therapy unless there is a clinically valid reason why the preferred treatment course cannot be used; **AND**
- Patient does not have a hypersensitivity to nitroimidazole derivatives (e.g., metronidazole, tinidazole); **AND**
- Patient does not have in vitro resistance to nitroimidazole derivatives (e.g., metronidazole, tinidazole, secnidazole); **AND**
- Patient does not have hepatic impairment or there is no concern with the patient and alcohol consumption

Proposed Criteria:

- Patient is 12 years of age or older; **AND**
- One of the following:
  - Diagnosis of bacterial vaginosis ~~supported by one of the following~~; **AND**
    - ~~One of the following to support the diagnosis:~~

- ~~Off-white/gray vaginal discharge~~
- ~~Vaginal pH ≥ 4.7~~
- ~~Clue cells ≥ 20% on microscopy~~
- ~~Positive 10% KOH whiff test~~
- ~~Nugent score ≥ 4 on gram stain;~~ ~~**AND**~~

– ~~Patient has tried and failed CDC recommended course of clindamycin therapy unless there is a clinically valid reason why the preferred treatment course cannot be used;~~ ~~**OR**~~

– *Trial and failure, contraindication, or intolerance to one of the following:*

- *Cleocin® vaginal cream*
- *Cleocin® vaginal suppository*
- *clindamycin capsules*
- *metronidazole tablets*
- *metronidazole vaginal gel*

○ Diagnosis of trichomoniasis caused by Trichomonas vaginalis; **AND**

– ~~Patient has tried and failed CDC recommended course of metronidazole therapy unless there is a clinically valid reason why the preferred treatment course cannot be used;~~ ~~**AND**~~

– *Trial and failure, contraindication, or intolerance to preferred metronidazole tablets;* ***AND***

- ~~Patient does not have a hypersensitivity to nitroimidazole derivatives (e.g., metronidazole, tinidazole);~~ ~~**AND**~~
- ~~Patient does not have in vitro resistance to nitroimidazole derivatives (e.g., metronidazole, tinidazole, secnidazole);~~ ~~**AND**~~
- ~~Patient does not have hepatic impairment or there is no concern with the patient and alcohol consumption~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for PYRIMETHAMINE

No drug specific criteria. Standard non-preferred PA criteria applies.

Proposed Criteria:

- *Treatment of toxoplasmosis when used in combination with a sulfonamide.*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for LIKMEZ

- Patient is unable to swallow solid dosage forms

Note: PA is not required for patients less than 12 years of age

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for nitazoxanide tablets

- Patient is > 12 years of age or older; **AND**
- One of the following:
  - Treatment of diarrhea caused by Cryptosporidium parvum (Note: Will not be approved for this indication in HIV-infected or immunodeficient patients)

- Treatment of diarrhea caused by Giardia lamblia; **AND**
  - Trial and failure, contraindication, or intolerance to tinidazole and metronidazole

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for SULFADIAZINE

- Treatment of Toxoplasma gondii encephalitis in combination with pyrimethamine; **OR**
- Rheumatic fever prophylaxis in patients who have a contraindication or intolerance to penicillin

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• benznidazole 12.5mg	6/day
• benznidazole 100mg	4/day
• nitazoxanide tablets	6/day
• SOLOSEC	~~2gm/Rx~~ *1 pack/month*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Ahmed M. Intestinal Parasitic Infections in 2023. Gastroenterology Res. 2023 Jun;16(3):127-140. doi: 10.14740/gr1622. Epub 2023 Jun 11. PMID: 37351081; PMCID: PMC10284646.
- Benznidazole [prescribing information]. Florham Park, NJ: Exeltis USA Inc; December 2021.
- Centers for Disease Control and Prevention. Sexually Transmitted Infections Treatment Guidelines. MMWR. 2021;70(No. RR-4):1-135.
- Drugs@FDA [database on the Internet]. Rockville, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2023. http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 2, 2023.
- Flagyl capsules (metronidazole) [prescribing information]. New York, NY: Pfizer Labs; October 2023.
- Flagyl tablets (metronidazole) [prescribing information]. New York, NY: Pfizer Labs; October 2023.
- Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Clinical Info HIV.gov. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/pneumocystis-0?view=full. Accessed January 5, 2024.
- Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Clinical Info HIV.gov. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/toxoplasma-gondii?view=full. Accessed January 5, 2024.
- Hooshyar H, Rostamkhani P, Arbabi M, Delavari M. Giardia lamblia infection: review of current diagnostic strategies. Gastroenterol Hepatol Bed Bench. 2019;12(1):3–12.
- Lampit (nifurtimox) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; June 2023.
- Likmez (metronidazole) [prescribing information]. Hauppauge, NY: Saptalis Pharmaceuticals LLC; September 2023.
- Mepron (atovaquone) [prescribing information]. Durham, NC: GlaxoSmithKline; July 2023.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2023. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed November 2, 2023.
- Parasites – American Trypanosomiasis (also known as Chagas Disease). Centers for Disease Control and Prevention. https://www.cdc.gov/parasites/chagas/index.html. Accessed January 5, 2024.
- Solosec (secnidazole) [prescribing information]. Baltimore, MD: Lupin Pharmaceuticals Inc; July 2022.
- Vivancos V, Gonzalez-Alvarez I, Bermejo M, Gonzalez-Alvarez M. Giardiasis: characteristics, pathogenesis and new insights about treatment. Curr Top Med Chem. 2018;18(15):1287–1303.
- Zulfiqar H, Mathew G, Horrall S. StatPearls. Treasure Island (FL): 2023. Amebiasis.

ANTIVIRALS: CYTOMEGALOVIRUS AGENTS

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred	
Cytomegalovirus Agents	VALCYTE solution (valganciclovir) valganciclovir solution valganciclovir tabs	LIVTENCITY [PA, QL] (maribavir) PREVYMIS [PA, QL] (letermovir)	VALCYTE tabs (valganciclovir)

Last Review Date: February 2022

Recent Significant Changes

- The 2023 National Comprehensive Cancer Network (NCCN) guideline for infections (2023)

Background

Cytomegalovirus (CMV), a member of the herpesvirus family, is a serious, life-threatening infection that causes significant health complications, especially in individuals with a weakened immune status. Viral transmission can occur perinatally, through sexual exposure, blood, and close contact. Immunoglobulin G (IgG) seroprevalence of CMV in the United States (US) is estimated to be approximately 48% and increases with age. During CMV infection, immunocompetent individuals are typically asymptomatic while some experience symptoms that are like that of mononucleosis (eg, fever, malaise, fatigue). Due to the infection being self-limiting in this population, antivirals typically are not necessary. After primary infection, CMV becomes latent and can reactivate in response to changes to an individual's immune status.

In high-risk populations, the clinical features of active disease vary, as well as the approach to prevention and treatment. These populations can include immunocompromised individuals, specifically individuals with human immunodeficiency virus (HIV) infection or solid organ transplant. In general, low lymphocyte counts due to uncontrolled HIV infection contribute increased risk of CMV infection in this population. CMV-mediated end-organ disease commonly presents as retinitis which progresses from unilateral disease to bilateral in the absence of therapy. Untreated lesions can involve the entire retina in less than 6 months. Other manifestations can occur but are at lower rates compared to retinitis (eg, colitis, esophagitis, pneumonitis, neurologic disease). Currently, CMV-end organ disease is best prevented using antiretroviral therapy (ART).

Drug-induced immunosuppression increases the risk of CMV disease in patients that are immunocompromised. The level of CMV infection risk varies based on seropositivity of the organ donor and recipient as well as the organ being transplanted. CMV can be prevented by prophylaxis (ie, the administration of antiviral) or by preemptive therapy (ie, the early diagnosis of viral replication).

A subset of solid-organ transplant patients has resistant or refractory disease. Resistance to antivirals is attributed to a mutation in the Unique Long (UL) 97 phosphotransferase gene and the UL54 polymerase gene. These mutations increase the need for novel treatment options. Individuals who undergo hematopoietic stem cell transplant (HSCT) receive an immunosuppressive regimen prior to transplant to prevent graft versus host disease and associated organ-tissue loss. D-/R+ patients are at higher risk for CMV after HSCT, due to lack of donor-transferred CMV-specific immunity during viral reactivation. Antiviral prophylaxis is recommended.

Agents for the treatment or prophylaxis of CMV infection include Livtencity (maribavir), Prevymis (letermovir), and Valcyte (valganciclovir). Valganciclovir is indicated for the treatment CMV retinitis and the prevention of CMV disease in patients with solid-organ transplants. Maribavir received break-through therapy from the FDA; it is a first in class treatment for CMV, indicated for post-transplant CMV patients who are refractory to previous treatments (eg, ganciclovir, valganciclovir, cidofovir). Letermovir is a first in class non-nucleoside CMV inhibitor indicated for prophylaxis of CMV infection in CMV- seropositive recipients (R+) adults with hematopoietic stem cell transplant (HSCT) and patients with kidney transplants at high-risk.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
LIVTENCITY (maribavir) tablet	-
PREVYMIS (letermovir) tablet	-
VALCYTE (valganciclovir) tablet, oral solution	✔

Table 2. Food and Drug Administration Approved Indications

Indication	LIVTENCITY (maribavir)	PREVYMIS (letermovir)	VALCYTE (valganciclovir)
Treatment of patients with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet	✔		
Prophylaxis of CMV infection and disease in adult CMV-R+ of an allogeneic HSCT and kidney transplant recipients at high risk (D+/R-)		✔	
Treatment of CMV retinitis in adults living with AIDS			✔
Prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk (D+/R-)			✔

Department of Health and Human Services (DHHS) guidelines for CMV disease in patients with HIV:

- Prevention: CMV-end organ disease is best prevented using ART. Primary prophylaxis with valganciclovir is not recommended.
- Treatment: For CMV retinitis, first-line treatment includes induction with IV ganciclovir or oral valganciclovir followed by chronic maintenance with oral valganciclovir. Maintenance therapy can be discontinued patients whose lesions have been treated for at least 3 to 6 months and are inactive, and who have sustained increases in increases in CD4 cell counts to > 100 cells/mm3 in response to ART.
- Oral valganciclovir does not have an established role in CMV-related neurologic disease.

CMV Guidelines of the American Society of Transplantation Infectious Diseases Community, 2021

Practice guidelines for recipients of solid-organ transplant:

- Prophylactic antiviral treatments include valganciclovir or IV ganciclovir in solid-organ transplant of kidney, pancreas, pancreas/kidney, liver, heart, intestinal, lung, heart/lung, and compositive tissue grafts (patients at highest risk of CMV). For kidney transplant recipients only, high dose valacyclovir is an alternative.
- Preemptive antiviral treatment with valganciclovir or IV ganciclovir is effective for CMV disease prevention.
- Treatment of CMV disease with IV ganciclovir is preferred for severe or life-threatening disease, those with very high viral load, or those with questionable GI absorption. Acyclovir, valacyclovir, and oral ganciclovir should not be used in the treatment of CMV disease.
- In pediatric patients, antiviral prophylaxis, preemptive therapy, and a hybrid approach are effective methods with valganciclovir or IV ganciclovir.

Transplantation Society International CMV Consensus Group: Guidelines on the management of CMV in SOT

- Prophylaxis may be preferred in donor and/or recipient seropositive patients whose risk for CMV may be increased. The choice of CMV prevention method should be determined by individual center, CMV disease incidence, immunosuppression, logistics of CMV surveillance, and economic aspects.
- For the treatment of CMV disease, first line treatments are oral valganciclovir and IV ganciclovir; foscarnet is recommended as a second-line option, particularly in patients intolerant to valganciclovir or IV ganciclovir. Acyclovir and valacyclovir are not recommended for the treatment of CMV.

Individuals undergoing allogeneic HSCT

Guidelines for the management of CMV infection in patients with hematological malignancies and after stem cell transplantation from the 2017 European conference on infections in leukemia recommends letermovir, valaciclovir, acyclovir, ganciclovir or valganciclovir, or foscarnet for CMV prophylaxis in HSCT patients. For preemptive CMV treatment, first-line treatments include IV ganciclovir, valganciclovir or foscarnet.

American Society for Transplantation (AST) and Cellular Therapy series recommends letermovir (grade A) for prevention of CMV after HSCT. If letermovir cannot be used, preemptive therapy is recommended. Prophylaxis with valganciclovir, ganciclovir, or foscarnet is not generally recommended (Grade D, level I). CMV management of resistant or refractory infections after HSCT indicates that ID consult for resistant CMV is recommended. If resistance suspected, genotypic testing should be obtained to determine definitive antiviral therapy for patient.

Safety Information
Virologic failure due to resistance can occur during and after treatment with maribavir. Maribavir has the potential to increase drug concentrations of immunosuppressant drugs. Prevymis is contraindicated in use with pitavastatin or simvastatin (when co-administered with cyclosporine), pimozide, and ergot alkaloids. Valcyte (valganciclovir) has a boxed warning for clinical toxicity of valganciclovir including hematologic toxicity (e.g., severe leukopenia, neutropenia, anemia), impairment of fertility, fetal toxicity, mutagenesis, and carcinogenesis. Valganciclovir may cause acute renal failure in elderly patients, patients receiving nephrotic drugs, and patients without adequate hydration. Common class adverse events are diarrhea, pyrexia, fatigue, tremor, neutropenia, anemia, leukopenia, thrombocytopenia, headache, insomnia, urinary tract infection, and vomiting.

Clinical Rationale

Letermovir and maribavir provide additional treatment options for CMV infections in HSCT and solid organ transplant patients who require an effective therapy. Valganciclovir remains a standard of care for CMV retinitis treatment, and the prevention of CMV disease in adult and pediatric solid organ transplant recipients.

Recommendation

It is recommended that valganciclovir be available for use. Due to its unique indication, letermovir *and maribavir* should be subject to prior authorization.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for PREVYMIS

Current Criteria:

- Patient is > 18 years of age and older; **AND**
- One of the following:
  - Patient is an allogeneic hematopoietic stem cell transplant (HSCT) recipient [approval duration 200 days]; **AND**
    - Patient is seropositive for CMV within 1 year before or < 100 days after HSCT
  - Patient is a kidney transplant recipient [PA approval duration 200 days]; **AND**
    - Patient is high risk for CMV Disease (e.g., Donor CMV seropositive/Recipient CMV seronegative [D+/R-]); **AND**
- Must be prescribed by, or in consultation with, an oncology, hematology, ID, or transplant specialist; **AND**
- Patient is NOT receiving concurrent therapy with any of the following:
  - Pimozide
  - Ergot alkaloids
  - Cyclosporine in conjunction with either pitavastatin or simvastatin

NOTE: When co-administered with cyclosporine the recommended dose of Prevymis is 240mg daily

Proposed Criteria:

Criteria: PA Duration: 200 days

- Patient is > 18 years of age and older; **AND**
- One of the following:
  - Patient is *scheduled or has received* an allogeneic hematopoietic stem cell transplant (HSCT) ~~recipient~~ *and meets ONE of the following* [~~PA approval duration 200 days~~]; **AND**

- Patient is seropositive for CMV ~~within 1 year before or < 100 days after HSCT~~
- *Treatment is for prophylaxis against CMV disease*

○ Patient is a kidney transplant recipient ~~[PA approval duration 200 days]~~; **AND**

- Patient is high risk for CMV Disease (e.g., Donor CMV seropositive/Recipient CMV seronegative [D+/R-]); **AND**

- Must be prescribed by, or in consultation with, an oncology, hematology, ID, or transplant specialist; **AND**
- Patient is NOT receiving concurrent therapy with any of the following:
  - Pimozide
  - Ergot alkaloids
  - Cyclosporine in conjunction with either pitavastatin or simvastatin

NOTE: When co-administered with cyclosporine the recommended dose of Prevymis is 240mg daily

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for LIVTENCITY

Current Criteria:

- Patient is ≥12 years of age and weighs ≥ 35kg; **AND**
- Diagnosis of post-transplant cytomegalovirus (CMV) infection; **AND**
- Infection is refractory to prior treatment with at least one of the following:
  - Ganciclovir, valganciclovir, cidofovir or foscarnet

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- LIVTENCITY 4/day
- PREVYMIS 1/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Department of Health and Human Services (DHHS). Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents: with HIV- cytomegalovirus disease. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection. Updated July 1, 2021.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/.
- Fowler K, Mucha J, Neumann M, et al. A systematic literature review of the global seroprevalence of cytomegalovirus: possible implications for treatment, screening, and vaccine development. BMC Public Health. 2022;22(1):1659.
- Hakki M, Aitken SL, Danziger-Isakov L, et al. American Society for Transplantation and Cellular Therapy Series: #3-Prevention of Cytomegalovirus Infection and Disease After Hematopoietic Cell Transplantation. Transplant Cell Ther. 2021;27(9):707-719.
- Kotton CN, Kumar D, Caliendo AM, et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation. 2018;102(6):900-931.
- Ljungman P, de la Camara R, Robin C, et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). Lancet Infect Dis. 2019;19(8):e260-e272.
- Nogalski MT, Collins-McMillen D, Yurochko AD. Overview of human cytomegalovirus pathogenesis. Methods Mol Biol. 2014;1119:15-28.
- Prevymis (letermovir) tablets and injection [prescribing information]. Rahway, NJ: Merck Sharp & Dohme LLC; August 2023.
- Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13512.
- Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective [Biol Blood Marrow Transplant. 2009;15(10):1143-1238.
- Valcyte (valganciclovir) [prescribing information]. Montgomery, AL: H2-Pharma LLC; April 2023.
- Yong MK, Shigle TL, Kim YJ, Carpenter PA, Chemaly RF, Papanicolaou GA. American Society for Transplantation and Cellular Therapy Series: #4 - Cytomegalovirus treatment and management of resistant or refractory infections after hematopoietic cell transplantation. Transplant Cell Ther. 2021;27(12):957-967.

ANTIVIRALS: HEPATITIS B

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred	
Hepatitis B	entecavir QL lamivudine-HBV QL tenofovir QL	adefovir PA, QL BARACLUDE soln PA (entecavir) BARACLUDE tabs QL (entecavir)	VEMLIDY PA, QL (tenofovir alafenamide) VIREAD powder PA (tenofovir disoproxil fumarate) VIREAD tablets QL (tenofovir disoproxil fumarate)

Last Review Date: February 2022

Recent Significant Changes

- Department of Health and Human Services (DHHS) guideline for the use of antiretroviral agents in adults and adolescents with HIV: Considerations for antiretroviral use in patients with coinfections, 2022

Background

The hepatitis B virus (HBV) is a deoxyribonucleic acid (DNA) virus that is transmitted by perinatal, percutaneous, and sexual exposure, and by close person-to-person contact (presumably by open cuts and sores, especially among children in hyperendemic areas). HBV contains numerous antigenic components, including hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg). HBsAg is the serologic hallmark of HBV infection, appearing in serum 1 to 10 weeks after an acute exposure and prior to the onset of symptoms or elevation of serum alanine aminotransferase (ALT) levels. In patients who recover, HBsAg usually becomes undetectable after 4 to 6 months, followed by the appearance of hepatitis B surface antibody (anti-HBs). HBcAg is expressed in infected hepatocytes and is not detectable in serum. Acute HBV infection is characterized by the presence of HBsAg and immunoglobulin M (IgM) antibody to HBcAg (anti-HBc). HBeAg is a marker of HBV replication and infectivity. Persistence of HBsAg for more than 6 months (with or without concurrent HBeAg) implies chronic infection.

Patients with chronic hepatitis B (CHB) are often asymptomatic. Although they may not be aware that they are infected, they are capable of infecting others. Chronic infection is responsible for most HBV-related morbidity and mortality, including chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma (HCC). An estimated 25% of patients who develop CHB as children and 15% who develop CHB as adults die prematurely from cirrhosis or liver cancer. HBV DNA levels, ALT levels, and HBeAg status are the important predictors of progression to cirrhosis, whereas HBV DNA levels (> 2000 IU/mL), HBeAg status, and cirrhosis are key determinants of HCC risk.

Traditionally, CHB is divided into 4 phases. Phases are of variable duration and not everyone will experience all phases. Regular monitoring of HBV DNA and ALT levels is important in determining the phase of infection.

Phases of CHB:

- Immune-tolerant phase: In this highly replicative phase/low inflammatory phase, HBV DNA levels are elevated, ALT levels are normal, and biopsies do not show signs of significant inflammation or fibrosis. There is an increased likelihood of transitioning from the immune-tolerant to the HBeAg-positive immune-active phase with increasing age.
- HBeAg-positive immune active phase: This phase is characterized by elevated ALT and HBV DNA levels as well as liver injury.
- Inactive CHB phase: In this phase, HBV DNA levels are low or undetectable, ALT levels are normal, and antibody to HBeAg (anti-HBe) is present. There is minimal necroinflammation, but variable fibrosis due to liver injury during the HBeAg-positive immune-active phase. Among those who undergo spontaneous HBeAg seroconversion, 67% to 80% will continue to remain in the inactive CHB phase, while 4% to 20% will revert back to being HBeAg positive.

- HBeAg-negative immune reactivation phase: Among those who seroconvert from HBeAg to anti-HBe positive, 10% to 30% will continue to have elevated ALT and high HBV DNA levels, and approximately 10% to 20% of inactive carriers may have reactivation of HBV replication and exacerbations of hepatitis. Liver histology shows necroinflammation and fibrosis.

A small proportion of patients with inactive CHB infection will clear HBsAg yearly, and most will develop anti-HBs. Clearance of HBsAg, whether spontaneous or after antiviral therapy, reduces the risk of hepatic decompensation and improves survival. Hepatitis B vaccination is recommended for all infants at birth, adolescents who have not been previously vaccinated, adults aged 19 to 59 with risk factors, and adults ≥ 60 years old with or without risk factors.

The goal of therapy for CHB is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC, and death. This goal can be achieved if HBV replication can be suppressed in a sustained manner. Sustained suppression of HBV replication has been associated with normalization of serum ALT, loss of HBeAg with or without detection of anti-HBe, and improvement in liver histology. An immunological cure may be defined by HBsAg loss and sustained HBV DNA suppression. A virological cure, defined by complete eradication of the virus, is currently not an attainable goal due to the persistence of covalently closed circular DNA in the nucleus of infected hepatocytes. The decision to initiate treatment is primarily based upon the presence or absence of cirrhosis, ALT level, and the HBV DNA level. Treatment strategies for chronic HBV typically include pegylated interferon (peg-IFN) or nucleoside/ nucleotide analogs (NAs).

There are 6 therapeutic agents approved by Food and Drug Administration (FDA) for the treatment of CHB: 5 NAs (adefovir dipivoxil [ADV], entecavir [ETV], lamivudine [LAM], tenofovir alafenamide [TAF], tenofovir disoproxil fumarate [TDF]) and 1 interferon alfa agent (peginterferon alfa-2a). Telbivudine (TBV) (Tyzeka) and interferon alfa-2b (Intron A) have been discontinued and will not be covered in this review.

Table 1. Medications Included Within Class Review

Drug	Abbreviation	Generic Availability
adefovir dipivoxil tablet	ADV	✔
BARACLUDE (entecavir) tablet, solution	ETV	✔ ‡
lamivudine (HBV)† tablet	LAM	✔
VEMLIDY (tenofovir alafenamide) tablet	TAF	-
VIREAD (tenofovir disoproxil fumarate) tablet, powder	TDF	✔ ‡

† Only the 100 mg strength is approved for HBV.
‡ Only the tablet is available generically.

Table 2. FDA Approved Indications

Indication	**adefovir dipivoxil** (ADV)	**BARACLUDE** (ETV)	**Lamivudine** (LAM)	**VEMLIDY** (TAF)	**VIREAD** (TDF)
Chronic HBV infection	✔	✔	✔	✔	✔
HIV-1 infection					✔

American Association for the Study of Liver Diseases (AASLD): Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B

Patients with CHB should be counseled regarding lifestyle modifications, prevention of transmission, and the importance of lifelong monitoring. Antiviral therapy is generally not necessary in patients with symptomatic acute hepatitis B because > 95% of immunocompetent adults with acute hepatitis B recover spontaneously. Antiviral treatment is indicated for patients with acute hepatitis B who have acute liver failure or who have a protracted, severe course, as indicated by total bilirubin > 3 mg/dL (or direct bilirubin > 1.5 mg/dL), international normalized ratio > 1.5, encephalopathy, or ascites. ETV, TDF, or TAF are the preferred antiviral drugs for acute symptomatic hepatitis B. Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation.

Table 1. Antiviral Options for Management of Antiviral Resistance

Antiviral resistance	Switch strategy (preferred)	Add strategy: 2 drugs without cross-resistance
LAM resistance	Tenofovir (TDF or TAF)	Continue LAM; add tenofovir (TDF or TAF) (or alternative emtricitabine-tenofovir)
ADV resistance	ETV or Tenofovir (TDF or TAF)	Continue ADV; add ETV
ETV resistance	Tenofovir (TDF or TAF)	Continue ETV; add tenofovir (TDF or TAF) (or alternative emtricitabine-tenofovir)
Tenofovir resistance	ETV	Continue tenofovir (TDF or TAF) and add ETV
Multidrug resistance	Tenofovir	Combined tenofovir (TDF or TAF) and ETV

TAF or entecavir should be considered in patients with risk for renal dysfunction or bone disease. TAF is not recommended in patients with creatinine clearance < 15 mL/min or those on dialysis. Head-to-head comparisons of antiviral therapies have not demonstrated superiority of one therapy over another in reducing the risk of liver-related complications. TAF is associated with lower rates of bone and renal abnormalities than TDF. Patients with suspected TDF-associated renal dysfunction and/or bone disease should be switched to TAF or ETV, with consideration for any previously known drug resistance. For pregnant women with CHB, antiviral therapy is suggested to reduce the risk of perinatal transmission of HBV in HBsAg-positive pregnant women with HBV DNA level > 200,000 IU/mL. Of the antivirals studied in pregnant women (LAM and TDF), TDF is preferred to minimize the risk of emergence of viral resistance during treatment. For HBeAg-positive children between the ages of 2 and 18 years, antiviral therapy is suggested if the patient has elevated ALT and measurable HBV-DNA.

All HBsAg-positive patients should be tested for HCV infection using the anti-HCV test. Additionally, all patients with HBV and HIV coinfection should initiate antiretroviral therapy, regardless of CD4 count. The DHHS guideline states that because emtricitabine (FTC), lamivudine (as 3TC), TDF, and TAF have activity against both HIV and HBV, an ART regimen for patients with coinfection should include (TAF or TDF) plus (3TC or FTC) as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive ARV regimen. Prior to the initiation of ART, all individuals positive for HBsAg should be tested for HBV DNA to determine the level of HBV replication, and the test should be repeated every 3 to 6 months to ensure effective HBV suppression. The goal of HBV therapy with NRTIs is to prevent liver disease complications by sustained HBV suppression. In the setting of confirmed LAM resistance in patients already receiving antiretroviral therapy, adding tenofovir is generally preferred. TAF is approved for HIV in combination with emtricitabine with or without other HIV drugs and is preferred to TDF because of its improved safety profile. ETV has been shown to decrease serum HIV-ribonucleic acid (RNA) levels in LAM-experienced and LAM-naïve patients and result in the selection of the M184V mutation. ETV should only be used in HBV- and HIV-coinfected patients receiving a fully suppressive antiretroviral regimen.

Table 5. Warnings

Warnings	adefovir dipivoxil (ADV)	BARACLUDE (ETV)	lamivudine (LAM)	VEMLIDY (TAF)	VIREAD (TDF)
Severe acute exacerbations of hepatitis after treatment is discontinued	BW	BW	BW	BW	BW
HIV-1 resistance if used in a patient with unrecognized or untreated HIV-1 infection	BW	BW	BW	✔	✔
Lactic acidosis and severe hepatomegaly with steatosis	BW	BW	✔	✔	✔
Nephrotoxicity	BW				
Resistance-associated HBV substitutions			✔		
New onset or worsening renal impairment				✔	✔
Clinical resistance	✔				
Avoid coadministration of products containing TAF or TDF	✔				
Immune reconstitution syndrome (HIV-1 infected patients)					✔
Bone loss and mineralization defects					✔

Abbreviations: BW = boxed warning

The most common adverse reactions for each agent are:

- ETV: Headache, fatigue, dizziness, and nausea
- LAM: Ear, nose, and throat infections, sore throat, and diarrhea
- ADV:
  - In compensated liver disease patients: Asthenia, headache, abdominal pain, and nausea
  - In pre- and post-transplantation LAM-resistant liver disease patients: Increased creatinine
- TAF: Headache
- TDF:
  - HBV with compensated liver disease: Nausea
  - HBV with decompensated liver disease: Abdominal pain, insomnia, pruritus, vomiting, dizziness, pyrexia

Clinical Rationale

Nucleotide analogs (NAs) are recommended first line for the treatment for chronic hepatitis B due to potent antiviral effect and favorable safety profile of the newer agents. Treatment of chronic hepatitis B decreases morbidity and mortality by preventing progression of the disease to cirrhosis, end-stage liver disease, and hepatocellular carcinoma.

Recommendation

It is recommended at least entecavir, lamivudine and tenofovir should be available for use.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for adefovir

Current Criteria:

- Patient is > 12 years of age and older; **AND**
- Diagnosis of Chronic Hepatitis B with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease; **AND**
- Inadequate treatment response (detectable HBV DNA level after 24 weeks), virologic breakthrough, resistance, intolerance, or contraindication to entecavir OR tenofovir disoproxil/ fumarate; **AND**
- Prescriber will monitor the following:
  - Severe acute exacerbations of hepatitis: Monitor hepatic function closely at repeated intervals for at least several months in patients who discontinue therapy.
  - Nephrotoxicity: Monitor renal function during therapy for all patients, particularly those with pre-existing or other risks for renal impairment; **AND**
- Patient will be offered HIV testing prior to initiating therapy; **AND**
- Patient will not concurrently take with products containing tenofovir disoproxil fumarate or tenofovir alafenamide

Proposed Criteria:

Remove PA Criteria; Standard non-preferred criteria will apply

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for VEMLIDY

Current Criteria:

- Patient is > 12 years of age and older; **AND**
- Diagnosis of Chronic Hepatitis B virus (HBV) infection in adults with compensated liver disease; **AND**

- Inadequate treatment response (detectable HBV DNA level after 24 weeks of therapy), virologic breakthrough, resistance, intolerance, or contraindication to entecavir; **AND**
- Patient is not using tenofovir alafenamide (Vemlidy) as monotherapy if (HIV)-1 positive. (Must have additional antiviral therapy if HIV-1 positive for coverage of both disease states); **AND**
- Prescriber will monitor hepatic function closely at repeated intervals for at least several months in patients who discontinue therapy; **AND**
- Prescriber will test for HIV infection testing prior to initiation of Vemlidy; **AND**
- At treatment initiation and during treatment, prescriber will monitor all of the following:
  - Serum creatinine,
  - Estimated creatinine clearance,
  - Urine glucose and urine protein
- Prescriber will assess serum phosphorus in patients with chronic kidney disease; **AND**
- Patient does not have decompensated (Child Pugh B or C) hepatic impairment

Proposed Criteria:

- Patient is > 12 years of age and older; **AND**
- Diagnosis of Chronic Hepatitis B virus (HBV) infection in adults with compensated liver disease; **AND**
- Inadequate treatment response (detectable HBV DNA level after 24 weeks of therapy), virologic breakthrough, resistance, intolerance, or contraindication to entecavir; **AND**
- *Patient has ONE of the following:*
  - *History of osteoporosis or osteopenia*
  - *Renal impairment defined by CrCL <50 mL/min*
  - *Clinically valid reason as to why the preferred tenofovir disoproxil fumarate (TDF) cannot be used*; ***AND***
- Patient is not using tenofovir alafenamide (Vemlidy) as monotherapy if (HIV)-1 positive. (Must have additional antiviral therapy if HIV-1 positive for coverage of both disease states); **AND**
- Prescriber will monitor hepatic function closely at repeated intervals for at least several months in patients who discontinue therapy; ~~**AND**~~
- ~~Prescriber will test for HIV infection testing prior to initiation of Vemlidy; **AND**~~
- ~~At treatment initiation and during treatment, prescriber will monitor all of the following:~~
  - ~~Serum creatinine,~~
  - ~~Estimated creatinine clearance,~~
  - ~~Urine glucose and urine protein~~
- ~~Prescriber will assess serum phosphorus in patients with chronic kidney disease; **AND**~~
- ~~Patient does not have decompensated (Child Pugh B or C) hepatic impairment~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for BARACLUDE SOLUTION

Current Criteria:

- Diagnosis of chronic hepatitis B virus infection with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease; **AND**
- Patient is unable to swallow tablets; **AND**
- Prescriber will monitor hepatic function closely for at least several months in patients who discontinue therapy

Note: Prior authorization is not required for patients 2 through 11 years of age

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for VIREAD POWDER

Current Criteria:

- Patient has had a trial and failure, contraindication, or intolerance to 2 preferred agents; **OR**
- Patient is 6 years of age or younger and being treated for post-exposure prophylaxis (PEP)

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• entecavir	1/day
• lamivudine-HBV	1/day
• adefovir	1/day
• BARACLUDE solution	20 mL/day
• BARACLUDE tablets	1/day
• tenofovir	1/day
• *VEMLIDY*	*1/day*
• VIREAD tablets	1/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Adenfovir dipivoxil [package insert], Weston, FL: Apotex Corp.: January 2019.
- Baraclude (entecavir) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; December 2018.
- Centers for Disease Control and Prevention (CDC). The Pink Book: Hepatitis B. https://www.cdc.gov/vaccines/pubs/pinkbook/hepb.html. Updated August 18, 2021. Accessed November 20, 2023.
- DHHS guideline for the use of antiretroviral agents in adults and adolescents with HIV: Considerations for antiretroviral use in patients with coinfections. Updated September 21, 2022. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/coinfections-hepatitis-b-virus-hbv-adult-adolescent-arv.pdf. Accessed November 20, 2023.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 20, 2023.
- European Association for the Study of the Liver (EASL). EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-398. doi: 10.1016/j.jhep.2017.03.021
- Hepsera (adefovir) [prescribing information]. Foster City, CA: Gilead Sciences Inc; December 2018.
- Lok A. Hepatitis B virus: Overview of management. UpToDate Web site. www.uptodate.com. Updated July 30, 2021. Accessed November 20, 2023.
- Lok A. Hepatitis B virus: Screening and diagnosis. UpToDate Web site. www.uptodate.com. Updated April 28, 2023. Accessed November 20, 2023.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed November 20, 2023.
- Purple Book: Lists of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations. Food and Drug Administration Web site. https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or. Accessed November 20, 2023
- Tang CM, Yau TO, Yu J. Management of chronic hepatitis B infection: current treatment guidelines, challenges, and new developments. World J Gastroenterol. 2014;20(20):6262-6278.
- Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63(1):261-283.
- Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560-1599. doi: 10.1002/hep.29800.
- Vemlidy (tenofovir alafenamide) [prescribing information]. Foster City, CA: Gilead Sciences Inc; October 2022.
- Viread [package insert], Foster City, CA: Gilead Sciences, Inc.; April 2019.
- Weng MK, Doshani M, Khan MA, et al. Universal hepatitis B vaccination in adults aged 19-59 years: Updated recommendations of the advisory committee on immunization practices-United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(13):477-483.

ANTIVIRALS: HEPATITIS C ANTIVIRALS

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	
Hepatitis C Antivirals	EPCLUSA tabs [PA, QL] (sofosbuvir/velpatasvir) HARVONI tabs [PA, QL] (ledipasvir/sofosbuvir) ledipasvir/sofosbuvir [PA, QL] MAVYRET pellets [PA, QL] (glecaprevir/pibrentasvir) MAVYRET tabs [PA, QL] (glecaprevir/pibrentasvir) sofosbuvir/velpatasvir [PA, QL]	EPCLUSA pellets [PA, QL] (sofosbuvir/velpatasvir) HARVONI pellets [PA, QL] (ledipasvir/sofosbuvir) SOVALDI pellets [PA, QL] (sofosbuvir) SOVALDI tabs [PA, QL] (sofosbuvir) VOSEVI [PA, QL] (velpatasvir/voxilaprevir) ZEPATIER [PA, QL] (elbasvir/grazoprevir)

Last Review Date: February 2023

Recent Significant Changes

- The American Association for the Study of Liver Diseases and the Infectious Disease Society of America (AASLD)-IDSA: Recommendations for testing, managing, and treating hepatitis C (2023)
- Discontinued Product:
  - Viekira (2023)

Background

The hepatitis C virus (HCV) is an enveloped ribonucleic acid (RNA) virus that is primarily transmitted through exposure to infected blood (Centers for Disease Control and Prevention. The CDC estimates that 2.4 million persons in the U.S. have chronic hepatitis C (CHC). Chronic HCV infection can lead to the development of active liver disease, including cirrhosis and liver cancer. It is one of the most common indications for liver transplant. There are 6 major genotypes of HCV, numbered 1 to 6. Genotypes are further divided into subtypes, designated by a letter. In the U.S., utilizing data from the Chronic Hepatitis Cohort study, the prevalence of genotype 1, 2, 3, 4, and 6 is 75.4%, 12.6%, 10.2%, 1.5%, and 0.3%, respectively.

The primary goal of therapy for hepatitis C is eradication of the virus. Sustained virologic response (SVR), defined as a continued undetectable viral load 12 weeks after the completion of therapy, is the key surrogate virologic parameter that may indicate cure of HCV. Obtaining an SVR is associated with a 97 to 100% chance of being HCV RNA negative during long-term follow-up. Furthermore, achieving an SVR is associated with decreased mortality, rates of hepatocellular carcinoma, liver-related complications, and need for liver transplant. Thus, success at obtaining SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications.

Table 1. Medications Included Within Class Review

Drug	Generic Availability	Type of agent		
		NS5A inhibitor	NS5B polymerase inhibitor	NS3/4A protease inhibitor
EPCLUSA (sofosbuvir-velpatasvir)	✔ †	✔	✔	--
HARVONI (ledipasvir-sofosbuvir)	✔ †	✔	✔	--
MAVYRET (glecaprevir-pibrentasvir)	--	--	✔	✔
SOVALDI (sofosbuvir)	--	✔	--	--
VOSEVI (sofosbuvir-velpatasvir-voxilaprevir)	--	✔	✔	✔
ZEPATIER (elbasvir-grazoprevir)	--		✔	✔

† Authorized generics of Epclusa 400-100 mg tablets and Harvoni 90-400 mg tablets are available.

Table 2. Food and Drug Administration Approved Indications

HCV Indication by genotype	GENOTYPE					
	1	2	3	4	5	6
Epclusa (sofosbuvir-velpatasvir)	✔	✔	✔	✔	✔	✔
Harvoni (ledipasvir-sofosbuvir)	✔	--	--	✔	✔	✔
Mavyret (glecaprevir-pibrentasvir)	✔	✔	✔	✔	✔	✔
Sovaldi (sofosbuvir)	✔	✔	✔	✔	--	--
Vosevi* (sofosbuvir-velpatasvir-voxilaprevir)	✔	✔	✔	✔	✔	✔
Zepatier (elbasvir-grazoprevir)	✔	--	--	✔	--	--

* Only approved in patients with genotypes 1, 2, 3, 4, 5, or 6 with prior failure to an NS5A inhibitor-containing regimen or patients with genotypes 1a or 3 previously treated with a sofosbuvir-containing regimen without an NS5A inhibitor

In order to provide healthcare professionals with timely guidance, the AASLD and IDSA have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management. Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and duration. The guidance lists alternative regimens, which are those that are effective but have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens.

Simplified treatment is recommended for adults with any genotype of chronic HCV who do not have cirrhosis and have not previously received hepatitis C treatment. Patients not eligible for simplified treatment include those who have previously been treated, HBsAg positive, current pregnancy, known or suspected hepatocellular carcinoma, or prior liver transplantation. Additionally, patients with compensated cirrhosis must meet the same eligibility criteria and must not have current or prior episode of decompensated cirrhosis or end-stage renal disease (ie, eGFR < 30 mL/min/m2).

- For the simplified approach without cirrhosis, Epclusa or Mavyret are recommended.
- For the simplified approach in treatment-naïve patients with compensated cirrhosis, Mavyret for genotypes 1 to 6 or Epclusa for genotypes 1, 2, 4, 5, or 6 are recommended. Patients with genotype 3 require baseline NS5A resistance-associated substitution (RAS) testing. Those without Y93H can be treated with Epclusa for 12 weeks. If Y93H is present, RBV should be added, or another recommended regimen should be administered.
- For treatment-naïve genotype 1a without cirrhosis or with compensated cirrhosis population, the guidance recommends 3 different regimens considered to have comparable efficacy: Epclusa, Harvoni, and Mavyret. For genotype 1b, recommended options include Mavyret, Epclusa, Harvoni, and Zepatier.
- The guidance recommends Epclusa and Mavyret for patients with genotype 2 or 3 infection although baseline NS5A RAS testing is required for patients with genotype 3 prior to initiating Epclusa.
- The guidance recommends Epclusa, Harvoni, Mavyret, and Zepatier for treatment of genotype 4 infection.
- The guidance recommends Epclusa, Harvoni, and Mavyret for treatment of genotype 5 or 6.

The guidance provides recommendations for several unique patient populations, including patients who have failed prior therapy with DAAs, decompensated cirrhosis, recurrent HCV infection in the post-transplant setting, renal impairment, pregnancy, and children. Some key recommendations include:

- Vosevi (sometimes with RBV) is recommended for patients with or without compensated cirrhosis (any genotype) and prior failure of Zepatier or Sovaldi-based regimens (ie, Epclusa or Harvoni).
- Mavyret + Sovaldi + RBV or Vosevi (sometimes with RBV) are recommended in patients with or without compensated cirrhosis who failed Mavyret.
- Extended treatment with Vosevi + RBV or Mavyret + Sovaldi + RBV are recommended in patients with or without compensated cirrhosis (any genotype) who failed Mavyret + Sovaldi or Vosevi.
- Sovaldi-based regimens (ie, Epclusa, Harvoni) + RBV if eligible are recommended for patients with decompensated cirrhosis. Protease inhibitor-containing regimens (ie, Mavyret, Zepatier) are not recommended in patients with decompensated liver disease.
- HIV/HCV-co-infected patients should be treated and re-treated the same as patients without HIV infection, after recognizing and managing drug interactions with antiretroviral medications.

- For patients with renal impairment, the guideline states no dose adjustment is required when using recommended DAA regimens.
- For treatment-naïve kidney transplant and treatment-naïve or treatment-experienced liver transplant recipients with or without compensated cirrhosis, Harvoni (genotypes 1, 4, 5, or 6), Mavyret, or Epclusa are recommended; interactions with calcineurin inhibitors should be reviewed when selecting a regimen.
- Harvoni (genotype 1, 4, 5, or 6), Epclusa (regardless of genotype), or Mavyret (regardless of genotype) may be used in treatment-naïve or interferon-experienced children and adolescents aged 3 years and older with or without compensated cirrhosis.
- Of note, recommendations for interferon or interferon plus first generation- protease inhibitor failures have been removed from failed prior therapy section of the guidelines. The cure rates with modern DAA regimens for this population is comparable to treatment-naïve patients and should be categorized as such.

Safety Information

Mavyret is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C) or with a history of prior hepatic decompensation and when co-administered with atazanavir or rifampin. Vosevi is contraindicated in patients with rifampin co-administration. Zepatier is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) or with a history of hepatic decompensation. It is also contraindicated with organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors (ie, atazanavir, cyclosporine), strong inducers of CYP3A (ie, rifampin), and efavirenz.

The DAAs include a boxed warning for the risk of hepatitis B virus (HBV) reactivation in patients coinfected with HCV and HBV. HBV reactivation, in some cases, has resulted in fulminant hepatitis, hepatic failure, and death. Serious symptomatic bradycardia may occur in patients taking amiodarone and sofosbuvir in combination with another DAA (eg, Epclusa, Harvoni, Sovaldi, Vosevi). Coadministration of sofosbuvir with inducers (ie, St. John's wort, rifampin) may reduce sofosbuvir levels and may lead to a reduced therapeutic effect of sofosbuvir. Concomitant use of Mavyret with carbamazepine, efavirenz containing regimens, or St. John's wort may result in significantly decreased plasma concentrations of Mavyret, leading to a reduced therapeutic effect.

Overall, DAA combination therapies are well tolerated and discontinuations due to adverse events are not common. The most common adverse events observed with each treatment regimen listed below include:

- Epclusa: headache and fatigue (adults) and vomiting and product use issues (patients younger than 6 years)
- Epclusa with RBV: fatigue, anemia, nausea, headache, insomnia, adiarrhea
- Harvoni: fatigue, headache, and asthenia
- Mavyret: headache and fatigue
- Sovaldi in combination with RBV: fatigue and headache (adults); decreased appetite (pediatrics)
- Sovaldi in combination with PegIFN alfa and RBV: fatigue, headache, nausea, insomnia, and anemia
- Vosevi: headache, fatigue, diarrhea, and nausea
- Zepatier: fatigue, headache, and nausea
- Zepatier with RBV: anemia and headache

Clinical Rationale

The AASLD HCV guidelines recommend Epclusa and Mavyret for the new simplified treatment algorithm for treatment-naïve without cirrhosis chronic Hep C patients. AASLD and IDSA have developed a web-based process to address several unique patient populations which include prior failed therapy with DAA, decompensated cirrhosis, recurrent HCV infection in the post-transplant setting, renal impairment, pregnancy, and children.

Recommendation

Due to the many parameters necessary for initiating, monitoring, and evaluating treatment outcomes, it is recommended that the hepatitis C antivirals be subject to clinical criteria.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for EPCLUSA TABLET, sofosbuvir/velpatasvir

Current Criteria:

- **Diagnosis of Chronic Hepatitis C, genotype 1, 2, 3, 4, 5, and 6**
  - Patients with OR without compensated cirrhosis (Child-Pugh A) (Total duration – 12 weeks); **OR**
  - Patients with decompensated cirrhosis (Child-Pugh B or C) AND given in combination with ribavirin (Total duration – 12 weeks); **OR**
  - Patients with decompensated cirrhosis (Child-Pugh B or C) who are ribavirin ineligible (Total duration – 24 weeks); **AND**
- If patient has a history of HIV, HBV co-infection, prior history with direct acting hepatitis C antivirals, or decompensated cirrhosis, authorization is being requested by or in consultation with a physician specialist with experience in the treatment of hepatitis C infection (e.g., Hepatology, Infectious Disease, or Gastroenterology); **AND**
- Patients requiring retreatment of HCV or 2nd course of therapy with Hepatitis C Direct Acting Antiviral, requires escalation and documentation of ALL the following:
  - Current quantitative HCV RNA levels
  - Quantitative HCV RNA level measured 12 weeks after completion of previous treatment
  - Previous treatment history
  - Genotype testing from current and previous infections; **AND**
- Patient has been screened for Hepatitis B prior to treatment with any direct-acting antiviral agent for Chronic Hepatitis C

Proposed Criteria:

- One of the following:
  - **Diagnosis of Chronic Hepatitis C, Genotype 1, 2, 3 (without baseline NS5A RAS Y93H), 4, 5, and 6**
    - *Treatment naïve* patients with OR without compensated cirrhosis (Child-Pugh A) (Total duration – 12 weeks); **OR**
    - Patients with decompensated cirrhosis (Child-Pugh B or C) AND given in combination with ribavirin (Total duration – 12 weeks); **OR**
    - Patients with decompensated cirrhosis (Child-Pugh B or C) who are ribavirin ineligible (Total duration – 24 weeks); ~~**AND**~~ ***OR***
  - ***Diagnosis of Chronic Hepatitis C, Genotype 3 with baseline NS5A RAS Y93H***
    - *Treatment naïve patients with compensated cirrhosis (Child-Pugh A) AND given in combination with ribavirin (Total duration – 12 weeks);* ***AND***
- If patient has a history of HIV, HBV co-infection, prior history with direct acting hepatitis C antivirals, or decompensated cirrhosis, authorization is being requested by or in consultation with a physician specialist with experience in the treatment of hepatitis C infection (e.g., Hepatology, Infectious Disease, or Gastroenterology); **AND**
- Patients requiring retreatment of HCV or 2nd course of therapy with Hepatitis C Direct Acting Antiviral, requires escalation and documentation of ALL the following:
  - *Requested HCV treatment regimen is recommended by the AASLD/IDSA guidelines for treatment-experienced patients (https://www.hcvguidelines.org/treatment-experienced)*
  - Current quantitative HCV RNA levels
  - Quantitative HCV RNA level measured 12 weeks after completion of previous treatment
  - Previous treatment history
  - Genotype testing from current and previous infections; **AND**
- Patient has been screened for Hepatitis B prior to treatment with any direct-acting antiviral agent for Chronic Hepatitis C

Note*: Patients previously treated with one the following are considered treatment-naïve: sofosbuvir+ daclatasvir, peginterferon alfa + ribavirin, paritaprevir/ritonavir/ombitasvir/dasabuvir, and telaprevir or boceprevir + pegylated interferon, ribavirin*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for HARVONI TABLET, ledipasvir/sofosbuvir

Current Criteria:

Diagnosis of Chronic Hepatitis C, genotype 1

- Patients without cirrhosis:
  - Treatment naïve patients with documentation of pre-treatment HCV RNA < 6 million IU/mL (Total duration – 8 weeks)
  - Treatment naïve patients with documentation of pre-treatment HCV RNA > 6 million IU/mL (Total duration – 12 weeks)
  - Treatment experienced patients (defined as patients who have failed treatment with either peginterferon alfa + ribavirin or (telaprevir [Incivek®] or boceprevir [Victrelis®]) + peginterferon alfa + ribavirin **AND** documentation of positive HCV RNA) (Total duration – 12 weeks)
  - Post-liver transplant patient given in combination with ribavirin (Total duration – 12 weeks); **OR**
- Patients with compensated cirrhosis (Child-Pugh A):
  - Treatment naïve patients (Total duration – 12 weeks)
  - Treatment experienced patients (defined as patients who have failed treatment with either peginterferon + ribavirin or (telaprevir [Incivek®] or boceprevir [Victrelis®]) + peginterferon alfa + ribavirin AND documentation of positive HCV RNA) in combination with ribavirin (Total duration – 12 weeks) or if ribavirin ineligible, may take as monotherapy (Total duration - 24-weeks)
  - Post-liver transplant patient given in combination with ribavirin (Total duration – 12 weeks); **OR**
- Patients with decompensated cirrhosis (Child-Pugh B or C):
  - Given in combination with ribavirin (Total duration – 12 weeks)
  - If a prior sofosbuvir treatment failure, in combination with ribavirin (Total duration – 24 weeks)
  - If ribavirin ineligible, may take as monotherapy (Total duration – 24 weeks); **OR**

Diagnosis of Chronic Hepatitis C, genotype 4

- Post-liver transplant patient with or without cirrhosis; **AND** given in combination with ribavirin (Total duration – 12 weeks)
- Patients with decompensated cirrhosis (Child-Pugh B or C) who are ribavirin ineligible (Total duration – 24 weeks); **OR**

Diagnosis of Chronic Hepatitis C, genotype 5

- Patients with decompensated cirrhosis (Child-Pugh B or C) who are ribavirin ineligible (Total duration – 24 weeks)
- All other genotype 5 (Total duration – 12 weeks); **OR**

Diagnosis of Chronic Hepatitis C, genotype 6

- Patients with decompensated cirrhosis (Child-Pugh B or C) who are ribavirin ineligible (Total duration – 24 weeks)
- All other genotype 6 (Total duration – 12 weeks); **AND**
- If patient has a history of HIV, HBV co-infection, prior history with direct acting hepatitis C antivirals, or decompensated cirrhosis, authorization is being requested by or in consultation with a physician specialist with experience in the treatment of hepatitis C infection (e.g., Hepatology, Infectious Disease or Gastroenterology); **AND**
- Patients requiring retreatment of HCV or 2nd course of therapy with Hepatitis C Direct Acting Antiviral, requires escalation and documentation of ALL the following:
  - Current quantitative HCV RNA levels
  - Quantitative HCV RNA level measured 12 weeks after completion of previous treatment
  - Previous treatment history
  - Genotype testing from current and previous infections; **AND**
- Patient has been screened for Hepatitis B prior to treatment with any direct-acting antiviral agent for Chronic Hepatitis C

Proposed Criteria:

- One of the following:
  - **Diagnosis of Chronic Hepatitis C, genotype 1**

- Patients without cirrhosis:
  - Treatment naïve patients with documentation of pre-treatment HCV RNA < 6 million IU/mL (Total duration – 8 weeks)
  - Treatment naïve patients with documentation of pre-treatment HCV RNA > 6 million IU/mL (Total duration – 12 weeks)
  - ~~Treatment experienced patients (defined as patients who have failed treatment with either peginterferon alfa + ribavirin or (telaprevir [Incivek®] or boceprevir [Victrelis®]) + peginterferon alfa + ribavirin **AND** documentation of positive HCV RNA) (Total duration – 12 weeks)~~
    - ~~Post-~~liver *or kidney* transplant patient ~~given in combination with ribavirin~~ (Total duration – 12 weeks); **OR**
- Patients with compensated cirrhosis (Child-Pugh A):
  - Treatment naïve patients (Total duration – 12 weeks)
  - ~~Treatment experienced patients (defined as patients who have failed treatment with either peginterferon + ribavirin or (telaprevir [Incivek®] or boceprevir [Victrelis®]) + peginterferon alfa + ribavirin AND documentation of positive HCV RNA) in combination with ribavirin (Total duration – 12 weeks) or if ribavirin ineligible, may take as monotherapy (Total duration – 24 weeks)~~
  - ~~Post-~~liver *or kidney* transplant patient ~~given in combination with ribavirin~~ (Total duration – 12 weeks); **OR**
- Patients with decompensated cirrhosis (Child-Pugh B or C):
  - Given in combination with ribavirin (Total duration – 12 weeks)
  - ~~If a prior sofosbuvir treatment failure, in combination with ribavirin (Total duration – 24 weeks)~~
  - If ribavirin ineligible, may take as monotherapy (Total duration – 24 weeks); **OR**

- **Diagnosis of Chronic Hepatitis C, genotype 4, *5, 6***
  - *Treatment naïve patients with OR without compensated cirrhosis (Child-Pugh A) (Total Duration- 12 weeks)*
  - Post-liver transplant patient with or without *compensated* cirrhosis *(Child-Pugh A)*; ~~**AND** given in combination with ribavirin~~ (Total duration – 12 weeks)
  - *Patients with decompensated cirrhosis (Child-Pugh B or C)*
    - Given in combination with ribavirin (Total duration – 12 weeks)
    - ~~Patients with decompensated cirrhosis (Child-Pugh B or C) who are~~ *If* ribavirin ineligible, *may take as monotherapy* (Total duration – 24 weeks); ~~**OR** ***AND***~~
- ~~**Diagnosis of Chronic Hepatitis C, genotype 5**~~
  - ~~Patients with decompensated cirrhosis (Child-Pugh B or C) who are ribavirin ineligible (Total duration – 24 weeks)~~
  - ~~All other genotype 5 (Total duration – 12 weeks); **OR**~~
- ~~**Diagnosis of Chronic Hepatitis C, genotype 6**~~
  - ~~Patients with decompensated cirrhosis (Child-Pugh B or C) who are ribavirin ineligible (Total duration – 24 weeks)~~
  - ~~All other genotype 6 (Total duration – 12 weeks); **AND**~~

- If patient has a history of HIV, HBV co-infection, prior history with direct acting hepatitis C antivirals, or decompensated cirrhosis, authorization is being requested by or in consultation with a physician specialist with experience in the treatment of hepatitis C infection (e.g., Hepatology, Infectious Disease or Gastroenterology); **AND**
- Patients requiring retreatment of HCV or 2nd course of therapy with Hepatitis C Direct Acting Antiviral, requires escalation and documentation of ALL the following:
  - *Requested HCV treatment regimen is recommended by the AASLD/IDSA guidelines for treatment-experienced patients (https://www.hcvguidelines.org/treatment-experienced)*
  - Current quantitative HCV RNA levels
  - Quantitative HCV RNA level measured 12 weeks after completion of previous treatment
  - Previous treatment history
  - Genotype testing from current and previous infections; **AND**

- Patient has been screened for Hepatitis B prior to treatment with any direct-acting antiviral agent for Chronic Hepatitis C

Note*: Patients previously treated with one the following are considered treatment-naïve: sofosbuvir+ daclatasvir, peginterferon alfa + ribavirin, paritaprevir/ritonavir/ombitasvir/dasabuvir, and telaprevir or boceprevir + pegylated interferon, ribavirin*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for MAVYRET

Current Criteria:

Diagnosis of Chronic Hepatitis C, genotype 1

- Patients without cirrhosis:
  - Treatment naïve patients (Total authorization – 8 weeks); **OR**
  - Liver or kidney transplant recipients (Total duration – 12 weeks); **OR**
  - Treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment with an HCV NS3/4A protease inhibitor or NS5A inhibitor (Total authorization – 8 weeks); **OR**
  - Treatment-experienced with regimens containing an NS3/4A protease inhibitor without prior treatment with an NS5A inhibitor (Total duration – 12 weeks); **OR** Treatment-experienced with regimens containing an NS5A inhibitor without prior treatment with an NS3/4A protease inhibitor (Total duration – 16 weeks)
- Patients with compensated cirrhosis (Child-Pugh A):
  - Treatment naïve patients (Total duration – 8 weeks); **OR**
  - Liver or kidney transplant recipients (Total duration – 12 weeks); **OR**
  - Treatment-experienced with regimens containing a NS3/4A protease inhibitor without prior treatment with an NS5A inhibitor (Total duration – 12 weeks); **OR**
  - Treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor (Total duration – 12 weeks); **OR**
  - Treatment-experienced with regimens containing an NS5A inhibitor without prior treatment with an NS3/4A protease inhibitor (Total duration – 16 weeks)

Diagnosis of Chronic Hepatitis C, genotypes 2, 4, 5, or 6

- Patients without cirrhosis:
  - Treatment naïve patients (Total authorization 8 weeks); **OR**
  - Liver or kidney transplant recipients (Total duration – 12 weeks); **OR**
  - Treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment with an HCV NS3/4A protease inhibitor or NS5A inhibitor (Total authorization – 8 weeks); **OR**
- Patients with compensated cirrhosis (Child-Pugh A):
  - Treatment naïve patients (Total duration – 8 weeks); **OR**
  - Liver or kidney transplant recipients (Total duration – 12 weeks); **OR**
- Treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor (Total duration – 12 weeks); **OR**

Diagnosis of Chronic Hepatitis C, genotype 3

- Patients without cirrhosis
  - Treatment naïve patients (Total authorization – 8 weeks); **OR**
  - Liver or kidney transplant recipients (Total duration – 12 weeks); **OR**

- Treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor (Total duration – 16 weeks)

- Patients with compensated cirrhosis (Child-Pugh A)
  - Treatment naïve patients (Total duration – 8 weeks); **OR**
  - Liver or kidney transplant recipients (Total duration – 12 weeks); **OR**
  - Treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor (Total duration – 16 weeks); **AND**
- If patient has a history of HIV, HBV co-infection, prior history with direct acting hepatitis C antivirals, or decompensated cirrhosis, authorization is being requested by or in consultation with a physician specialist with experience in the treatment of hepatitis C infection (e.g., Hepatology, Infectious Disease or Gastroenterology); **AND**
- Patients requiring retreatment of HCV or 2nd course of therapy with Hepatitis C Direct Acting Antiviral, requires escalation and documentation of ALL the following:
  - Current quantitative HCV RNA levels
  - Quantitative HCV RNA level measured 12 weeks after completion of previous treatment
  - Previous treatment history
  - Genotype testing from current and previous infections; **AND**
- Patient has been screened for Hepatitis B prior to treatment with any direct-acting antiviral agent for Chronic Hepatitis C

Proposed Criteria:

~~**Diagnosis of Chronic Hepatitis C, genotype 1**~~

- ~~Patients without cirrhosis:~~
  - ~~Treatment naïve patients (Total authorization – 8 weeks); **OR**~~
  - ~~Liver or kidney transplant recipients (Total duration – 12 weeks); **OR**~~
  - ~~Treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment with an HCV NS3/4A protease inhibitor or NS5A inhibitor (Total authorization – 8 weeks); **OR**~~
  - ~~Treatment-experienced with regimens containing an NS3/4A protease inhibitor without prior treatment with an NS5A inhibitor (Total duration – 12 weeks); **OR** Treatment-experienced with regimens containing an NS5A inhibitor without prior treatment with an NS3/4A protease inhibitor (Total duration – 16 weeks)~~
- ~~Patients with compensated cirrhosis (Child-Pugh A):~~
  - ~~Treatment naïve patients (Total duration – 8 weeks); **OR**~~
  - ~~Liver or kidney transplant recipients (Total duration – 12 weeks); **OR**~~
  - ~~Treatment-experienced with regimens containing a NS3/4A protease inhibitor without prior treatment with an NS5A inhibitor (Total duration – 12 weeks); **OR**~~
  - ~~Treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor (Total duration – 12 weeks); **OR**~~
  - ~~Treatment-experienced with regimens containing an NS5A inhibitor without prior treatment with an NS3/4A protease inhibitor (Total duration – 16 weeks)~~

~~**Diagnosis of Chronic Hepatitis C, genotypes 2, 4, 5, or 6**~~

- ~~Patients without cirrhosis:~~
  - ~~Treatment naïve patients (Total authorization 8 weeks); **OR**~~
  - ~~Liver or kidney transplant recipients (Total duration – 12 weeks); **OR**~~
  - ~~Treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment with an HCV NS3/4A protease inhibitor or NS5A inhibitor (Total authorization – 8 weeks); **OR**~~
- ~~Patients with compensated cirrhosis (Child-Pugh A):~~

~~○ Treatment naïve patients (Total duration – 8 weeks); **OR**~~
~~○ Liver or kidney transplant recipients (Total duration – 12 weeks); **OR**~~

~~• Treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor (Total duration – 12 weeks); **OR**~~

~~**Diagnosis of Chronic Hepatitis C, genotype 3**~~

~~• Patients without cirrhosis~~
~~○ Treatment naïve patients (Total authorization – 8 weeks); **OR**~~
~~○ Liver or kidney transplant recipients (Total duration – 12 weeks); **OR**~~
~~○ Treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor (Total duration – 16 weeks)~~

~~• Patients with compensated cirrhosis (Child-Pugh A)~~
~~○ Treatment naïve patients (Total duration – 8 weeks); **OR**~~
~~○ Liver or kidney transplant recipients (Total duration – 12 weeks); **OR**~~
~~○ Treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor (Total duration – 16 weeks); **AND**~~

- If patient has a history of HIV, HBV co-infection, prior history with direct acting hepatitis C antivirals, or decompensated cirrhosis, authorization is being requested by or in consultation with a physician specialist with experience in the treatment of hepatitis C infection (e.g., Hepatology, Infectious Disease or Gastroenterology); **AND**
- Patients requiring retreatment of HCV or 2nd course of therapy with Hepatitis C Direct Acting Antiviral, requires escalation and documentation of ALL the following:
  - *Requested HCV treatment regimen is recommended by the AASLD/IDSA guidelines for treatment-experienced patients (https://www.hcvguidelines.org/treatment-experienced)*
  - Current quantitative HCV RNA levels
  - Quantitative HCV RNA level measured 12 weeks after completion of previous treatment
  - Previous treatment history
  - Genotype testing from current and previous infections; **AND**
- Patient has been screened for Hepatitis B prior to treatment with any direct-acting antiviral agent for Chronic Hepatitis C

Note*: Patients previously treated with one the following are considered treatment-naïve: sofosbuvir+ daclatasvir, peginterferon alfa + ribavirin, paritaprevir/ritonavir/ombitasvir/dasabuvir, and telaprevir or boceprevir + pegylated interferon, ribavirin*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for SOVALDI, SOVALDI PELLET

Current Criteria:

Diagnosis of Chronic Hepatitis C, genotype 1 (Total duration – 12 weeks):

- Used in combination with ribavirin and peginterferon alfa; **AND**
- Patient must have a contraindication or drug-drug interaction with two preferred agents; **AND**
- Patients must be treatment naïve to all HCV therapy (including therapies with pegylated interferon or ribavirin); **OR**
- Patient is co-infected with HIV; **OR**
- If patient has a documented contraindication to interferon:
  - May use in combination with ribavirin alone (Total duration – 24 weeks)

Diagnosis of Chronic Hepatitis C, genotype 2 (Total duration – 12 weeks):

- Treatment-naïve and treatment-experienced with or without cirrhosis (Child-Pugh A); **AND**

- Requires contraindication or drug-drug interaction with two preferred agents; **AND**
- Used in combination with ribavirin

Diagnosis of Chronic Hepatitis C, genotype 3 (Total duration – 24 weeks):

- Treatment-naïve and treatment-experienced without cirrhosis or with compensated cirrhosis (Child-Pugh A); **AND**
- Requires contraindication or drug-drug interaction with Mavyret and Epclusa; **AND**
- Used in combination with ribavirin

Diagnosis of Chronic Hepatitis C, genotype 4 (Total duration – 12 weeks):

- Patient without cirrhosis or with compensated cirrhosis (Child-Pugh A); **AND**
- Requires contraindication or drug-drug interaction with two preferred agents; **AND**
- Patients must be treatment naïve to all HCV therapy (including therapies with pegylated interferon or ribavirin); **AND**
- Used in combination with ribavirin and peginterferon alfa

Diagnosis of Hepatocellular Carcinoma awaiting liver transplant (Length of authorization: 48 weeks); **AND**

- Must be used in combination with ribavirin; **AND**
- Must meet ALL Milan criteria, defined as:
    - The presence of a tumor 5 cm or less in diameter in subjects with single hepatocellular carcinoma
    - No more than three tumor nodules, each 3 cm or less in diameter, in subjects with multiple tumors
    - No extrahepatic manifestations of the cancer and no evidence of vascular invasion of the tumor; **AND**
- If patient has a history of HIV, HBV co-infection, prior history with direct acting hepatitis C antivirals, or decompensated cirrhosis, authorization is being requested by or in consultation with a physician specialist with experience in the treatment of hepatitis C infection (e.g., Hepatology, Infectious Disease, or Gastroenterology); **AND**
- Patients requiring retreatment of HCV or 2nd course of therapy with Hepatitis C Direct Acting Antiviral, requires escalation and documentation of ALL the following:
    - Current quantitative HCV RNA levels
    - Quantitative HCV RNA level measured 12 weeks after completion of previous treatment
    - Previous treatment history
    - Genotype testing from current and previous infections; **AND**
- Patient must not be pregnant; **AND**
- Patient must not have severe renal impairment (eGFR less than 30 ml/min/1.73m2) or ESRD requiring hemodialysis; **AND**
- Patient has been screened for Hepatitis B prior to treatment with any direct-acting antiviral agent for Chronic Hepatitis C
- If request is for Sovaldi pellet, patient must be unable to swallow tablets.

Proposed Criteria:

- One of the following:
    - **Diagnosis of Chronic Hepatitis C, genotype 1 *or 4*** (Total duration – 12 weeks):
        - Used in combination with ribavirin and peginterferon alfa; **AND**
        - Patient must have a contraindication or drug-drug interaction with two preferred agents; **AND**
        - One of the following:
            - Patients must be treatment naïve to all HCV therapy (including therapies with pegylated interferon or ribavirin); **OR**
            - ~~Patient is co-infected with HIV; **OR**~~
            - If patient has a documented contraindication to interferon, may use in combination with ribavirin alone (Total duration – 24 weeks)
    - **Diagnosis of Chronic Hepatitis C, genotype 2** (Total duration – 12 weeks):
        - Treatment-naïve and treatment-experienced with or without cirrhosis (Child-Pugh A); **AND**
        - Requires contraindication or drug-drug interaction with two preferred agents; **AND**
        - Used in combination with ribavirin
    - **Diagnosis of Chronic Hepatitis C, genotype 3** (Total duration – 24 weeks):

- Treatment-naïve ~~and treatment-experienced~~ without cirrhosis or with compensated cirrhosis (Child-Pugh A); **AND**
- Requires contraindication or drug-drug interaction with Mavyret and Epclusa; **AND**
- Used in combination with ribavirin

- ~~**Diagnosis of Chronic Hepatitis C, genotype 4** (Total duration – 12 weeks):~~
  - ~~Patient without cirrhosis or with compensated cirrhosis (Child-Pugh A); **AND**~~
  - ~~Requires contraindication or drug-drug interaction with two preferred agents; **AND**~~
  - ~~Patients must be treatment naïve to all HCV therapy (including therapies with pegylated interferon or ribavirin); **AND**~~
  - ~~Used in combination with ribavirin and peginterferon alfa~~

- If patient has a history of HIV, HBV co-infection, prior history with direct acting hepatitis C antivirals, or decompensated cirrhosis, authorization is being requested by or in consultation with a physician specialist with experience in the treatment of hepatitis C infection (e.g., Hepatology, Infectious Disease, or Gastroenterology); **AND**
- Patients requiring retreatment of HCV or 2nd course of therapy with Hepatitis C Direct Acting Antiviral, requires escalation and documentation of ALL the following:
  - Requested HCV treatment regimen is recommended by the AASLD/IDSA guidelines for treatment-experienced patients (https://www.hcvguidelines.org/treatment-experienced)
  - Current quantitative HCV RNA levels
  - Quantitative HCV RNA level measured 12 weeks after completion of previous treatment
  - Previous treatment history
  - Genotype testing from current and previous infections
- ~~Patient must not be pregnant; **AND**~~
- ~~Patient must not have severe renal impairment (eGFR less than 30 ml/min/1.73m2) or ESRD requiring hemodialysis; **AND**~~
- Patient has been screened for Hepatitis B prior to treatment with any direct-acting antiviral agent for Chronic Hepatitis C; **AND**
- If request is for diagnosis of Hepatocellular Carcinoma awaiting liver transplant (Length of authorization: 48 wks), must be used in combination with ribavirin; **AND**
  - Must meet ALL Milan criteria, defined as:
    - The presence of a tumor 5 cm or less in diameter in subjects with single hepatocellular carcinoma
    - No more than three tumor nodules, each 3 cm or less in diameter, in subjects with multiple tumors
    - No extrahepatic manifestations of the cancer and no evidence of vascular invasion of the tumor; **AND**
- If request is for Sovaldi pellet, patient must be unable to swallow tablets.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for Vosevi

Current Criteria:

Diagnosis of chronic Hepatitis C, genotype 1–6 – (Total duration – 12 weeks)

- Patient without cirrhosis or with compensated cirrhosis (Child-Pugh A); **AND**
- Treatment-experienced with an NS5A inhibitor (e.g., elbasvir, ledipasvir, ombitasvir, or velpatasvir); **AND**
- Contraindication or Drug-Drug Interaction with two preferred agents; **OR**

Diagnosis of chronic Hepatitis C, genotype 1a or 3 – (Total duration – 12 weeks)

- Patient without cirrhosis or with compensated cirrhosis (Child-Pugh A); **AND**
- Treatment-experienced with sofosbuvir without an NS5A inhibitor (e.g., elbasvir, ledipasvir, ombitasvir, velpatasvir); **AND**
- Contraindication or drug-drug interaction with two preferred agents; **AND**
- If patient has a history of HIV, HBV co-infection, prior history with direct acting hepatitis C antivirals, or decompensated cirrhosis, authorization is being requested by or in consultation with a physician specialist

with experience in the treatment of hepatitis C infection (e.g., Hepatology, Infectious Disease or Gastroenterology); **AND**

- Patients requiring retreatment of HCV or 2nd course of therapy with Hepatitis C Direct Acting Antiviral, requires escalation and documentation of all the following:
  - Current quantitative HCV RNA levels
  - Quantitative HCV RNA level measured 12 weeks after completion of previous treatment
  - Previous treatment history
  - Genotype testing from current and previous infections; **AND**
- Patient is NOT co-infected with HIV; **AND**
- Patient does not have, nor has ever had, decompensated cirrhosis [Child-Pugh score greater than 6 (class B or C)]; **AND**
- Patient has been screened for Hepatitis B prior to treatment with any direct-acting antiviral agent for Chronic Hepatitis C

Proposed Criteria:

- **Diagnosis of chronic Hepatitis C, genotype 1–6 –** ~~(Total duration – 12 weeks)~~
  - *One of the following:*
    - *Sofosbuvir- based treatment failures, with or without compensated* cirrhosis *(Total duration – 12 weeks)*
    - *Glecaprevir/Pibrentasvir treatment failure with or without compensated cirrhosis (Total duration – 12 weeks)*
    - *Multiple Direct-Acting Antiviral (DAA) treatment failures in combination with weight-based ribavirin (Total duration- 24 weeks)*
  - ~~Patient without cirrhosis or with compensated cirrhosis (Child-Pugh A);~~ ~~**AND**~~
  - ~~Treatment-experienced with an NS5A inhibitor (e.g., elbasvir, ledipasvir, ombitasvir, velpatasvir);~~ ~~**AND**~~
  - ~~Contraindication or Drug-Drug Interaction with two preferred agents;~~ ~~**OR**~~
- ~~**Diagnosis of chronic Hepatitis C, genotype 1a or 3 –**~~ ~~(Total duration – 12 weeks)~~
  - ~~Patient without cirrhosis or with compensated cirrhosis (Child-Pugh A);~~ ~~**AND**~~
  - ~~Treatment-experienced with sofosbuvir without an NS5A inhibitor (e.g., elbasvir, ledipasvir, ombitasvir, velpatasvir);~~ ~~**AND**~~
  - ~~Contraindication or drug-drug interaction with two preferred agents;~~ ~~**AND**~~
- If patient has a history of HIV, HBV co-infection, prior history with direct acting hepatitis C antivirals, or decompensated cirrhosis, authorization is being requested by or in consultation with a physician specialist with experience in the treatment of hepatitis C infection (e.g., Hepatology, Infectious Disease or Gastroenterology); **AND**
- Patients requiring retreatment of HCV or 2nd course of therapy with Hepatitis C Direct Acting Antiviral, requires escalation and documentation of all the following:
  - *Requested HCV treatment regimen is recommended by the AASLD/IDSA guidelines for treatment-experienced patients (https://www.hcvguidelines.org/treatment-experienced)*
  - Current quantitative HCV RNA levels
  - Quantitative HCV RNA level measured 12 weeks after completion of previous treatment
  - Previous treatment history
  - Genotype testing from current and previous infections; **AND**
- ~~Patient is NOT co-infected with HIV;~~ ~~**AND**~~
- Patient does not have~~, nor has ever had,~~ decompensated cirrhosis [Child-Pugh score greater than 6 (class B or C)]; **AND**
- Patient has been screened for Hepatitis B prior to treatment with any direct-acting antiviral agent for Chronic Hepatitis C

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for ZEPATIER

Current Criteria:

Diagnosis of Chronic Hepatitis C, genotype 1 (Total duration – 12 weeks);

- **Genotype 1a without NS5A polymorphism:**
  - Patient treatment naïve to all HCV therapy (including previous therapies with pegylated interferon or ribavirin); **OR**
  - Patient failed prior treatment with peginterferon alfa + ribavirin; **AND**
  - Patient must have a contraindication or drug-drug interaction with two preferred agents; **OR**
- **Genotype 1b:**
  - Patient treatment naïve to all HCV therapy (including previous therapies with pegylated interferon or ribavirin); **OR**
  - Patient failed prior treatment with peginterferon alfa + ribavirin; **AND**
  - Patient must have a contraindication or drug-drug interaction with two preferred agents; **OR**
- **Genotype 1a or 1b:**
  - Patient failed prior therapy with peginterferon alfa + ribavirin + HCV NS3/4A protease inhibitor (e.g., boceprevir, telaprevir, or simeprevir); **AND**
  - Used in combination with ribavirin; **AND**
  - Patient must have a contraindication or drug-drug interaction with two preferred agents; **OR**

Diagnosis of Chronic Hepatitis C, genotype 1a WITH NS5A polymorphism (Total duration – 16 weeks);

- Patient treatment naïve to all HCV therapy (including therapies with pegylated interferon or ribavirin); **OR**
- Patient failed prior treatment with peginterferon alfa + ribavirin; **AND**
- Used in combination with ribavirin; **AND**
- Patient must have a contraindication or drug-drug interaction with two preferred agents; **OR**

Diagnosis of Chronic Hepatitis C, genotype 4 (Total duration – 12 weeks)

- Patient treatment naïve to all HCV therapy (including therapies with pegylated interferon or ribavirin); **AND**
- Requires contraindication or drug-drug interaction with two preferred agents; **OR**

Diagnosis of Chronic Hepatitis C, genotype 4 (Total duration – 16 weeks)

- Patient failed prior treatment with peginterferon alfa + ribavirin; **AND**
- Used in combination with ribavirin; **AND**
- Patient must have a contraindication or drug-drug interaction with two preferred agents; **AND**
- If patient has a history of HIV, HBV co-infection, prior history with direct acting hepatitis C antivirals, or decompensated cirrhosis, authorization is being requested by or in consultation with a physician specialist with experience in the treatment of hepatitis C infection (e.g., Hepatology, Infectious Disease or Gastroenterology); **AND**
- Patients requiring retreatment of HCV or 2nd course of therapy with Hepatitis C Direct Acting Antiviral, approval requires:
  - Current quantitative HCV RNA levels
  - Quantitative HCV RNA level measured 12 weeks after completion of previous treatment
  - Previous treatment history
  - Genotype testing from current and future infections; **AND**
- Patient does not have decompensated cirrhosis (defined as a Child-Pugh score > 6 [class B or C]); **AND**
- Patient has been screened for Hepatitis B prior to treatment with any direct-acting antiviral agent for Chronic Hepatitis C

Proposed Criteria:

- One of the following:
  - **Diagnosis of Chronic Hepatitis C, genotype 1*a* without NS5A polymorphism, genotype 1b, genotype 4** (Total duration – 12 weeks);
    - *Patient must have a contraindication or drug-drug interaction with two preferred agents*
  - ~~**Genotype 1a without NS5A polymorphism:**~~
    - ~~Patient treatment naïve to all HCV therapy (including previous therapies with pegylated interferon or ribavirin); **OR**~~

- ~~Patient failed prior treatment with peginterferon alfa + ribavirin; **AND**~~
- ~~Patient must have a contraindication or drug-drug interaction with two preferred agents; **OR**~~

- ~~**Genotype 1b:**~~
  - ~~Patient treatment naïve to all HCV therapy (including previous therapies with pegylated interferon or ribavirin); **OR**~~
  - ~~Patient failed prior treatment with peginterferon alfa + ribavirin; **AND**~~
  - ~~Patient must have a contraindication or drug-drug interaction with two preferred agents; **OR**~~
- ~~**Genotype 1a or 1b:**~~
  - ~~Patient failed prior therapy with peginterferon alfa + ribavirin + HCV NS3/4A protease inhibitor (e.g., boceprevir, telaprevir, or simeprevir); **AND**~~
  - ~~Used in combination with ribavirin; **AND**~~
  - ~~Patient must have a contraindication or drug-drug interaction with two preferred agents; **OR**~~
- **Diagnosis of Chronic Hepatitis C, genotype 1a WITH NS5A polymorphism** (Total duration – 16 weeks);
  - ~~Patient treatment naïve to all HCV therapy (including previous therapies with pegylated interferon or ribavirin); **OR**~~
  - ~~Patient failed prior treatment with peginterferon alfa + ribavirin; **AND**~~
  - ~~Used in combination with ribavirin; **AND**~~
  - Patient must have a contraindication or drug-drug interaction with two preferred agents; **OR**
- ~~**Diagnosis of Chronic Hepatitis C, genotype 4** (Total duration – 12 weeks)~~
  - ~~Patient treatment naïve to all HCV therapy (including previous therapies with pegylated interferon or ribavirin); **AND**~~
  - ~~Requires contraindication or drug-drug interaction with two preferred agents; **OR**~~
- **Diagnosis of Chronic Hepatitis C, genotype 4** (Total duration – 16 weeks)
  - Patient failed prior treatment with peginterferon alfa + ribavirin; **AND**
  - ~~Used in combination with ribavirin; **AND**~~
  - Patient must have a contraindication or drug-drug interaction with two preferred agents; **AND**

- If patient has a history of HIV, HBV co-infection, prior history with direct acting hepatitis C antivirals, or decompensated cirrhosis, authorization is being requested by or in consultation with a physician specialist with experience in the treatment of hepatitis C infection (e.g., Hepatology, Infectious Disease or Gastroenterology); **AND**
- Patients requiring retreatment of HCV or 2nd course of therapy with Hepatitis C Direct Acting Antiviral, approval requires:
  - *Requested HCV treatment regimen is recommended by the AASLD/IDSA guidelines for treatment-experienced patients (https://www.hcvguidelines.org/treatment-experienced)*
  - Current quantitative HCV RNA levels
  - Quantitative HCV RNA level measured 12 weeks after completion of previous treatment
  - Previous treatment history
  - Genotype testing from current and future infections; **AND**
- Patient does not have decompensated cirrhosis (defined as a Child-Pugh score > 6 [class B or C]); **AND**
- Patient has been screened for Hepatitis B prior to treatment with any direct-acting antiviral agent for Chronic Hepatitis C

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for MAVYRET PELLET

Current Criteria:

- See MAVYRET prior authorization criteria; **AND**
- Patient is unable to swallow tablets

Proposed Criteria:
Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for EPCLUSA PELLET

Current Criteria:
- See EPCLUSA prior authorization criteria; **AND**
- Patient is unable to swallow tablets

Proposed Criteria:
Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for HARVONI PELLET

Current Criteria:
- See HARVONI prior authorization criteria; **AND**
- Patient is unable to swallow tablets

Proposed Criteria:
Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• EPCLUSA tablet	1/day
• HARVONI tablet	1/day
• ledipasvir/sofosbuvir	1/day
• MAVYRET	3/day
• MAVYRET pellet	5/day
• sofosbuvir/velpatasvir	1/day
• EPCLUSA pellet 150mg	1/day
• EPCLUSA pellet 200mg	2/day
• HARVONI pellet	1 pak/28 days
• SOVALDI	1/day
• SOVALDI PAK	1 pak/28 days
• VOSEVI	1/day
• ZEPATIER	1/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. Updated December 19, 2023. http://www.hcvguidelines.org. Accessed December 29, 2023
- Centers for Disease Control and Prevention. Hepatitis C FAQs for Health Professionals. Updated October 31, 2023. https://www.cdc.gov/hepatitis/HCV/HCVfaq.htm. Accessed November 15, 2023.

- Chen J, Florian J, Carter W, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology. 2013;144:1450-1455.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf. Accessed November 15, 2023.
- Epclusa (sofosbuvir/velpatasvir) [prescribing information]. Foster City, CA: Gilead Sciences Inc; April 2022.
- Gordon SC, Trudeau S, Li J, et al. Race, age, and geography impact hepatitis C genotype distribution in the United States. J Clin Gastroenterol. 2019;53(1):40-50. doi:10.1097/MCG.0000000000000872.
- Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61(1 Suppl):S45-57.
- Harvoni (ledipasvir/sofosbuvir) [prescribing information]. Foster City, CA: Gilead Sciences Inc; March 2020.
- Mavyret (glecaprevir/pibrentasvir) [prescribing information]. North Chicago, IL: AbbVie Inc; September 2021.
- Sovaldi (sofosbuvir) [prescribing information]. Foster City, CA; Gilead Sciences Inc; March 2020.
- United State Preventive Services Task Force. Screening for hepatitis C virus infection in adolescents and adults: US preventive services task force recommendation statement. JAMA. 2020;323:970-975. doi:10.1001/jama.2020.1123.
- Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabuvir) [prescribing information]. North Chicago, IL: AbbVie Inc; December 2019.
- Vosevi (sofosbuvir, velpatasvir, voxilaprevir) [prescribing information]. Foster City, CA: Gilead Sciences Inc; November 2019.
- Zepatier (elbasvir and grazoprevir) [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; January 2022.

HIV General Overview

Re-Review: Pharmacy Initiatives

Last Review Date: February 2022

Recent Significant Changes

- Department of Health and Human Services (DHHS) Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2023)
- DHHS Guidelines for the Use of ARV Agents in Pediatric HIV Infection (2023)
- DHHS Recommendations for the Use of ARV Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States (2023)
- US Preventative Services Task Force (USPSTF)**:** Preexposure Prophylaxis (PreP) to Prevent Acquisition of HIV (2023)

Background

Human immunodeficiency virus (HIV) infects cells expressing cluster of differentiation 4 (CD4) receptors, such as T-helper lymphocytes, monocytes, macrophages, dendritic cells, and brain microglia. HIV is characterized by a progressive decline in CD4 cell count, leading to the development of severe immunosuppression which increases the risk for infectious diseases caused by opportunistic pathogens. In 2019, there were approximately 1.2 million persons aged ≥ 13 years with HIV-1 infection in the United States (US), including an estimated 158,500 people whose infections had not been diagnosed.

Pre-exposure prophylaxis (PrEP) is highly effective at preventing individuals from acquiring HIV, when taken as prescribed. PrEP reduces the risk of acquiring HIV from sex by about 99% and from injection drug use by at least 74%. PrEP is less effective when not taken as prescribed. Since PrEP only protects against HIV, condom use is still important for the protection against other sexually transmitted diseases. The key to HIV prevention is education, condom use and clean syringe access, reducing stigma, and adherence. Reducing barriers are essential to HIV prevention. Should individuals acquire HIV, detection is important to promote appropriate access to antiretroviral (ARV) treatment and to minimize resistance.

Should an individual acquire HIV, the goal of antiretroviral therapy (ART) is multifaceted. Treatment should be continued to maximally suppress plasma HIV, restore, and preserve immunologic function, prevent transmission, reduce HIV-associated morbidity and mortality, and prolong the duration or quality of survival. Currently, ART is considered lifelong. The recommendations for initial treatment of HIV usually include a minimum of 3 ARV agents: 1 “anchor” drug and 2 “backbone” drugs. The backbone is usually 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). The anchor can be a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI). In adults, some 2 drug regimens have also demonstrated efficacy. There is an increased risk for HIV to select for ARV-resistant variants. Therefore, individuals should be tested for susceptibility via genotypic (preferred) or phenotypic resistance testing at treatment entry and when virologic failure occurs.

More than 30 medications in 6 classes are Food and Drug Administration (FDA)-approved for treatment of HIV infection. Drug classes that are active against the HIV virus include the NRTIs, NNRTIs, PIs, INSTIs, and the entry inhibitors (including a fusion inhibitor, CC chemokine receptor 5 [CCR5] inhibitor, post-attachment or CD4 inhibitor, and a gp120 attachment inhibitor). In addition, 2 drugs, ritonavir (RTV or r) and cobicistat (COBI or c), are used solely as pharmacokinetic (PK) enhancers to improve the PK profiles of some ARV drugs.

Table 1: Antiretroviral Agents

Drug	Abbreviation
Attachment Inhibitors	
fostemsavir	FTR
Capsid Inhibitors	
lenacapavir	LEN
CC Chemokine Receptor 5 (CCR5) Antagonists	
maraviroc	MVC
Fusion Inhibitors	
enfuvirtide	T-20
Integrase Inhibitors	
bictegravir	BIC
dolutegravir	DTG
raltegravir	RAL
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
efavirenz	EFV
etravirine	ETR
doravirine	DOR
nevirapine	NVP
rilpivirine	RPV
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
abacavir	ABC
didanosine	ddI
emtricitabine	FTC
lamivudine	3TC
stavudine	d4T
tenofovir alafenamide	TAF
tenofovir disoproxil fumarate	TDF
zidovudine	ZDV
Protease Inhibitors (PI)	
atazanavir	ATV
darunavir	DRV
fosamprenavir	FPV
nelfinavir	NFV
tipranavir	TPV

DHHS Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2023)

This guideline recommends ART for all individuals with HIV, regardless of CD4 T lymphocyte cell count, and initiated as soon as possible after HIV diagnosis. The goals of treatment are to maximally suppress plasma HIV-1 RNA and maintain a durable response, restore/preserve immunologic function, reduce the morbidity and mortality associated with HIV, prevent HIV transmission, prolong the duration or quality of survival. Viral suppression is achieved in those expressing less than 200 copies/mL. Initial treatment of HIV usually should include a minimum of 3 antiretroviral (ARV) agents: 1 “anchor” drug and 2 “backbone” drugs. The backbone is usually 2 NRTIs. The anchor can be a NNRTI, a boosted PI, or an INSTI. In adults, some 2 drug regimens have also demonstrated efficacy.

Recommended preferred initial regimens for most people with HIV include:

- INSTI plus 2 NRTIs
  - BIC/TAF/FTC
  - DTG/ABC/3TC—if HLA-B*5701 negative
  - DTG plus (TAF or TDF) plus (FTC or 3TC)

- INSTI plus 1 NRTI
  - DTG/3TC, except for individuals with HIV-1 RNA > 500,000 copies/mL, HBV coinfection or in individuals in whom ART is to be started before results of resistance testing or HBV testing are available.

Selection of a regimen should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug–drug interaction potential, resistance-test results, comorbid conditions, and access. Although guidelines recommend INSTI anchored regimens for most patients, NNRTIs and boosted PIs can be used as initial regimens in certain clinical situations and prescribers are encouraged to use their clinical judgement.

TAF and TDF are 2 forms of tenofovir approved by FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. FTC and 3TC are considered interchangeable in combination with other ARV drugs. ABC should not be used in patients who test positive for HLA-B*5701 because of the risk of developing a hypersensitivity reaction (HSR).

There are some special considerations specific to individuals with HBV co-infection. Before initiation of ART, all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for HBV deoxyribonucleic acid (DNA) using a quantitative assay to determine the level of HBV replication. NRTIs including FTC, 3TC, TDF, and TAF have activity against both HIV and HBV. Therefore, an ART regimen for individuals with HIV/HBV coinfection should include TAF or TDF plus 3TC or FTC as the NRTI backbone of a fully suppressive regimen.

DHHS Guidelines for the Use of ARV Agents in Pediatric HIV Infection (2023)

This guideline recommends that ART be initiated in all infants and children with HIV infection. For treatment-naive children, the guideline recommends initiating ART with 3 drugs: a dual-NRTI backbone plus an INSTI, a NNRTI, or a boosted PI. In treatment-naïve children living with HIV, ART should be initiated in all infants and children with HIV infection, otherwise known as rapid ART initiation (defined as initiating ART immediately or within days of diagnosis). Treatment initiation in young infants with HIV during the early stages of HIV infection may control viral replication before HIV can evolve into diverse and potentially more pathogenic quasi-species. Early therapy also preserves immune function, preventing clinical disease progression.

ZDV plus 3TC or FTC is recommended as a preferred dual-NRTI combination for infants and children from birth to age ≤1 month and as an alternative combination in children aged ≥ 1 month and adolescents. ABC plus 3TC or FTC is recommended as the preferred dual-NRTI combination for children aged ≥ 3 months. FTC/TAF is recommended as a preferred dual-NRTI combination in children and adolescents weighing ≥ 25 kg who have estimated CrCL ≥ 30 mL/min when this combination is used with an INSTI or NNRTI. In addition, this combination is considered a preferred dual-NRTI combination when used with a PI in children and adolescents weighing ≥ 35 kg who have estimated CrCL ≥ 30 mL/min.

Table 2: Preferred Initial Pediatric Regimens

Infants, birth to age < 14 days	
Weight ≥ 2 kg	2 NRTIs plus RAL
Weight not specified	2 NRTIs plus NVP
Neonates ≥ 14 days to age < 4 weeks	
Weight ≥ 2 kg	2 NRTIs plus RAL
Weight ≥ 2 kg	2 NRTIs plus lopinavir (LPV)/r
Infants and children age ≥ 4 weeks to < 6 years	
Weight ≥ 3 kg	2 NRTIs plus DTG
Children age ≥ 6 years	
Weight ≥ 25 kg	2 NRTIs plus BIC (the FDA has recently approved use in ≥ 14 kg)
Weight ≥ 25 kg	2 NRTIs plus DTG
Adolescents aged ≥ 12 years with sexual maturity rating (SMR) 4 to 5	
Refer to adult and adolescent ARV guidelines (previously summarized above)	

Treatment advantages and disadvantages of NRTIs in children include:

- ABC + (3TC or FTC)
  - Advantages: Palatable liquid formulations, can take with food, and a 1 tablet combination.
  - Disadvantages: Risk of ABC HSRs; perform HLA-B*5701 screening before initiation of ABC.
- FTC/TAF
  - Advantages: Once daily dosing, small tablet, lower risk of renal and bone toxicity with TAF vs TDF in adults, and a 1 tablet combination.
  - Disadvantages: Limited data for this combination in children and increased lipid levels.
- TDF + (3TC or FTC)
  - Advantages: Once daily dosing, resistance is slow to develop, lower risk of mitochondrial toxicity than other NRTIs, can take with food, available as reduced-strength tablet and oral powder for use in younger children, and a 1 tablet combination.
  - Disadvantages: Limited pediatric experience, potential bone and renal toxicity, and numerous drug-drug interactions with other ARV agents (i.e., LPV/r, ATV, and TPV).
- ZDV + (3TC or FTC)
  - Advantages: Extensive pediatric experience, co-formulations of ZDV and 3TC are available for children weighing ≥ 30 kg, palatable liquid formulations, can take with food, FTC is available as a palatable liquid formulation that can be administered once daily.
  - Disadvantages: Bone marrow suppression and lipoatrophy with ZDV
- ZDV + ABC
  - Advantages: Palatable liquid formulations, and can take with food
  - Disadvantages: Risk of ABC HSRs; perform HLA-B*5701 screening before initiation of ABC, bone marrow suppression, and lipoatrophy with ZDV.

DHHS Recommendations for the Use of ARV Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States (2023)

This guideline recommends that all pregnant women with HIV should initiate ART as early in pregnancy as possible, regardless of their HIV RNA level or CD4 cell count, to maximize their health and prevent perinatal HIV transmission and secondary sexual transmission. Women with HIV should maintain an HIV viral load that is below the limit of detection during pregnancy, postpartum, and throughout their lives. Currently, DTG[INSTI] and DRV/r [boosted PI] plus 2 NRTI are the preferred regimens for pregnant people who have never received ART. Neonates should receive antiretroviral prophylaxis or presumptive HIV therapy appropriate to their risk of perinatal HIV acquisition.

DHHS Recommendations for the Management of Treatment-Experienced Patients with HIV Infection

Assessing and managing patients with ART failure can be complex and should include evaluation of ART adherence, drug-drug and food-drug interactions, drug tolerability, HIV-RNA levels, CD4 cell count trends, ART history, and drug-resistance test results. Virologic failure is defined as the inability to achieve or maintain suppression of viral replication to HIV-1 RNA levels ≤ 200 copies/mL.

As in initial therapy, the goal for treat-experienced patients is to achieve virological suppression. A new regimen should include two fully active ARV drugs, with at least one with a high resistance barrier (e.g., dolutegravir). In cases where there is multiple or extensive drug resistance with few treatment options, drugs with novel mechanism of action (e.g., attachment inhibitor fostemsavir (FTR), the capsid inhibitor lenacapavir (LEN), the fusion inhibitor enfuvirtide (T-20), or the CCR5 antagonist maraviroc (MVC)) are recommended. The long-acting ARV combination of injectable cabotegravir (CAB) and RPV is not recommended. In some rare highly ART-experienced patients, maximized virologic suppression may not be possible, but is still important for the patient to continue therapy.

USPSTF: Preexposure Prophylaxis (PrEP) to Prevent Acquisition of HIV (2023)

The USPSTF performed an assessment of the magnitude of the net benefit of PrEP, and concluded with high certainty that there is a substantial net benefit from the use of effective ART to reduce the risk of HIV acquisition in individuals at increased risk of acquiring HIV. The USPSTF recommends that the following persons be considered for PrEP since they are at increased risk of acquiring HIV:

- Sexually active adults and adolescents weighing ≥ 35 kg who have engaged in anal or vaginal sex in the past 6 months and have any of the following:
  - A sexual partner with HIV (especially if the partner has an unknown or detectable viral load)
  - A bacterial STD in the past 6 months
  - A history of inconsistent or no condom use with sex partner(s) whose HIV status is unknown
- Individuals who inject drugs and share injection equipment or have a drug-injecting partner with HIV
- The agents that are currently available for PrEP include:
- Oral TDF/FTC and injectable CAB: FDA-approved for use in at-risk adults and adolescents weighing ≥ 35 kg to reduce the risk of sexually acquired HIV
- Oral TAF/FTC: FDA-approved for use in at-risk adults and adolescents weighing ≥ 35 kg to reduce the risk of sexually acquired HIV, excluding those at risk from receptive vaginal sex
- Per the CDC, individuals who inject drugs are likely to benefit with any FDA-approved PrEP medication.

CDC: US Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis (2018)

Start postexposure prophylaxis (PEP) medication regimens as soon as possible after occupational exposure to HIV and continue them for a 4-week duration. PEP regimens should contain 3 (or more) ARV drugs. The preferred PEP regimen is TDF/FTC plus RAL.

CDC: US Public Health Service Guidelines for ARV Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Non-Occupational Exposure to HIV (2018)

A 28-day course of non-occupational post exposure prophylaxis (nPEP) is recommended for HIV-uninfected persons who seek care ≤ 72 hours after a non-occupational exposure to blood, genital secretions, or other potentially infected body fluids of persons known to be HIV infected or of unknown HIV status when that exposure represents a substantial risk for HIV acquisition. PEP regimens should contain 3 (or more) ARV drugs Preferred ARV nPEP regimens:

- Adults and adolescents aged ≥ 13 years, including pregnant women, with normal renal function:
  - TDF/FTC (Truvada) or TAF/FTC (Descovy) plus RAL or DTG (Tivicay); OR
  - BIC/TAF/FTC (Biktarvy)
- Adults and adolescents aged ≥ 13 years with renal dysfunction (CrCL < 59 mL/min): ZDV/3TC (renally dose adjusted) plus RAL or DTG
- Children aged 2 to 12 years: TDF/3TC plus RAL
- Children aged 4 weeks to < 2 years: ZDV/3TC (oral solutions) plus RAL or LPV/r (oral solutions)

References

- Anderson PL, Brooks KM, Fletcher CV. Chapter 148: Human immunodeficiency virus infection. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey M, editors. Dipiro's Pharmacotherapy: A Pathophysiologic Approach, 12th edition. McGraw-Hill, 2023.
- Centers for Disease Control and Prevention (CDC). HIV Surveillance Report. Updated August 10, 2022[a]. https://www.cdc.gov/hiv/statistics/overview/index.html. Accessed November 7, 2023.
- CDC. Pre-Exposure Prophylaxis (PrEP). Updated July 5, 2022[b]. https://www.cdc.gov/hiv/risk/prep/index.html. Accessed November 7, 2023.
- CDC. US Public Health Service Preexposure Prophylaxis for The Prevention Of HIV Infection in the United States – 2021 Update. 2021. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. Accessed November 7, 2023.
- CDC. US Public Health Service. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. Updated May 23, 2018[a]. Website. https://stacks.cdc.gov/view/cdc/20711. Accessed November 7, 2023.
- CDC. US Public Health Service. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV. Updated May 23, 2018[b]. Website. https://stacks.cdc.gov/view/cdc/38856. Accessed November 7, 2023.

- DHHS panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Updated March 23, 2023[a]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed November 7, 2023.
- DHHS panel on antiretroviral therapy and medical management of children living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Updated April 11, 2023[b]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf. Accessed November 7, 2023.
- DHHS panel on treatment of HIV during pregnancy and prevention of perinatal transmission. Recommendations for the use of antiretroviral drugs during pregnancy and interventions to reduce perinatal HIV transmission in the United States. Updated January 31, 2023[c]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/perinatal-hiv/guidelines-perinatal.pdf. Accessed November 7, 2023.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 7, 2023.
- Hsu KK, Rakhmanina NY; for the Committee on Pediatric AIDS for the American Academy of Pediatrics (AAP). Adolescents and young adults: the pediatrician's role in HIV testing and pre- and postexposure HIV prophylaxis. Pediatrics. 2022 Jan 1;149(1):e2021055207.
- *Non-Occupational Post-Exposer HIV Prevention*. AIDS Education and Training Centers Program. November 2021. https://aidsetc.org/sites/default/files/resources_files/AETC-nPEP-guide-111721.pdf
- US Preventive Services Task Force, Barry MJ, Nicholson WK, et al. Preexposure Prophylaxis to Prevent Acquisition of HIV: US Preventive Services Task Force Recommendation Statement. JAMA. 2023;330(8):736-745.
- Wood BR. The natural history and clinical features of HIV infection in adults and adolescents. UpToDate. Website. Updated February 15, 2023. https://www.uptodate.com/contents/the-natural-history-and-clinical-features-of-hiv-infection-in-adults-and-adolescents. Accessed November 7, 2023.

ANTIVIRALS: HIV INTEGRASE INHIBITORS

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
HIV Integrase Inhibitors	ISENTRESS ~~PA~~, QL (raltegravir) TIVICAY ~~PA~~, QL (dolutegravir) TIVICAY PD PA, QL (dolutegravir)	ISENTRESS HD PA, QL (raltegravir) JULUCA PA, QL (dolutegravir/rilpivirine)

Last Review Date: February 2022

Recent Significant Changes

- Department of Health and Human Services (DHHS) Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2023)
- DHHS Guidelines for the Use of ARV Agents in Pediatric HIV Infection (2023)
- DHHS Recommendations for the Use of ARV Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States (2023)

Background (see HIV General Overview for further details)

Integrase strand transfer inhibitors (INSTIs) are one of the preferred anchor drug regimens for treatment-naïve adults. The INSTIs are divided into first generation INSTIs, which have a lower genetic barrier to resistance and include raltegravir (RAL) and elvitegravir (EVG). There is a high level of cross-resistance between RAL and EVG. The second generation INSTIs, which have a higher genetic barrier to resistance, include bictegravir (BIC) and dolutegravir (DTG). BIC and EVG are only available in combination products (e.g., Biktarvy, Genvoya, Stribild) and are not included in this review. See "Antivirals: HIV NRTI Combos" for information on those products. Most INSTIs are available in multiple drug formulations called single table regimens (STR) or complete regimens.

Table 1. Medications Included Within Class Review

Drug	Abbreviation	Generic Availability
ISENTRESS (raltegravir)	RAL	--
TIVICAY (dolutegravir)	DTG	--
JULUCA (dolutegravir/rilpivirine)	DTG/RPV	--

Table 2. FDA Approved Indications

	ISENTRESS; ISENTRESS HD	TIVICAY; TIVICAY PD	JULUCA
In combination with other ARV agents for the treatment of HIV-1 in adults and pediatric patients	✔	✔	
In combination with RPV as a complete regimen for the treatment of HIV-1 infection in adults to replace the current ARV regimen in those who are virologically suppressed (< 50 copies/mL) on a stable ARV regimen (with no history of treatment failure) for at least 6 months		✔	
Treatment Experienced: to replace the current ARV regimen in those who are virologically suppressed (< 50 copies/mL) on a stable ARV regimen			✔ ^

^ Stable regimen defined as no history of treatment failure

RAL and DTG may cause severe hypersensitivity reactions with rash, hepatotoxicity, embryo-fetal toxicity (eg, neural tube defects, which may occur when used at the time of conception and in early pregnancy), and immune reconstitution syndrome when treated with combination ARV. Pregnancy testing is recommended prior to starting a DTG-containing regimen, as is consistent use of effective contraception for adolescents and adults of

child-bearing potential during treatment. There is a warning for depressive disorders with use of RPV- or DTG-containing regimens (Juluca). Severe, potentially life-threatening, and fatal skin reactions, immune reconstitution syndrome. The most common (≥ 2%) adverse events (AEs) with RAL were insomnia, headache, dizziness, nausea, and fatigue. Other AE's include creatinine kinase elevations, myopathy, and rhabdomyolysis. The most common AEs (≥ 2%) with DTG were insomnia, fatigue, and headache.

RAL has interactions with drugs that are strong inducers of UGT1A1, such as rifampin, which may decrease RAL concentrations. DTG has drug interactions with metabolic inducers. DTG use with dofetilide is contraindicated due to the risk of increased concentrations of dofetilide which has been associated with serious or life-threatening events (e.g., torsades de pointes). RPV use is contraindicated with drugs that may significantly decrease RPV plasma concentrations, resulting in loss of viral response.

Clinical Rationale

INSTI based regimens are the preferred ARV regimen for children and adults living with HIV due to virologic potency, higher barrier to resistance, and availability in multiple drug formulations called single tablet regimens (STR) or complete regimens. Single use formulations are available for patients who cannot administer or tolerate the STR formulations.

Recommendation

It is recommended that the integrase inhibitors be available for use. ~~subject to prior authorization criteria to ensure use with other antiretroviral (ARV) therapy~~. Additionally, formulations should be available for pediatric patients or those patients who cannot swallow.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for Isentress

Current Criteria:

- Verification that agent will be administered in combination with other antiretroviral agents; **AND**
- Patient is monitored for fatal skin reactions (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis) and immune reconstitution syndrome; **AND**
- Patient does not have phenylalanine hydroxylase deficiency or phenylketonuria (Isentress chewables only)

Proposed Criteria:

Remove PA Criteria

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for Tivicay

Current Criteria:

- Verification that agent will be administered in combination with other antiretroviral agents; **AND**
- Patient will not concurrently take with dofetilide
-

Proposed Criteria:

Remove PA Criteria

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for TIVICAY PD

Current Criteria:

- Verification that it will be administered in combination with other antiretroviral agents; **AND**
- Patient will not concurrently take with dofetilide; **AND**
- Patient is ≤ 6 years of age or there is a clinically valid reason why the patient cannot use Tivicay tablets

Proposed Criteria:

- ~~Verification that it will be administered in combination with other antiretroviral agents; **AND**~~
- ~~Patient will not concurrently take with dofetilide; **AND**~~
- *Patient meets ONE of the following:*
  - Patient is ≤ 6 years of age ~~or there is a~~
  - *Patient is unable to swallow solid dosage forms*
  - Clinically valid reason why the patient cannot use Tivicay tablets

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for ISENTRESS HD

Current Criteria:

- Diagnosis of an FDA-approved indication; **AND**
- Verification that agent will be administered in combination with other antiretroviral agents; **AND**
- Patient is monitored for fatal skin reactions (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis) and immune reconstitution syndrome; **AND**
- Clinically valid reason why the patient cannot use the preferred agents

Proposed Criteria:

- ~~Diagnosis of an FDA-approved indication; **AND**~~
- Verification that agent will be administered in combination with other antiretroviral agents; **AND**
- ~~Patient is monitored for fatal skin reactions (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis) and immune reconstitution syndrome; **AND**~~
- Clinically valid reason why the patient cannot use the preferred agents

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for JULUCA

Current Criteria:

- Patient has a diagnosis of HIV; **AND**
- Patient will not concurrently take dofetilide or other ART medications; **AND**
- Patient does not have any prior history of treatment failure to other HIV agents OR known resistance to the individual components (dolutegravir/rilpivirine); **AND**
- Patient is virologically suppressed (HIV-1 RNA < 50 copies/mL) on a current ART regimen for ≥ 6 months; **AND**
- Patient is not pregnant; **AND**
- Patient is being monitored for hypersensitivity reactions (e.g., Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]), hepatotoxicity, and depressive disorders

Proposed Criteria:

- Patient has a diagnosis of HIV; **AND**

- ~~Patient will not concurrently take dofetilide or other ART medications; **AND**~~
- Patient does not have any prior history of treatment failure to other HIV agents OR known resistance to the individual components (dolutegravir/rilpivirine); **AND**
- Patient is virologically suppressed (HIV-1 RNA < 50 copies/mL) on a current ART regimen for ≥ 6 months; ~~**AND**~~
- ~~Patient is not pregnant; **AND**~~
- ~~Patient is being monitored for hypersensitivity reactions (e.g., Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]), hepatotoxicity, and depressive disorders~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• ISENTRESS tabs	2/day
• ISENTRESS chews	6/day
• ISENTRESS granules	2 packs/day
• TIVICAY	2/day
• TIVICAY PD	3 bottles/30 days
• ISENTRESS HD	2/day
• JULUCA	1/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Anderson PL, Kakuda TN, Fletcher CV. Chapter 143: Human immunodeficiency virus infection. In: DiPiro JT, Yee GC, Posey LM, Haines ST, Nolin TD, Ellingrod V, editors. Pharmacotherapy: A Pathophysiologic Approach, 11th edition. McGraw-Hill Medical, 2020.
- Clinical Pharmacology. Gold Standard, Inc.; 2022. https://www.clinicalpharmacology.com. Accessed February 18, 2022.
- DHHS panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Updated January 20, 2022. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Accessed February 18, 2022.
- DHHS panel on antiretroviral guidelines for pediatric ARV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Updated December 30, 2021[a]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/PedARV_GL.pdf. Accessed February 18, 2022.
- DHHS panel on antiretroviral guidelines for perinatal ARV. Guidelines for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. Updated December 30, 2021[b].
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 18, 2022.
- Facts & Comparisons Website. https://fco.factsandcomparisons.com. Accessed February 18, 2022.
- Isentress (raltegravir) [prescribing information]. Rahway, NJ: Merck Sharp & Dohme LLC; May 2022.
- Juluca (dolutegravir/rilpivirine) [prescribing information]. Durham, NC: GlaxoSmithKline; October 2022.
- Tivicay (dolutegravir) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; October 2022.

ANTIVIRALS: HIV NRTI COMBOS

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred		Non-Preferred
HIV NRTI Combos	abacavir/lamivudine QL BIKTARVY PA, QL (BIC/FTC/TAF) COMBIVIR QL (3TC/ZDV) COMPLERA QL (RPV/FTC/TDF) DELSTRIGO QL (DOR/3TC/TDF) DESCOVY QL (FTC/TAF) DOVATO PA, QL (DTG/3TC) emtricitabine/tenofovir QL GENVOYA QL (EVG/c/FTC/TAF)	lamivudine/zidovudine QL ODEFSEY QL (RPV/FTC/TAF) STRIBILD QL (EVG/c/FTC/TDF) SYMTUZA PA, QL (DRV/c/ FTC/TAF) TRIUMEQ QL (DTG/ABC/3TC)	ATRIPLA QL (EFV/FTC/TDF) CIMDUO QL (3TC/TDF) efavirenz/lamivudine/tenofovir QL EPZICOM QL (ABC/3TC) SYMFI QL (EFV/3TC/TDF) SYMFI Lo QL (EFV/3TC/TDF) TRIZIVIR PA, QL (ABC/3TC/ZDV) TRIUMEQ PD QL (DTG/ABC/3TC) TRUVADA QL (FTC/TDF)

Last Review Date: February 2022

Recent Significant Changes

- Department of Health and Human Services (DHHS) Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2023)
- DHHS Guidelines for the Use of ARV Agents in Pediatric HIV Infection (2023)
- DHHS Recommendations for the Use of ARV Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States (2023)
- US Preventative Services Task Force (USPSTF): Preexposure Prophylaxis to Prevent Acquisition of HIV (2023)
- Discontinued Drug:
  - abacavir/lamivudine/zidovudine, 2023

Background (see HIV General Overview for further details)

The recommendations for initial treatment of HIV usually include a minimum of 3 antiretroviral (ARV) agents: 1 "anchor" drug and 2 "backbone" drugs. The backbone is usually 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). The anchor can be a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI). In adults, some 2 drug regimens have also demonstrated efficacy. There is an increased risk for HIV to select for ARV-resistant variants. Therefore, individuals should be tested for susceptibility via genotypic (preferred) or phenotypic resistance testing at treatment entry and when virologic failure occurs.

Table 1. Medications Included Within Class Review

Drug	Abbreviation	Generic Availability
ATRIPLA (efavirenz [600 mg]/emtricitabine/tenofovir disoproxil fumarate)	EFV/FTC/TDF	✔
BIKTARVY (bictegravir/emtricitabine/tenofovir alafenamide)	BIC/FTC/TAF	-
CIMDUO (lamivudine/tenofovir disoproxil fumarate)	3TC/TDF	-
COMBIVIR (lamivudine/zidovudine)	3TC/ZDV	✔
COMPLERA (rilpivirine/emtricitabine/tenofovir disoproxil fumarate)	RPV/FTC/TDF	-
DELSTRIGO (doravirine/lamivudine/tenofovir disoproxil fumarate)	DOR/3TC/TDF	-
DESCOVY (emtricitabine/tenofovir alafenamide)	FTC/TAF	-
DOVATO (dolutegravir/lamivudine)	DTG/3TC	-
EPZICOM (abacavir/lamivudine)	ABC/3TC	✔
GENVOYA (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide)	EVG/c/FTC/TAF	-

Drug	Abbreviation	Generic Availability
ODEFSEY (rilpivirine/emtricitabine/tenofovir alafenamide)	RPV/FTC/TAF	-
STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate)	EVG/c/FTC/TDF	-
SYMFI (efavirenz [600 mg]/lamivudine/tenofovir disoproxil fumarate)	EFV/3TC/TDF	✔
SYMFI LO (efavirenz [400 mg]/lamivudine/tenofovir disoproxil fumarate)	EFV/3TC/TDF	✔
TRIUMEQ (dolutegravir/abacavir/lamivudine)	DTG/ABC/3TC	-
TRIZIVIR (abacavir/lamivudine/zidovudine)	ABC/3TC/ZDV	✔
TRUVADA (emtricitabine/tenofovir disoproxil fumarate)	FTC/TDF	✔

Table 2. Food and Drug Administration Approved Indications – NRTI Only Combinations

Brand name (generic)	In combination with other ARV agents for the treatment of HIV-1 infection	In combination with other ARV-treatment, other than PIs that require a CYP 3A inhibitor, in HIV-1 infection	In combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 in at-risk patients
CIMDUO (3TC/TDF)	✓		
COMBIVIR (3TC/ZDV)	✓		
DESCOVY (FTC/TAF)	✓	✓	✓
EPZICOM (ABC/3TC)	✓		
TRIZIVIR (ABC/3TC/ZDV)	✓		
TRUVADA (FTC/TDF)	✓		✓

NRTI Combinations

Abacavir, Epzicom, and Trizivir are contraindicated in those positive for HLA-B*5701 allele and those with moderate to severe hepatic impairment. There are multiple warnings and precautions with each agent. Key safety concerns associated with the NRTI class are due to hallmark mitochondrial toxicity that may manifest as lactic acidosis, severe hepatomegaly with steatosis, peripheral neuropathy, myopathy, lipoatrophy, and immune reconstitution syndrome. The incidence of these adverse events (AEs) are much lower with the newer NRTIs (i.e., 3TC, FTC, ABC, TDF, TAF).

The most common AEs are as followed:

- Cimduo: headache, pain, depression, diarrhea, and rash
- Combivir: headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, cough
- Descovy:
  - HIV-1 infected patients: nausea
  - HIV-1 uninfected patients in PrEP trials: diarrhea
- Epzicom: hypersensitivity, insomnia, depression, headache, fatigue, dizziness, nausea, diarrhea
- Trizivir: nausea, headache, malaise, fatigue, vomiting
- Truvada, Descovy:
  - HIV-1 infected patients: diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, rash
  - HIV-1 uninfected patients in PrEP trials: headache, abdominal pain, weight decrease

Table 3. FDA Approved Indications – NRTI + INSTI Combinations

Multiple drug formulation (STRs)	Treatment of HIV-1 infection	Treatment of HIV-1 infection in those who have no ARV treatment history	To replace the current ARV regimen in those who are virologically suppressed (< 50 copies/mL) on a stable ARV regimen
BIKTARVY (BIC/FTC/TAF)	-	✔	✔
DOVATO (DTG/3TC)	-	✔	✔

Multiple drug formulation (STRs)	Treatment of HIV-1 infection	Treatment of HIV-1 infection in those who have no ARV treatment history	To replace the current ARV regimen in those who are virologically suppressed (< 50 copies/mL) on a stable ARV regimen
GENVOYA (EVG/c/FTC/TAF)	-	✔	✔
STRIBILD (EVG/c/TFC/TDF)	-	✔	✔
TRIUMEQ (DTG/ABC/3TC)	✔	-	-
TRIUMEQ PD (DTG/ABC/3TC)	✔		

NRTI/INSTI Combinations

Biktarvy, Dovato, and Triumeq/Triumeq PD are contraindicated with dofetilide use due to BIC and DTG increasing dofetilide concentrations and increasing risk for serious and/or life-threatening events (QT prolongation). Biktarvy is contraindicated with rifampin due to decreased BIC concentrations. Triumeq/Triumeq PD are contraindicated in the presence of HLA-B*5701 allele and in moderate or severe hepatic impairment.

The most common AEs are as followed:

- Biktarvy: diarrhea, nausea, and headache
- Dovato: headache, diarrhea, nausea, insomnia, fatigue, and anxiety
- Genvoya: nausea
- Stribild: nausea and diarrhea
- Triumeq/Triumeq PD: headache, insomnia, and fatigue

Table 4. FDA Approved Indications – NRTI + NNRTI Combinations

Brand (generic)	Treatment of HIV-1 infection	Treatment of HIV-1 infection in patients with no ARV treatment history	To replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA < 50 c/mL) on a stable ARV regimen with no history of treatment failure
ATRIPLA (EFV/FTC/TDF)	✔		
COMPLERA (RPV/FTC/TDF)		✔	
DELSTRIGO (DOR/3TC/TDF)		✔	✔
ODEFSEY (RPV/FTC/TAF)		✔	
SYMFI (EFV (600mg)/3TC/TDF)		✔	
SYMFI LO (EFV(400mg)/3TC/TDF)		✔	

NRTI + NNRTI Combinations

Complera and Odefsey are contraindicated in co-administration with certain drugs due to potential loss of virologic response and possible resistance; these drugs include anticonvulsants (i.e., carbamazepine, oxcarbazepine, phenobarbital, phenytoin), antimycobacterials (i.e., rifampin, rifapentine), systemic glucocorticoids (i.e., dexamethasone), proton pump inhibitors, and herbal products (i.e., St. John's wort). Delstrigo is contraindicated in co-administration with strong CYP3A enzyme inducers.

The most common AEs are as followed:

- Atripla: diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, rash
- Complera: depressive disorders, insomnia, and headache
- Delstrigo: dizziness, nausea, and abnormal dreams
- Odefsey: headache and sleep disturbances
- Symfi: impaired concentration, abnormal dreams, headache, nausea, malaise and fatigue, nasal symptoms, diarrhea, rash, dizziness, insomnia, pain, depression, asthenia, cough
- Symfi Lo: rash, dizziness

Table 5. FDA Approved Indications – NRTI + PI Combinations

Indication	Treatment of HIV-1 infection
SYMTUZA (DRV/c/FTC/TAF)	✔

NRTI + PI Combination

Darunavir and cobicistat are inhibitors of cytochrome P450 (CYP)3A isoform. Therefore, Symtuza is contraindicated in use with drugs that are highly dependent on cytochrome P450 (CYP)3A for clearance Symtuza co-administration with CYP3A inducers could lead to loss of efficacy, and development of resistance. Patients should be monitored for hepatotoxicity and severe skin reactions, and new onset or worsening renal impairment. Symtuza's most common AEs are diarrhea, rash, nausea, fatigue, headache, abdominal discomfort, and flatulence.

Clinical Rationale

Dual-NRTI regimens have demonstrated virologic potency and durability when paired with an INSTI, NNRTI, or a boosted PI. NRTIs are also available in combination with INSTI, NNRTI, and PI creating single tablet regimens which decrease pill burden and dosing frequency. In addition, the HIV NRTI combination agents are recommended first line for PrEP and PEP.

Recommendation

It is recommended that NRTI combination agents indicated for the treatment of HIV-1 infections be available. ~~Given that abacavir/lamivudine/zidovudine is considered inferior to efavirenz or PI-containing regimens due to toxicities and drug-drug interactions, it should be subject to prior authorization.~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for BIKTARVY

Current Criteria:

- Patient has a diagnosis of HIV; **AND**
- Patient has been tested for hepatitis B infection prior to initiation of therapy; **AND**
- Patient has a creatinine clearance (CrCl) ≥ 30 mL/min; **AND**
- Patient does NOT meet any of the following:
  - Patient has moderate to severe hepatic impairment
  - Concomitantly on other ART medications
  - Patient will concurrently take dofetilide or rifampin

Proposed Criteria:

Remove PA Criteria

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for DOVATO

Current Criteria:

Initial Criteria:

- Patient has a diagnosis of HIV; **AND**
- Patient has no known resistance to the individual components (lamivudine/dolutegravir); **AND**

- Patient has been tested for hepatitis B infection prior to initiation of therapy; **AND**
- Patient has a creatinine clearance (CrCl) ≥ 50 mL/min; **AND**
- Patient does **NOT** meet any of the following:
  - Patient has moderate to severe hepatic impairment
  - Concomitantly on dofetilide or other ART medications
  - In patients of childbearing age, patient is pregnant

Renewal Criteria:

- Patient will not be taking any other antiretroviral ARV medications; **AND**
- Patient will not be taking medications contraindicated with Dovato; **AND**
- Patient has a creatinine clearance (CrCl) ≥ 50 mL/min; **AND**
- Patient does not have moderate to severe hepatic impairment; **AND**
- Patient of childbearing age is not pregnant; **AND**
- Patient demonstrates documented efficacy (e.g., reduced viral load/improved CD4, remain virologically suppressed); **AND**
- Patient does not have any treatment-limiting adverse effects

Proposed Criteria:

- Patient has a diagnosis of HIV; **AND**
- Patient has no known resistance to the individual components (lamivudine/dolutegravir); **AND**
- *Patient meets ONE of the following:*
  - *Patient is ARV treatment-naïve*
  - *Patient is virologically suppressed (HIV-1 RNA < 50 copies/mL) on a current ART regimen for ≥ 6 months*
- ~~Patient has been tested for hepatitis B infection prior to initiation of therapy; **AND**~~
- ~~Patient has a creatinine clearance (CrCl) ≥ 50 mL/min; **AND**~~
- ~~Patient does **NOT** meet any of the following:~~
  - ~~Patient has moderate to severe hepatic impairment~~
  - ~~Concomitantly on dofetilide or other ART medications~~
  - ~~In patients of childbearing age, patient is pregnant~~

Renewal Criteria

- ~~Patient will not be taking any other antiretroviral ARV medications; **AND**~~
- ~~Patient will not be taking medications contraindicated with Dovato; **AND**~~
- ~~Patient has a creatinine clearance (CrCl) ≥ 50 mL/min; **AND**~~
- ~~Patient does not have moderate to severe hepatic impairment; **AND**~~
- ~~Patient of childbearing age is not pregnant; **AND**~~
- Patient demonstrates documented efficacy (e.g., reduced viral load/improved CD4, remain virologically suppressed); ~~**AND**~~
- ~~Patient does not have any treatment-limiting adverse effects~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for SYMTUZA

Current Criteria:

Initial Criteria:

- Patient has a diagnosis of HIV-1; **AND**
- Patient is will not be taking any other antiretroviral (ARV) medications; **AND**
- Patient is not concurrently taking any medications contraindicated with Symtuza; **AND**
- Patient is ARV treatment-naïve; **OR**
- Patient is ARV treatment-experienced and meets the following requirements:

- Virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ARV regimen for ≥ 6 months; **AND**
- Patient has no known substitutions associated with resistance to darunavir or tenofovir; **AND**
- Patient is switching within class (e.g., another protease inhibitor to darunavir, boosting agent of ritonavir to cobicistat, or another nucleoside reverse transcriptase inhibitors [NRTI] or tenofovir disoproxil fumarate [TDF] to tenofovir alafenamide [TAF]) due adverse effects or documented compliance issues due to pill burden or dosing frequency; **OR**
- Patient is switching between classes due to adverse effects or documented compliance issues due to pill burden or dosing frequency and activity of every component has been verified.

Renewal Criteria:

- Patient will not be taking any other antiretroviral ARV medications; **AND**
- Patient will not be taking medications contraindicated with Symtuza; **AND**
- Patient demonstrates documented efficacy (e.g., reduced viral load/improved CD4, remaining virologically suppressed); **AND**
- Patient does not have any treatment-limiting adverse effects.

Proposed Criteria:

- Patient has a diagnosis of HIV-1; **AND**
- *Patient has no known substitutions associated with resistance to darunavir or tenofovir;* ***AND***
- ~~Patient is will not be taking any other antiretroviral (ARV) medications;~~ ~~**AND**~~
- ~~Patient is not concurrently taking any medications contraindicated with Symtuza;~~ ~~**AND**~~
- Patient is ARV treatment-naïve; **OR**
- Patient is ARV treatment-experienced and meets the *ONE* following requirements:
  - Virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ARV regimen for ≥ 6 months; **OR** ~~**AND**~~
  - ~~Patient has no known substitutions associated with resistance to darunavir or tenofovir;~~ ~~**AND**~~
  - Patient is switching *medication* ~~within class (e.g., another protease inhibitor to darunavir, boosting agent of ritonavir to cobicistat, or another nucleoside reverse transcriptase inhibitors [NRTI] or tenofovir disoproxil fumarate [TDF] to tenofovir alafenamide [TAF])~~ due adverse effects or documented compliance issues due to pill burden or dosing frequency; ~~**OR**~~
  - ~~Patient is switching between classes due to adverse effects or documented compliance issues due to pill burden or dosing frequency and activity of every component has been verified.~~

Renewal Criteria

- ~~Patient will not be taking any other antiretroviral ARV medications;~~ ~~**AND**~~
- ~~Patient will not be taking medications contraindicated with Symtuza;~~ ~~**AND**~~
- Patient demonstrates documented efficacy (e.g., reduced viral load/improved CD4, remaining virologically suppressed); ~~**AND**~~
- ~~Patient does not have any treatment-limiting adverse effects.~~

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for TRIZIVIR

Current Criteria:

- Patient has a diagnosis of HIV; **AND**
- Patient has had a trial and failure, contraindication, or intolerance to 2 preferred HIV NRTI combination regimens; **AND**
- Patient has been tested for hepatitis B infection prior to initiation of therapy; **AND**
- Provider agrees to perform a baseline CBC and CMP labs prior to initiating therapy and periodically throughout therapy; **AND**
- Patient does NOT meet any of the following:

- Prior hypersensitivity with abacavir-containing products
- Positive for the HLA-B*5701 allelle
- Moderate to severe hepatic impairment

Proposed Criteria:

Remove PA Criteria. Standard non-preferred criteria will apply.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• abacavir/lamivudine	1/day
• BIKTARVY	1/day
• COMBIVIR	2/day
• COMPLERA	1/day
• DELSTRIGO	1/day
• DESCOVY	1/day
• DOVATO	1/day
• emtricitabine/tenofovir	1/day
• efavirenz/emtricitabine/tenofovir	1/day
• GENVOYA	1/day
• lamivudine/zidovudine	2/day
• ODEFSEY	1/day
• STRIBILD	1/day
• SYMTUZA	1/day
• TRIUMEQ	1/day
• TRIZIVIR	2/day
• ATRIPLA	1/day
• CIMDUO	1/day
• efavirenz/lamivudine/tenofovir	1/day
• EPZICOM	1/day
• SYMFI	1/day
• SYMFI Lo	1/day
• TRIUMEQ PD	6/day
• TRUVADA	1/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Anderson PL, Brooks KM, Fletcher CV. Chapter 148: Human immunodeficiency virus infection. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey M, editors. Dipiro's Pharmacotherapy: A Pathophysiologic Approach, 12th edition. McGraw-Hill, 2023.
- Atripla (efavirenz/emtricitabine/tenofovir) [prescribing information]. Foster City, CA: Gilead Sciences Inc; December 2021.
- Biktarvy (bictegravir, emtricitabine, tenofovir alafenamide) [prescribing information]. Foster City, CA: Gilead Sciences; November 2022.
- Cimduo (lamivudine/tenofovir disoproxil fumarate) [prescribing information]. Morgantown, WV; Mylan Specialty L.P: February 2021.
- Combivir (lamivudine/zidovudine) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; May 2019.
- Complera (emtricitabine, rilpivirine, tenofovir disoproxil fumarate) [prescribing information]. Foster City, CA: Gilead Sciences Inc; November 2019.
- Delstrigo (doravirine, lamivudine, and tenofovir disoproxil fumarate) [prescribing information]. Rahway, NJ: Merck Sharp & Dohme LLC; June 2022.
- Descovy (emtricitabine and tenofovir alafenamide) [prescribing information]. Foster City, CA: Gilead Sciences Inc; January 2022.
- DHHS panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Updated March 23, 2023[a]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed November 6, 2023.
- DHHS panel on antiretroviral therapy and medical management of children living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Updated April 11, 2023[b]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf. Accessed November 6, 2023.

- DHHS panel on treatment of pregnant women with HIV infection and prevention of perinatal transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. Updated January 31, 2023[c]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/perinatal-hiv/guidelines-perinatal.pdf. Accessed November 6, 2023.
- Dovato (dolutegravir/lamivudine) [prescribing information]. Research Triangle Park, NC: ViiV Healthcare; December 2021.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 7, 2023.
- Epzicom (abacavir and lamivudine) [prescribing information]. Durham, NC: ViiV Healthcare; December 2022.
- Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) [prescribing information]. Foster City, CA: Gilead Sciences Inc; January 2022.
- Odefsey (emtricitabine/rilpivirine/tenofovir alafenamide fumarate) [prescribing information]. Foster City, CA: Gilead Sciences Inc; September 2021.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed November 7, 2023.
- Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) [prescribing information]. Foster City, CA: Gilead Sciences Inc; September 2021.
- Symfi (efavirenz/lamivudine/tenofovir disoproxil fumarate) [prescribing information]. Morgantown, WV: Mylan Specialty LP; May 2019.
- Symfi Lo (efavirenz/lamivudine/tenofovir disoproxil fumarate) [prescribing information]. Morgantown, WV: Mylan Specialty LP; October 2019.
- Symtuza (darunavir/cobicistat/emtricitabine/tenofovir alafenamide) [prescribing information]. Horsham, PA: Janssen Products LP; March 2023.
- Triumeq and Triumeq PD (abacavir/dolutegravir/lamivudine) [prescribing information]. Durham, NC: ViiV Healthcare; June 2023.
- Trizivir (abacavir/lamivudine/zidovudine) [prescribing information]. Research Triangle Park, NC: Viiv Healthcare; February 2021.
- Truvada (emtricitabine/tenofovir disoproxil fumarate) [prescribing information]. Foster City, CA: Gilead Sciences; October 2023.
- US Preventive Services Task Force, Barry MJ, Nicholson WK, et al. Preexposure Prophylaxis to Prevent Acquisition of HIV: US Preventive Services Task Force Recommendation Statement. JAMA. 2023;330(8):736-745.

ANTIVIRAL: HIV ATTACHMENT INHIBITORS

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
HIV Attachment Inhibitors	N/A	RUKOBIA PA, QL (fostemsavir)

Last Review Date: February 2022

Recent Significant Changes

- Department of Health and Human Services (DHHS) Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2023)

Background (see HIV General Overview for further details)

Rukobia (fostemsavir) is a prodrug metabolized to its active metabolite, temsavir. The active metabolite is a human immunodeficiency virus (HIV) attachment inhibitor that binds to the glycoprotein 120 subunit within the HIV-1 envelope and selectively inhibits the interaction between the virus and cellular cluster of differentiation 4 (CD4) receptors. This agent is reserved for heavily treatment-experienced adults with multidrug-resistant (MDR) HIV infections who are failing their current antiretroviral (ARV) regimen and is often a last line option for patients who lack sufficient treatment options to construct a fully suppressive ARV regimen. There is no commercially available resistance test for fostemsavir.

Table 1. Medications Included Within Class Review

Drug	Abbreviation	Generic Availability
RUKOBIA (fostemsavir)	FTR	--

The entry inhibitors are recommended in certain clinical situations, generally as later line therapy in treatment-experienced patients living with HIV. None of the entry inhibitors are recommended for initial therapy. Fostemsavir is approved in combination with other ARV agents for the treatment of HIV-1 infection in heavily treatment-experienced adults with MDR HIV-1 infection failing their current ARV regimen. It may be considered for patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen.

Fostemsavir should be used with caution in patients who are susceptible to QTc interval prolongation (either due to underlying cardiac conditions or concomitant treatment with drugs that prolong the QTc interval). Elevations in hepatic transaminases and bilirubin have been reported, particularly in patients with hepatitis B or C virus co-infection. Immune reconstitution syndrome has also been reported. Co administration with CYP3A inducers is contraindication. The most common adverse reaction is nausea.

Clinical Rationale

Entry inhibitors are prescribed as last line therapy for treatment-experienced HIV patients. Since this agent is not recommended as initial ART therapy, it should be subjected to prior authorization to ensure appropriate use.

Recommendation

It is recommended that attachment inhibitors are available for use for and are subject to clinical criteria.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for RUKOBIA

Current Criteria:

- Patient has multidrug-resistant HIV infection; **AND**
- Patient is virally unsuppressed and has persistent plasma HIV RNA levels greater than or equal to 200 copies/mL; **AND**
- Verification that agent will be administered in combination with other antiretroviral agents; **AND**
- Verification of exposure, contraindication, intolerance, or resistance to BOTH of the following:
  - Two NRTIS
  - One INSTI, NNRTI, or PI; **AND**
- Will not be used with strong cytochrome P450 (CYP)3A inducers

Proposed Criteria:

Initial Criteria

- ~~Patient has~~ *Diagnosis of treatment-experienced* multidrug-resistant HIV-*1* infection; **AND**
- ~~Patient is virally unsuppressed and has persistent plasma~~ HIV-*1* RNA ≥ ~~levels greater than or equal to~~ 200 copies/mL; **AND**
- *Prescriber attests that the patient lacks sufficient treatment options due to resistance, intolerability, contraindication, or other safety concerns to construct a fully suppressive antiretroviral regimen;* ***AND***
- ~~Verification that~~ Agent will be administered in combination with ~~other~~ *an optimized* antiretroviral *regimen* ~~agents~~; **AND**
- ~~Verification of exposure, contraindication, intolerance, or resistance to BOTH of the following:~~
  - ~~Two NRTIS~~
  - ~~One INSTI, NNRTI, or PI;~~ ~~**AND**~~
- ~~Will not be used with Strong cytochrome P450 (CYP)3A inducers;~~ ~~**AND**~~
- *Prescribed by, or in consultation with or by an infectious disease specialist*

Renewal Criteria

- *Patient demonstrates documented efficacy (e.g., reduced viral load/improved CD4, remain virologically suppressed)*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• RUKOBIA	2/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Centers for Disease Control and Prevention. HIV Surveillance Report. Last Reviewed: August 10, 2022. https://www.cdc.gov/hiv/statistics/overview/index.html. Accessed November 6, 2023.
- DHHS panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Updated March 23, 2023[a]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed November 6, 2023.
- Drugs@FDA: FDA approved drug products. Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 6, 2023.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed November 6, 2023.
- Purple Book: Database of Licensed Biological Products [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2023. Available at: https://purplebooksearch.fda.gov/. Accessed November 6, 2023.
- Rukobia (fostemsavir) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; January 2022.

ANTIVIRALS: HIV CAPSID INHIBITORS

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
HIV Capsid Inhibitors	SUNLENCA [PA] (lenacapavir)	N/A

Last Review Date: August 2023

Recent Significant Changes

- Department of Health and Human Services (DHHS) Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2023)

Background (see HIV General Overview for further details)

Sunlenca (lenacapavir) is a capsid inhibitor that directly binds to the interface between capsid protein (p24) subunits in hexamers and inhibits human immunodeficiency virus (HIV-1) replication through interference in multiple steps of the virus lifecycle, including capsid-mediated nuclear uptake of HIV-1 proviral DNA, virus assembly and release, and capsid core formation. It is reserved for patients living with HIV who are treatment-experienced, have multidrug-resistant (MDR) virus, and are failing their current regimen. There is currently no drug resistance test available for lenacapavir. Sunlenca is Food and Drug Administration (FDA) approved in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant (MDR) HIV-1 infection failing their current antiretroviral regimen.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
SUNLENCA (lenacapavir)	--

Lenacapavir may be considered for patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen. Lenacapavir is initiated with loading dose consisting of oral tablets plus subcutaneous injections, followed by SC maintenance injections every 6 months by a healthcare professional. Lenacapavir has been studied for up to 52 weeks versus placebo in heavily ART-experienced patients and has demonstrated reductions in viral load 15 days after initiation. The safety and efficacy in children and adolescents have not been established. There is no data to inform the use in pregnancy.

Sunlenca is contraindicated in use with strong CYP3A inducers due to significant decreases in their plasma concentrations and loss of virologic response. Sunlenca may cause local injection site reactions, including nodules and indurations that may take longer to resolve than other injection site reactions. In clinical trials, 30% of nodules and 13% of indurations had not fully resolved after a median follow-up of 553 days. Residual concentrations of lenacapavir may remain in the circulation for up to 12 months or longer after the last injection. Patients must be counseled on the importance of adherence since missed doses or non-adherence may result in loss of virologic response and the development of resistance.

Clinical Rationale

Capsid inhibitors are prescribed as last line therapy for treatment-experienced HIV patients. Since this agent is not recommended as initial ART therapy, it should be subjected to prior authorization to ensure appropriate use.

Recommendation

It is recommended that capsid inhibitors are available for use for and are subject to clinical criteria.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for SUNLENCA

Current Criteria:

- Diagnosis of Treatment-experienced multidrug-resistant HIV-1 as confirmed by:
  - HIV-1 RNA≥ 400 copies/mL; **AND**
  - Patient has tried and failed an adequate trail of, has resistance, contraindication, or intolerance to two agents from 3 out of 4 main anti-retroviral classes (e.g., PI, NNRTI, NRTI, INSTI); **AND**
- Sunlenca will be used in combination with antiretroviral therapy (ART); **AND**
- Prescriber attests the patient has received or will receive the subcutaneous dose; **AND**
- Requested agent will NOT be used in combination with any of the following:
  - Strong or moderate CYP3A inducers
  - Long active ARV combination of injectable cabotegravir (CAB) and rilpivirine (RPV); **AND**
- Prescribed by, or in consultation with or by an infectious disease specialist

Proposed Criteria:

- Diagnosis of Treatment-experienced multidrug-resistant HIV-1; **AND** ~~as confirmed by:~~
- HIV-1 RNA≥ ~~400~~ *200* copies/mL; **AND**
  - ~~Patient has tried and failed an adequate trail of, has resistance, contraindication, or intolerance to two agents from 3 out of 4 main anti-retroviral classes (e.g., PI, NNRTI, NRTI, INSTI);~~ **AND**
- *Prescriber attests that the patient lacks sufficient treatment options due to resistance, intolerability, contraindication, or other safety concerns to construct a fully suppressive antiretroviral regimen;* ***AND***
- ~~Sunlenca~~ *Agent* will be used in combination with *an optimized* antiretroviral *regimen* ~~therapy (ART)~~; **AND**
- Prescriber attests the patient has received or will receive the subcutaneous dose; **AND**
- ~~Requested agent will NOT be used in combination with any of the following:~~
  - ~~Strong or moderate CYP3A inducers~~
  - ~~Long active ARV combination of injectable cabotegravir (CAB) and rilpivirine (RPV);~~ ~~**AND**~~
- Prescribed by, or in consultation with or by an infectious disease specialist

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- SUNLENCA 1 pack/year

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- DHHS panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Updated March 23, 2023[a]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed November 6, 2023.
- Drugs@FDA: FDA approved drug products. Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 6, 2023.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed November 6, 2023.
- Sunlenca (lenacapavir) [prescribing information]. Foster City, CA: Gilead Sciences Inc; December 2022.

ANTIVIRALS: HIV FUSION INHIBITORS

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
HIV Fusion Inhibitors	FUZEON solution PA, QL (enfuvirtide)	N/A

Last Review Date: February 2022

Recent Significant Changes

- Department of Health and Human Services (DHHS) Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2023)

Background (see HIV General Overview for further details)

Fuzeon (enfuvirtide) is a fusion inhibitor and the mechanism by which enfuvirtide exerts its action is by interfering with the entry of human immunodeficiency virus (HIV-1) into cells by inhibiting fusion of viral and cellular membranes. Enfuvirtide binds to a subunit of the viral envelope glycoprotein and prevents the conformational changes required for the fusion of viral and cellular membranes. It inhibits the proper conformation of viral envelope protein gp41. Enfuvirtide is effective in treatment-experienced patients; however, twice-daily injections make it difficult to maintain patients on this drug long-term. Resistance to enfuvirtide emerges quickly, and a single mutation can result in high resistance and subsequent virologic failure.

Table 1. Medications Included Within Class Review

Drug	Abbreviation	Generic Availability
FUZEON (enfuvirtide)	T-20	--

Fuzeon is currently Food and Drug Administration (FDA) approved in combination with other ARV agents and indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing ARV therapy. The entry inhibitors are recommended in certain clinical situations, generally as later line therapy in treatment-experienced patients living with HIV. None of the entry inhibitors are recommended for initial therapy. Enfuvirtide has only been studied in patients with virologic failure, requires twice daily injectable (SC) administration, and has a high rate of injection site reactions.

Enfuvirtide is an archived drug within the DHHS pediatric guidelines. Archived Drugs includes older ARV drugs that the Panel does not recommend for use in children because they have unacceptable toxicities, inferior virologic efficacy, a high pill burden, pharmacologic concerns, and/or a limited amount of pediatric data. Although enfuvirtide is FDA-approved for use in children, it is not commonly prescribed. Additionally, the use of deep salvage regimens has waned since integrase strand transfer inhibitors (INSTIs) and other entry inhibitors have become available.

Almost all patients experience local injection site reactions (87 to 98%), with an average duration of 3 to 7 days but > 7 days has been observed in 24% of patients. Less common, but more severe adverse events include bacterial pneumonia. Hypersensitivity reactions occur in < 1% of patients; however, rechallenging therapy in these cases is not recommended. The most common adverse reactions are diarrhea, dizziness, nausea, and rash.

Clinical Rationale

Entry inhibitors are prescribed as last line therapy for treatment-experienced HIV patients. Since this agent is not recommended as initial ART therapy, it should be subjected to prior authorization to ensure appropriate use.

Recommendation

It is recommended that fusion inhibitors be available for use and subject to criteria.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for FUZEON

Current Criteria:

- Patient is virally unsuppressed and has persistent plasma HIV RNA levels greater than or equal to 200 copies/mL; **AND**
- Verification of exposure, contraindication, intolerance, or resistance to BOTH of the following:
  - Two NRTIS
  - One INSTI, NNRTI, or PI; **AND**
- Verification that agent will be administered in combination with other antiretroviral agents

Proposed Criteria:

Initial Criteria

- *Diagnosis of treatment-experienced HIV-1 infection; **AND***
- ~~Patient is virally unsuppressed and has persistent plasma~~ HIV-1 RNA levels ~~greater than or equal to~~ ≥ 200 copies/mL; **AND**
- *Pprescriber attests that the patient lacks sufficient treatment options due to resistance, intolerability, contraindication, or other safety concerns to construct a fully suppressive antiretroviral regimen; **AND***
- ~~Verification of exposure, contraindication, intolerance, or resistance to BOTH of the following:~~
  - ~~Two NRTIS~~
  - ~~One INSTI, NNRTI, or PI; **AND**~~
- ~~Verification that~~ agent will be administered in combination with ~~other~~ *an optimized* antiretroviral *regimen* ~~agents~~; **AND**
- *Prescribed by, or in consultation with or by an infectious disease specialist*

Renewal Criteria

- *Patient demonstrates documented efficacy (e.g., reduced viral load/improved CD4, remain virologically suppressed)*

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- FUZEON 1 kit/30 days (2 vials/day)

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Centers for Disease Control and Prevention. HIV Surveillance Report. Last Reviewed: August 10, 2022. https://www.cdc.gov/hiv/statistics/overview/index.html. Accessed November 6, 2023.
- DHHS panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Updated March 23, 2023[a]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed November 6, 2023.
- Drugs@FDA: FDA approved drug products. Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 6, 2023.
- Fuzeon (enfuvirtide) [prescribing information]. South San Francisco, CA: Genentech USA Inc; December 2019.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed November 6, 2023.

Abbreviated Drug Class Reviews

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ANTIBIOTICS: CEPHALOSPORINS FIRST GENERATION

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred		Non-Preferred
Cephalosporins-First Generation	cefadroxil caps cefadroxil susp	cephalexin caps cephalexin susp	cefadroxil tabs cephalexin tabs

Last Review Date: February 2022

Recent Significant Changes

- Infectious Diseases Society of America (IDSA) Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections, 2023

Recommendation

It is recommended that both cefadroxil and cephalexin are available for use, including oral suspension formulations.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Cefadroxil capsules [prescribing information]. East Windsor, NJ: Aurobindo Pharma USA Inc; May 2022.
- Cefadroxil suspension [prescribing information]. East Windsor, NJ: Aurobindo Pharma USA Inc; September 2021.
- Cefadroxil tablets [prescribing information]. North Wales, PA: Teva Pharmaceuticals; July 2018.
- Cephalexin (capsules, powder for suspension, tablets) [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc; December 2020.
- Cephalexin (oral suspension, USP) [prescribing information]. Congers, NY: Chartwell RX LLC; December 2021.
- Clinical Infectious Diseases, ciad428, https://doi.org/10.1093/cid/ciad428. Published: 18 July 2023

ANTIBIOTICS: CEPHALOSPORINS SECOND GENERATION

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred		Non-Preferred
Cephalosporins - Second Generation	cefaclor caps cefprozil	cefuroxime tabs	cefaclor ER

Last Review Date: February 2022

Recent Significant Changes

- Infectious Diseases Society of America (IDSA) Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections, 2023
- No rebateable products currently available for cefaclor susp

Recommendation

It is recommended that at least 2 second generation cephalosporins should be available, one of which should be cefuroxime. Additionally, a liquid formulation should be available for the pediatric population.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Cefaclor capsules [prescribing information]. Eatontown, NJ: West-Ward Pharmaceuticals; November 2020.
- Cefaclor extended-release tablets [prescribing information]. North Wales, PA: Teva Pharmaceuticals; July 2019.
- Cefprozil powder for suspension [prescribing information]. East Windsor, NJ: Aurobindo Pharma USA, Inc; September 2019.
- Cefprozil tablet [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc; August 2018.
- Cefuroxime suspension [prescribing information]. Jacksonville, FL: Ranbaxy Pharmaceuticals Inc; September 2007.
- Cefuroxime tablet [prescribing information]. East Windsor, NJ: Aurobindo Pharma USA, Inc; October 2021.
- Clinical Infectious Diseases, ciad428, https://doi.org/10.1093/cid/ciad428. Published: 18 July 2023

ANTIBIOTICS: CEPHALOSPORINS THIRD GENERATION

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred		Non-Preferred
Cephalosporins-Third Generation	cefdinir caps cefdinir susp cefixime caps	cefixime susp cefpodoxime tabs	cefpodoxime susp [PA]

Last Review Date: February 2022

Recent Significant Changes

- Discontinued Drugs:
  - cefditoren, 2022
  - ceftibuten, 2019

Recommendation

It is recommended that at least three third generation cephalosporin agents are available that will allow for full antibacterial coverage within the class. Additionally, a liquid formulation should be available for the pediatric population.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for cefpodoxime suspension

Current Criteria:

- Patients less than 12 years of age and treatment is for genitourinary infection; **OR**
- Patient is unable to swallow solid dosage forms

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Cefdinir capsules [prescribing information]. BluePoint Laboratories; August 2018.
- Cefdinir for oral suspension [prescribing information]. Baltimore, MD; Lupin Pharmaceuticals Inc; March 2020.
- Cefpodoxime proxetil [package insert]. Allendale, NJ: Rising Pharmaceuticals; May 2017.
- Cefpodoxime proxetil for oral suspension [prescribing information]. Princeton, NJ: Sandoz Inc; 2014.
- Cefpodoxime proxetil tablets [prescribing information]. East Windsor, NJ: Aurobindo Pharma USA, Inc; July 2018.
- Cefdinir for oral suspension [prescribing information]. Parsippany, NJ: Ascend Laboratories, LLC; August 2019.
- Cefixime capsule [prescribing information]. Parsippany, NJ: Ascend Laboratories, LLC; December 2018.
- Cefixime suspension [prescribing information]. East Windsor, NJ: Aurobindo Pharma USA, Inc; October 2021.

ANTIBIOTICS: LINCOSAMIDES, ORAL

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
Oral Lincosamides	clindamycin caps clindamycin soln [PA]	CLEOCIN (clindamycin) CLEOCIN PEDIATRIC GRANULES [PA] (clindamycin)

Last Review Date: February 2022

Recent Significant Changes

- No significant updates since last review

Recommendation

It is recommended that oral clindamycin, including the pediatric dosage form, be available for use.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for clindamycin pediatric solution

Current Criteria:

- Patient is unable to swallow solid dosage forms
  Note: PA not required for patients less than 12 years of age

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for CLEOCIN PEDIATRIC GRANULES

Current Criteria:

- Patient is unable to swallow solid dosage forms

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Cleocin hydrochloride capsules (clindamycin) [prescribing information]. New York, NY: Pfizer; May 2022.
- Cleocin Pediatric oral solution, USP (clindamycin) [prescribing information]. New York, NY: Pharmacia & Upjohn Company LLC; January 2023.

ANTIBIOTICS: MACROLIDES

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
Macrolides	azithromycin packet, susp, and tabs QL	clarithromycin ER QL
	clarithromycin tabs & susp	DIFICID tabs & susp PA, QL (fidaxomicin)
	E.E.S. tabs (erythromycin)	E.E.S GRANULES (erythromycin)
	erythromycin caps	ERYPED (erythromycin)
	erythromycin EC tabs	ERYTHROCIN tabs (erythromycin)
	erythromycin ethyl succinate tabs	erythromycin base and stearate tabs
	erythromycin susp	ZITHROMAX packet, susp, and tabs QL (azithromycin)

Last Review Date: February 2022

Recent Significant Changes

- Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2023)

Recommendation

~~Due to its narrow spectrum of activity and lack of endorsement by current clinical guidelines,~~ It is recommended fidaxomicin should be subject to clinical criteria to ensure appropriate use.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for DIFICID TABLETS & SUSPENSION

Current Criteria:

- Diagnosis of *Clostridium difficile (C.diff)* associated diarrhea; **OR**
- Patient is continuing therapy from an inpatient hospital stay (to facilitate completion of therapy)

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- ZITHROMAX (azithromycin) packet 2g/Rx
- ZITHROMAX (azithromycin) 250mg, 500mg 12/Rx
- ZITHROMAX (azithromycin) 600mg 8/month
- DIFICID tablets; clarithromycin ER 2/day
- DIFICID suspension 1 bottle/Rx

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Azithromycin suspension [eMC summary of product characteristics]. Camberley, Surrey, United Kingdom: Sandoz Limited; August 2020.
- Dificid (fidaxomicin) [prescribing information] Rahway, NJ: Merck Sharp & Dohme LLC; June 2022.
- Erythromycin [prescribing information]. Piscataway, NJ: Appco Pharma LLC; January 2022.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2023 report). https://goldcopd.org/2023-gold-report-2/. Accessed November 15, 2023

ANTIBIOTICS: NITROFURANS, ORAL

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
Oral Nitrofurans	nitrofurantoin caps nitrofurantoin susp [PA]	MACROBID (nitrofurantoin) MACRODANTIN (nitrofurantoin)

Last Review Date: February 2022

Recent Significant Changes

- Discontinued Drugs:
  - FURADANTIN, 2021

Recommendation

It is recommended that at least nitrofurantoin macrocrystalline should be available for use. Additionally, nitrofurantoin suspension should be available for use in the pediatric population as well as for those with difficulty swallowing.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for nitrofurantoin suspension

Current Criteria:

- Patient is unable to swallow solid dosage forms

Note: PA not required for patients less than 12 years of age.

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Macrobid (nitrofurantoin) [prescribing information]. Morristown, NJ: Almatica Pharma LLC; December 2020.
- Macrodantin (nitrofurantoin) [prescribing information]. Morristown, NJ: Almatica Pharma LLC; June 2020.
- Nitrofurantoin oral suspension [prescribing information]. East Windsor, NJ: Aurobindo Pharma USA Inc; June 2022.

ANTIBIOTICS: PENICILLINS

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred		Non-Preferred
Penicillins	amoxicillin amoxicillin/clavulanate ampicillin	dicloxacillin penicillin	All brand penicillins amoxicillin/clavulanic acid XR

Last Review Date: February 2022

Recent Significant Changes

- No significant updates since last review

Recommendation

It is recommended that at least 3 oral penicillin agents are available for use. Additionally, due to high utilization in the pediatric population, at least one liquid formulation should be available.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Lexicomp. (n.d.). Penicillin, antistaphylococcal penicillins, and broad-spectrum penicillins. Topic. UpToDate. Accessed January 2, 2024
- Penicillin V potassium (tablets, USP and Oral Solution, USP) [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA Inc; October 2018.

ANTIBIOTICS: SULFONAMIDES, FOLATE ANTAGONIST

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
Sulfonamides, Folate Antagonist	sulfamethoxazole/trimethoprim (TMP) trimethoprim (TMP)	BACTRIM (sulfamethoxazole/trimethoprim) BACTRIM DS (sulfamethoxazole/trimethoprim)

Last Review Date: February 2022

Recent Significant Changes

- Discontinued Drugs:
  - PRIMSOL, 2023

Recommendation

It is recommended that at least the combination SMZ/TMP, including the oral suspension, be available for use.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Bactrim and Bactrim DS (sulfamethoxazole and trimethoprim) [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries Inc; April 2021.
- Bactrim Pedatric Suspension (sulfamethoxazole and trimethoprim) [prescribing information]. Cranbury, NJ: Sun Pharmaceuticals; May 2021.
- Primsol Solution (trimethoprim) oral solution [prescribing information]. Englewood, CO: Aytu Pharmaceuticals; November 2015.
- Sulfadiazine [prescribing information]. Laurelton, NY: Epic Pharma LLC; July 2021.

ANTIBIOTICS: UTI AGENTS, MISCELLANEOUS

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
UTI Agents, Miscellaneous	N/A	fosfomycin powder packets [PA, QL]

Last Review Date: February 2022

Recent Significant Changes

- No significant updates since last review

Recommendation

It is recommended that fosfomycin be subject to clinical criteria restricting its use to patients who are not candidates for other less costly treatment options.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for fosfomycin

Current Criteria:

- Trial and failure, contraindication, intolerance, or resistance to at least 2 of the following agents:
  - Sulfamethoxazole/trimethoprim
  - Quinolones
  - Nitrofurantoin

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- fosfomycin 1 packet (3g) per course of therapy

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Monurol (fosfomycin tromethamine) [prescribing information]. Madison, NJ: Allergan USA, Inc; October 2019.

ANTIBIOTICS, VAGINAL

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
Antibiotics, Vaginal	CLEOCIN suppositories (clindamycin) CLEOCIN cream QL (clindamycin) metronidazole 0.75% vaginal gel QL NUVESSA QL (metronidazole) VANDAZOLE QL (metronidazole)	clindamycin phos 2% cream QL CLINDESSE vaginal cream QL (clindamycin) XACIATO vaginal gel QL (clindamycin)

Last Review Date: February 2022

Recent Significant Changes

- No significant changes since last review

Recommendation

It is recommended that at least one vaginal metronidazole and one vaginal clindamycin product be available for use.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• CLEOCIN cream	40 g/Rx
• metronidazole 0.75% vaginal gel	70 g/Rx
• NUVESSA	5 g/Rx
• VANDAZOLE	70 g/Rx
• clindamycin phos 2% cream	40 g/Rx
• CLINDESSE vaginal cream	5 g/Rx
• XACIATO	5g/Rx

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Cleocin vaginal cream (clindamycin) [prescribing information]. New York, NY: Pharmacia & Upjohn; May 2022.
- Cleocin vaginal suppository (clindamycin) [prescribing information]. New York, NY: Pharmacia & Upjohn; July 2022.
- Clindamycin phosphate vaginal cream [prescribing information]. Peapack, NJ: Greenstone LLC; May 2022.
- Clindesse (clindamycin) vaginal cream [prescribing information]. Allegan, MI: Padagis; May 2022.
- Nuvessa (metronidazole) [prescribing information]. Florham Park, NJ: Exeltis USA Inc; April 2022.
- Vandazole (metronidazole) [prescribing information]. Maple Grove, MN: Upsher-Smith Laboratories LLC; February 2021.
- Xaciato [package insert], Jersey City, NJ: Organon LLC.; October 2023.

ANTIFUNGALS, VAGINAL

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
Antifungals, Vaginal	GYNAZOLE-1 [QL] (butoconazole) miconazole-3 kit [QL] *miconazole-3 vaginal supp* [QL] terconazole [QL]	

Last Review Date: February 2022

Recent Significant Changes

- No significant changes since last review

Recommendation

It is recommended that at least two prescription vaginal antifungals be available as preferred.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- Gynazole-1 max 5 gram/day
- miconazole-3 kit 1 box/Rx
- terconazole 1 box/Rx
- miconazole-3 vaginal supp 1 box/Rx

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Gynazole-1 (butoconazole) [prescribing information]. Allegan, MI: Padagis; May 2022.
- Miconazole 7 (miconazole topical) [prescribing information]. Parsippany, NJ: Actavis Pharma, Inc; March 2015.
- Terconazole cream (terconazole) [prescribing information]. Hawthorne, NY: Taro Pharmaceuticals USA, Inc; January 2019.
- Terconazole suppositories (terconazole) [prescribing information]. Allegan, MI: Perrigo; December 2018.

ANTI-INFECTIVES: ANTHELMINTICS

Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred		Non-Preferred	
Anthelmintics	albendazole PA BILTRICIDE (praziquantel)	ivermectin tabs QL pyrantel pamoate	EMVERM PA (mebendazole) praziquantel	KRINTAFEL (tafenoquine) STROMECTOL QL (ivermectin)

Last Review Date: February 2022

Recent Significant Changes

- Discontinued Drugs:
  - ALBENZA, 2023

Recommendation

It is recommended at least one agent for the treatment of pinworm and one agent for the treatment of roundworm should be available for use. Additionally, it is recommended that albendazole and mebendazole be subject to prior authorization.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for albendazole

Current Criteria:

- Treatment of neurocysticercosis caused by *Taenia solium*; **AND**
  - Prescribed by, or in consultation with, an Infectious Disease specialist; **OR**
- Treatment of cystic hydatid disease caused by *Echinococcus granulosus*; **OR**
- Treatment of hookworm

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for EMVERM

Current Criteria:

- Treatment of Enterobius vermicularis (pinworm) in single or mixed infections; **AND**
  - Trial and failure, contraindication, or intolerance to pyrantel pamoate; **OR**
- Treatment of Ancylostoma duodenale (common hookworm) or Necator americanus (American hookworm); **AND**
  - Trial and failure, contraindication, or intolerance to Albenza; **OR**
- Treatment of Trichuris trichiura (whipworm) or Ascaris lumbricoides (common roundworm); **AND**
  - Trial and failure, contraindication, or intolerance to to ivermectin

Length of authorization: Will be based on FDA indication

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• ivermectin tablets	20/90 days
• STROMECTOL	20/90 days

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Albendazole tablets [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc; May 2020.
- Albenza (albendazole) tablets [prescribing information]. Bridgewater, NJ: Amneal Pharmaceuticals LLC; September 2019.
- Biltricide (praziquantel) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; January 2019.
- Emverm (mebendazole) [prescribing information]. Wilmington, NC: Alcami; August 2021.
- Krintafel (tafenoquine) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; December 2021.
- Pyrantel pamoate suspension [prescribing information]. Northfield, MN: Jefferson Labs; January 2018.
- Pyrantel pamoate tablet [prescribing information]. Miami, FL: Pro-Mex; January 2018.
- Stromectol (ivermectin) [prescribing information]. Rahway, NJ: Merck Sharp & Dohme; May 2022.

ANTI-INFECTIVES: ANTIMALARIALS

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred		Non-Preferred	
Antimalarials	atovaquone/proguanil	primaquine	COARTEM (artemether/lumefantrine)	QUALAQUIN (quinine)
	chloroquine	quinine sulfate	KRINTAFEL (tafenoquine)	
	mefloquine		MALARONE (atovaquone/proguanil)	

Last Review Date: February 2022

Recent Significant Changes

- No significant updates since last review

Recommendation

It is recommended that at least chloroquine plus at least two other antimalarial agents for use in chloroquine resistant P. falciparum malaria be available for use.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Centers for Disease Control and Prevention (CDC). Malaria. CDC Web site. Updated August 19, 2022. https://www.cdc.gov/parasites/malaria/index.html. Accessed February 23, 2023.
- Coartem (artemether and lumefantrine) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; August 2019.
- Daraprim [package insert], New York, NY: Vyera Pharmaceuticals LLC. August 2017
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. Drugs@FDA: FDA-Approved Drugs. Accessed February 23, 2023.
- Krintafel (tafenoquine) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; December 2021.
- Malarone (atovaquone and proguanil) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; June 2016.
- Qualaquin (quinine sulfate) [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc; August 2019.

ANTIVIRALS: COVID TREATMENT

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
COVID Treatment	LAGEVRIO [PA, QL] (molnupiravir) PAXLOVID [PA, QL] (nirmatrelvir/ritonavir	N/A

Last Review Date: February 2023

Recent Significant Changes

- Beginning November 1, 2023, distribution of Emergency Use Authorization (EUA)-labeled ritonavir-boosted nirmatrelvir by the U.S. government will transition to distribution of commercially available, FDA-approved Paxlovid by Pfizer. The PAXCESS Patient Assistance Program managed by Pfizer on behalf of the government is designed to cover all patients that are uninsured or have government insurance (Medicare/Medicaid/Tricare etc.). Patients, caregivers, prescribers, and pharmacists are authorized to enroll into the program via a website PAXCESS Patient Support Program (iassist.com) or by calling into the program and given a voucher to present to any of the participating pharmacies.

Recommendation

It is recommended that treatments for COVID be available for use.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for LAGEVRIO

Current Criteria:

- Patient is ≥ 18 years of age and older

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for PAXLOVID

Current Criteria:

- Patient is ≥ 12 years of age and older

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- LAGEVRIO 40/5 days
- PAXLOVID 30/5 days

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- "COVID-19 Therapeutics Transition to Commercial Distribution". U.S. Department of Health and Human Services. December 20, 2023. https://aspr.hhs.gov/COVID-19/Therapeutics/updates/Pages/Commercialization-FAQ-Nov2023.aspx
- Lagevrio (molnupiravir) [prescribing information]. Rahway, NJ: Merck Sharp & Dohme LLC; June 2022.
- Paxlovid (nirmatrelvir and ritonavir) [prescribing information]. New York, NY: Pfizer Labs; May 2023.
- PAXCESS. Patient Support Program. Pfizer Inc. 2023. https://paxlovid.iassist.com/

ANTIVIRALS: HEPATITIS B & C INTERFERONS

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
Hepatitis B & C Interferons	ALFERON N (interferon alfa-n3)	N/A

Last Review Date: February 2022

Recent Significant Changes

- Discontinued Drugs:
  - INTRON A, April 2024

Recommendation

Therefore, it is recommended that at least one interferon be available for use.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Alferon N (interferon alfa-n3) [prescribing information]. Philadelphia, PA: Hemispherx Biopharma; August 2012.
- Intron-A (interferon alfa-2b) [prescribing information]. Rahway, NJ: Merck Sharp & Dohme LLC; March 2023.

ANTIVIRALS: HEPATITIS C PEGYLATED INTERFERONS

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
Hepatitis C Pegylated Interferons	PEGASYS syringes PA>24 weeks, QL (peginterferon alfa-2a) PEGASYS vials PA>24 weeks, QL (peginterferon alfa-2a)	N/A

Last Review Date: February 2022

Recent Significant Changes

- No significant changes since last review

Recommendation

It is recommended that peginterferon alfa-2a be available for use, with quantity limits to ensure appropriate duration of therapy.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for PEGASYS SYRINGES AND VIALS

Current Criteria:

- Chronic Hepatitis C and one of the following:
  - Adult Patients: In combination therapy with other hepatitis C virus drugs for adults with compensated liver disease. Pegasys monotherapy is indicated only if patient has contraindication or significant intolerance to other Hepatitis C drugs
  - Pediatric Patients: In combination with ribavirin for pediatric patients 5 years of age and older with compensated liver disease; **OR**
- Chronic Hepatitis B and one of the following:
  - Adult Patients: Treatment of adults with HBeAg-positive and HBeAg-negative chronic hepatitis B (CHB) infection who have compensated liver disease and evidence of viral replication and liver inflammation
  - Pediatric Patients: Treatment of non-cirrhotic pediatric patients 3 years of age and older with HBeAg-positive CHB and evidence of viral replication and elevations in serum alanine aminotransferase (ALT)

Note: Prior authorization will be required after 24 weeks of therapy

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- PEGASYS syringes and vials 4/24 days

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Pegasys (peginterferon alfa-2a) [prescribing information]. Lee's Summit, MO: Summit SD LLC; March 2022.

ANTIVIRALS: HEPATITIS C RIBAVIRINS

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
Hepatitis C Ribavirins	ribavirin capsules ribavirin tablets	

Last Review Date: February 2022

Recent Significant Changes

- Discontinued Drugs:
  - RIBASPHERE (all strengths/dosage forms), 2021
  - RIBAPAK, 2021

Recommendation

It is recommended that at least one ribavirin formulation be available for use.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Ribavirin capsule [package insert], East Windsor, NJ: Aurobindo Pharma USA, Inc.; July 2023.
- Ribavirin tablet [package insert], East Windsor, NJ: Aurobindo Pharma USA, Inc; May 2023.

ANTIVIRALS: HERPES AGENTS, ORAL

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred		Non-Preferred
Herpes Agents, Oral	acyclovir caps, susp, and tabs famciclovir QL	valacyclovir QL	SITAVIG QL (acyclovir) VALTREX QL (valacyclovir)

Last Review Date: February 2022

Recent Significant Changes

- No significant changes since last review

Recommendation

It is recommended that at least two agents in this class should be available for use. Additionally, a suspension or liquid formulation should be available for pediatric patients or those unable to swallow solid oral dosage forms.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• famciclovir 125mg	20/30 days
• famciclovir 250mg	60/30 days
• famciclovir 500mg	3/day and 21/Rx
• valacyclovir 500mg	60/30 days
• valacyclovir 1000mg	30/Rx
• SITAVIG buccal tabs	2/Rx
• VALTREX 500mg	60/30 days
• VALTREX 1000mg	30/Rx

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Acyclovir capsule, tablet [prescribing information]. Fort Lee, NJ: DAVA Pharmaceuticals, Inc; April 2014.
- Famciclovir tablets [prescribing information]. Warren, NJ: Cipla USA Inc; June 2020.
- Sitavig (acyclovir) [prescribing information]. Charleston, SC: EPI Health LLC; December 2019.
- Valtrex (valacyclovir) [prescribing information]. Durham, NC: GlaxoSmithKline; November 2022.

ANTIVIRALS: HIV CCR5 ANTAGONISTS

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred
HIV CCR5 Antagonists	SELZENTRY tablets [PA, QL] (maraviroc) maraviroc tablet [PA, QL]	SELZENTRY solution [PA] (maraviroc)

Last Review Date: February 2022

Recent Significant Changes

- Department of Health and Human Services (DHHS) Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2023)
- DHHS Guidelines for the Use of ARV Agents in Pediatric HIV Infection (2023)
- DHHS Recommendations for the Use of ARV Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States (2023)
- Note: The 2023 DHHS updates remain unchanged for this drug class

Recommendation

It is recommended that CCR5 antagonists be available for use and subject to prior authorization. Additionally, formulations should be available for pediatric patients and patients who cannot swallow.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for SELZENTRY TABLETS, maraviroc tablets

Current Criteria:

- Diagnosis of CCR5-tropic HIV-1 via a co-receptor tropism; **AND**
- Verification that agent will be administered in combination with other antiretroviral agents.

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for SELZENTRY SOLUTION

Current Criteria:

- Diagnosis of CCR5-tropic HIV-1 via a co-receptor tropism; **AND**
- Verification that agent will be administered in combination with other antiretroviral agents; **AND**
- Patient is 11 years of age or younger OR patient is unable to swallow tablets

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- SELZENTRY tablets (75mg, 150mg) 2/day
- SELZENTRY tablets (25mg, 300mg) 4/day
- maraviroc tablets (150mg) 2/day
- maraviroc tablets (300mg) 4/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- DHHS panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Updated March 23, 2023[a]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed November 6, 2023.
- DHHS panel on antiretroviral therapy and medical management of children living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Updated April 11, 2023[b]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf. Accessed November 6, 2023.
- DHHS panel on treatment of pregnant women with HIV infection and prevention of perinatal transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. Updated January 31, 2023[c]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/perinatal-hiv/guidelines-perinatal.pdf. Accessed November 6, 2023.
- Drugs@FDA: FDA approved drug products. Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 6, 2023.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed November 6, 2023.
- Purple Book: Database of Licensed Biological Products [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2023. Available at: https://purplebooksearch.fda.gov/. Accessed November 6, 2023.
- Selzentry (maraviroc) [prescribing information]. Durham, NC: ViiV Healthcare; September 2022.

ANTIVIRALS: HIV NNRTIS

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred		Non-Preferred
Antivirals: HIV NNRTIs	EDURANT (rilpivirine) efavirenz [QL] INTELENCE [PA, QL] (etravirine)	nevirapine [QL] PIFELTRO [QL] (doravirine)	etravirine [PA, QL] nevirapine ER [QL]

Last Review Date: February 2022

Recent Significant Changes

- Department of Health and Human Services (DHHS) Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2023)
- DHHS Guidelines for the Use of ARV Agents in Pediatric HIV Infection (2023)
- DHHS Recommendations for the Use of ARV Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States
- Note: The 2023 DHHS updates remain unchanged for this drug class
- Discontinued Drugs:
  - RESCRIPTOR, 2020
  - SUSTIVA, 2023
  - VIRAMUNE, 2023
  - VIRAMUNE XR, 2023

Recommendation

It is recommended that Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) be available for use. However, etravirine should be subject to prior authorization criteria to ensure use is reserved for treatment-experienced patients with HIV-1 strain resistance and other antiretroviral (ARV) therapy. Additionally, formulations should be available for pediatric patients and those patients who cannot swallow.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for INTELENCE, etravirine

Current Criteria:

- Patient is treatment-experienced; **AND**
- Patient will concomitantly take at least two additional antiretroviral agents; **AND**
- Patient has documented non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• efavirenz 50mg	7/day
• efavirenz 200mg	2/day
• efavirenz 600mg	1/day

- INTELENCE 2/day
- nevirapine 2/day
- nevirapine ER 1/day
- nevirapine suspension 40 mL/day
- PIFELTRO 1/day
- SUSTIVA 50mg 7/day
- SUSTIVA 200mg 2/day
- SUSTIVA 600mg 1/day
- etravirine 2/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- DHHS panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Updated January 20, 2022. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Accessed February 18, 2022.
- DHHS panel on antiretroviral guidelines for pediatric ARV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Updated December 30, 2021[a]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/PedARV_GL.pdf. Accessed February 18, 2022.
- DHHS panel on antiretroviral guidelines for perinatal ARV. Guidelines for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. Updated December 30, 2021[b].
- Edurant (rilpivirine) [prescribing information]. Titusville, NJ: Janssen Therapeutics; October 2022.
- Intelence (etravirine) [prescribing information]. Horsham, PA: Janssen Products LP; March 2023.
- Pifeltro (doravirine) [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; October 2020.
- Rescriptor (delavirdine) [prescribing information]. Research Triangle Park, NC: ViiV Healthcare; August 2019.
- Sustiva (efavirenz) [prescribing information]. Princeton, NJ: Bristol Myers Squibb; December 2020.
- Viramune (nevirapine) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; June 2022.
- Viramune XR (nevirapine) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; June 2022.

ANTIVIRAL: HIV NRTIS

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred		Non-Preferred	
HIV NRTIs	abacavir tablets/solution QL	stavudine QL	EPIVIR tabs/soln QL (lamivudine)	ZIAGEN tabs/soln QL (abacavir)
	emtricitabine QL	tenofovir QL	RETROVIR QL (zidovudine)	
	EMTRIVA QL (emtricitabine)	zidovudine QL	VIREAD tablets QL (tenofovir)	
	lamivudine tabs/soln QL		VIREAD powder (tenofovir)	

Last Review Date: February 2022

Recent Significant Changes

- Department of Health and Human Services (DHHS) Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2023)
- DHHS Guidelines for the Use of ARV Agents in Pediatric HIV Infection (2023)
- DHHS Recommendations for the Use of ARV Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States
- Note: The 2023 DHHS updates remain unchanged for this drug class
- Discontinued Drugs:
  - didanosine, 2022
  - VIDEX, 2021

Recommendation

It is recommended that unique nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) entities indicated for the treatment of HIV-1 infections be available.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for VIREAD POWDER

Current Criteria:

- Patient has had a trial and failure, contraindication, or intolerance to 2 preferred agents; **OR**
- Patient is 6 years of age or younger and being treated for post-exposure prophylaxis (PEP)

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• abacavir tablets	2/day
• abacavir solution	30 mL/day
• emtricitabine	1/day
• EMTRIVA capsules	1/day
• EMTRIVA solution	24 mL/day
• lamivudine 100mg & 300mg tablets	1/day
• lamivudine 150mg tablets	2/day
• lamivudine solution	*30 mL/day*

- stavudine capsules 2/day
- stavudine solution 80 mL/day
- tenofovir 1/day
- zidovudine 100mg 6/day
- zidovudine 300mg 2/day
- zidovudine syrup 60 mL/day
- EPIVIR 150mg tablets 2/day
- EPIVIR 300mg tablets 1/day
- EPIVIR solution *30 mL/day*
- RETROVIR 100mg 6/day
- RETROVIR syrup 60 mL/day
- VIREAD tablets 1/day
- ZIAGEN tablets 2/day
- ZIAGEN solution 30 mL/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- DHHS panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Updated March 23, 2023[a]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed November 6, 2023.
- DHHS panel on antiretroviral therapy and medical management of children living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Updated April 11, 2023[b]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf. Accessed November 6, 2023.
- DHHS panel on treatment of pregnant women with HIV infection and prevention of perinatal transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. Updated January 31, 2023[c]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/perinatal-hiv/guidelines-perinatal.pdf. Accessed November 6, 2023.
- Emtriva (emtricitabine) [prescribing information]. Foster, CA: Gilead Sciences; December 2018.
- Epivir (lamivudine) [prescribing information]. Research Triangle Park, NC: ViiV Healthcare; September 2020.
- Retrovir (zidovudine) [prescribing information]. Durham, NC: ViiV Healthcare; June 2023.
- Stavudine [prescribing information]. Saddle Brook, NJ: Rising Pharmaceuticals Inc; February 2019.
- Videx EC (didanosine) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; December 2020.
- Videx pediatric powder for oral solution (didanosine) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; January 2018.
- Viread (tenofovir) [prescribing information]. Foster City, CA: Gilead Sciences Inc; April 2019.
- Ziagen (abacavir sulfate) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; November 2020.

ANTIVIRALS: PHARMACOKINETIC ENHANCERS

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred	Non-Preferred	
Pharmacokinetic Enhancers	NORVIR solution [QL] (ritonavir) ritonavir tablet [QL]	NORVIR tablet [QL] (ritonavir) NORVIR powder pack [PA, QL] (ritonavir)	TYBOST [PA, QL] (cobicistat)

Last Review Date: February 2022

Recent Significant Changes

- Department of Health and Human Services (DHHS) Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2023)
- DHHS Guidelines for the Use of ARV Agents in Pediatric HIV Infection (2023)
- DHHS Recommendations for the Use of ARV Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States
- Note: The 2023 DHHS updates remain unchanged for this drug class

Recommendation

It is recommended to have ritonavir available for use due to its safety and tolerability in various age groups and in pregnancy/breast feeding. It is recommended that cobicistat be subject to criteria due to potential adverse effects.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for NORVIR POWDER PACK

Current Criteria:

- One of the following:
  - Patient has a diagnosis of HIV-1; **AND**
    - Patient will be taking in combination with other antiretroviral agents; **AND**
    - Patient is ≤ 18 years of age; **OR**
  - Clinically valid reason why the preferred ritonavir (e.g., Norvir) oral solution cannot be used, including patients with polyurethane feeding tubes.

Note: Norvir oral powder should only be used for dosing increments of 100 mg; prescribed dosing should not be written for <100 mg increments

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for TYBOST

Current Criteria:

- Verification that agent will be administered in combination with Prezista® (darunavir) **OR** atazanavir; **AND**
- Patient has a contraindication to OR has experienced an adverse reaction to ritonavir; **AND**
- Patient is not pregnant; **AND**
- Patient does not have renal impairment

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

- ritonavir tablet 12/day
- NORVIR solution 15 mL/day
- NORVIR tablets powder pack 12/day
- NORVIR tablets (150mg) 12/day
- TYBOST 1/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- DHHS panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Updated March 23, 2023[a]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed November 6, 2023.
- DHHS panel on antiretroviral therapy and medical management of children living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Updated April 11, 2023[b]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf. Accessed November 6, 2023.
- DHHS panel on treatment of pregnant women with HIV infection and prevention of perinatal transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. Updated January 31, 2023[c]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/perinatal-hiv/guidelines-perinatal.pdf. Accessed November 6, 2023.
- Norvir (ritonavir) capsules [prescribing information]. North Chicago, IL: AbbVie Inc; October 2020.
- Norvir (ritonavir) tablets, oral solution, and oral powder [prescribing information]. North Chicago, IL: AbbVie Inc; December 2022.
- Tybost (cobicistat) [prescribing information]. Foster City, CA: Gilead Sciences Inc; September 2021.

ANTIVIRALS: HIV PROTEASE INHIBITORS

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred		Non-Preferred
HIV Protease Inhibitors	atazanavir capsules QL darunavir QL EVOTAZ QL (atazanavir/cobicistat) fosamprenavir QL LEXIVA QL (fosamprenavir)	lopinavir/ritonavir QL PREZCOBIX QL (darunavir/cobicistat) REYATAZ powder QL (atazanavir) VIRACEPT QL (nelfinavir)	APTIVUS PA, QL (tipranavir) KALETRA QL (lopinavir/ritonavir) PREZISTA QL (darunavir) REYATAZ caps QL (atazanavir)

Last Review Date: February 2022

Recent Significant Changes

- Department of Health and Human Services (DHHS) Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2023)
- DHHS Guidelines for the Use of ARV Agents in Pediatric HIV Infection (2023)
- DHHS Recommendations for the Use of ARV Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States
- Note: The 2023 DHHS updates remain unchanged for this drug class
- Discontinued Drugs:
  - INVIRASE, 2023

Recommendation

It is recommended that all first-line Protease Inhibitors (PI) for treatment-naïve patients be available for use. ~~However, it is recommended that tipranavir, fosamprenavir, indinavir, nelfinavir, and saquinavir be reserved for use in treatment experienced patients.~~ Additionally, formulations should be available for pediatric patients. ~~or those patients who cannot swallow~~.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for APTIVUS

Current Criteria:

- Confirm that patient has had previous exposure to at least one PI indicated for first line therapy

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• APTIVUS capsules	4/day
• APTIVUS solution	10 mL/day
• atazanavir 300mg capsules	1/day
• atazanavir 150mg, 200mg capsules	2/day
• EVOTAZ	1/day
• fosamprenavir	4/day

- INVIRASE 200mg 10/day
- INVIRASE 500mg 4/day
- LEXIVA 700mg 4/day
- LEXIVA suspension 56 mL/day
- lopinavir/ritonavir tablets 6/day
- lopinavir/ritonavir solution 15 mL/day
- PREZCOBIX 1/day
- PREZISTA 800mg 1/day
- PREZISTA (all other strengths) 2/day
- PREZISTA suspension 12 mL/day
- REYATAZ powder 5/day
- VIRACEPT tablets 4/day
- darunavir 800mg 1/day
- darunavir (all other strengths) 2/day
- darunavir suspension 12 mL/day
- KALETRA tablets 6/day
- KALETRA solution 15 mL/day
- REYATAZ 300mg capsules 1/day
- REYATAZ 150mg, 200mg capsules 2/day

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- Aptivus (tipranavir) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; June 2020.
- Atazanavir capsules [prescribing information]. Piscataway, NJ: Camber Pharmaceuticals; January 2022.
- DHHS panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Updated March 23, 2023[a]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed November 6, 2023.
- DHHS panel on antiretroviral therapy and medical management of children living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Updated April 11, 2023[b]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf. Accessed November 6, 2023.
- DHHS panel on treatment of pregnant women with HIV infection and prevention of perinatal transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. Updated January 31, 2023[c]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/perinatal-hiv/guidelines-perinatal.pdf. Accessed November 6, 2023.
- Evotaz (atazanavir and cobicistat) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; May 2023.
- Invirase (saquinavir) [prescribing information]. South San Francisco, CA: Genentech Inc; September 2020.
- Keletra (lopinavir and ritonavir) capsule [prescribing information]. North Chicago, IL: AbbVie Inc; October 2020.
- Keletra (lopinavir and ritonavir) tablets and oral solution [prescribing information]. North Chicago, IL: AbbVie Inc; April 2020.
- Lexiva (fosamprenavir) [prescribing information]. Research Triangle Park, NC: ViiV Healthcare; October 2020.
- Prezcobix (darunavir/cobicistat) [prescribing information]. Horsham, PA: Janssen Products LP; March 2023.
- Prezista (darunavir) [prescribing information]. Titusville, NJ: Janssen Therapeutics; June 2020.
- Viracept (nelfinavir) [prescribing information]. Research Triangle Park, NC: ViiV Healthcare Company; March 2021.

ANTIVIRALS: INFLUENZA

Abbreviated Re-Review: Pharmacy Initiatives

PDL Placement:

	Preferred		Non-Preferred	
Antivirals: Influenza	oseltamivir caps QL oseltamivir susp QL	RELENZA QL (zanamivir)	TAMIFLU caps QL (oseltamivir) TAMIFLU susp QL (oseltamivir)	XOFLUZA PA, QL (baloxavir marboxil)

Last Review Date: May 2019

Recent Significant Changes

- American Academy of Pediatrics Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children (2023-2024)
- Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians. (2023)

Recommendation

It is recommended that at least 2 influenza agents be available for use. Baloxavir should be reserved for strains resistant to preferred agents.

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Prior Authorization criteria for XOFLUZA

Current Criteria:

- Agent is being used for treatment of influenza OR post-exposure prophylaxis of influenza; **AND**
- Treatment is being used for ONE of the following:
  - Acute uncomplicated influenza in patients > 5 years of age who have been symptomatic for no more than 48 hours and who are otherwise healthy
  - Acute uncomplicated influenza in patients > 12 years of age who are at high risk of developing influenza-related complications
  - Post-exposure prophylaxis of influenza in patients > 5 years of age; **AND**
- One of the following:
  - Contraindication to both Relenza® and Tamiflu® that is not associated with requested agent
  - Area surveillance data that indicates an oseltamivir resistant strain
  - Recurrent documented influenza in the same flu season that was previously treated with a preferred agent

Proposed Criteria:

Same as current

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

Quantity Limits

• oseltamivir caps	20/180 days
• oseltamivir 6 mg/mL susp	~~240~~ *300* mL/180 days
• RELENZA	40/180 days
• TAMIFLU caps	20/180 days
• TAMIFLU 6 mg/mL	~~240~~ *300* mL/180 days
• XOFLUZA	2/Rx

COMMITTEE VOTE

APPROVED **DISAPPROVED** **APPROVED with MODIFICATION**

References

- American Academy of Pediatrics Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2023-2024. Pediatrics. 2023; 152 (4):e2023063772. doi:10.1542/peds.2023-063772
- Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians. Updated September 27, 2023. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed November 16, 2023.
- Oseltamivir [prescribing information]. Morristown, NJ: Alvogen, Inc; December 2020.
- Relenza (zanamivir) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; October 2021.
- Tamiflu (oseltamivir) [prescribing information]. South San Francisco, CA: Genentech, Inc; August 2019.
- Xofluza [package insert], South San Francisco, CA: Genentech, Inc; June 2023.

Low Utilization and/or Low-Cost Drug Classes

Identified drug classes have been reviewed but will not be included in the drug class reviews based on low utilization and/ or low-cost of the drug class. These classes have no professional guideline updates and do not have prior authorization criteria changes.

- **Antibiotics: Aminoglycosides, Oral**
- **Antibiotics: Methenamine and Combinations**
- **Anti-Infectives: Amebicides**