PREFERRED SPECIALTY MANAGEMENT POLICY

POLICY: Human Immunodeficiency Virus - Prezcobix Preferred Specialty Management Policy (Basic Formulary)

- atazanavir capsules (generic only – multiple manufacturers)
- Kaletra® (lopinavir/ritonavir tablets/oral solution – AbbVie, generic [oral solution only])
- Prezcobix® (darunavir/cobicistat tablets – Janssen)
- Prezista® (darunavir tablets – AbbVie)
- ritonavir tablets (generic only – multiple manufacturers)

REVIEW DATE: 05/18/2022

OVERVIEW

Prezcobix is a two-drug combination of darunavir, a human immunodeficiency virus (HIV)-1 protease inhibitor (PI), and cobicistat, a cytochrome P450(CYP)3A inhibitor.[1] It is indicated for the treatment of **HIV-1 infection** in treatment-naïve and treatment-experienced adults and pediatric patients ≥ 40 kg with no darunavir resistance-associated substitutions.

Other FDA-approved PIs are: Reyataz® (atazanavir capsule [generics], oral powder), Evotaz® (atazanavir/cobicistat tablet), Prezista® (darunavir tablets), Lexiva® (fosamprenavir tablets [generics]/oral solution), Crixivan® (indinavir capsules), Kaletra® (lopinavir/ritonavir oral solution [generics], tablets), Viracept® (nelfinavir tablet), Norvir® (tablet [generics]/powder packet/solution), Invirase® (saquinavir tablet), and Aptivus® (tipranavir capsule/oral solution).[4-14] In addition, cobicistat is available as a single-entity product, Tybost®, which is indicated to increase systemic exposure of atazanavir or darunavir (once daily [QD] dosing regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection.[3]

All of the PIs (boosted by either ritonavir or cobicistat) inhibit the CYP3A4 isoenzyme, which may lead to significant drug-drug interactions.[2] PI-based regimens with pharmacokinetic enhancement (boosting) have demonstrated virologic potency, durability in treatment-naive patients, and a high barrier to resistance.

Table 1 provides the indications for selected protease inhibitors applicable to this *Preferred Specialty Management Policy.*

Table 1. Indications for Selected Protease Inhibitors.[1,4-6,8] *

Name	Indication
Protease Inhibitor/Pharmacokinetic Booster Combinations	
Evotaz® (atazanavir/cobicistat tablets)	For use in combination with other ARVs for the treatment of HIV-1 infection in adults and pediatric patients ≥ 35 kg. Use of Evotaz in treatment-experienced patients should be guided by the number of baseline primary protease inhibitor resistance substitutions.
Kaletra® (lopinavir/ritonavir oral solution [generics], tablets)	In combination with other ARVs for the treatment of HIV-1 infection in adults and pediatric patients (≥ 14 days).

Table 1 (continued). Indications for Selected Protease Inhibitors.[1,4-6,8] *

Name	Indication
Protease Inhibitor/Pharmacokinetic Booster Combinations (continued)	
Prezcobix® (atazanavir/cobicistat tablets)	For the treatment of HIV-1 infection in treatment-naïve and treatment-experienced adults with no darunavir resistance-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V).
Protease Inhibitor Single-Entity Products	
Norvir® (ritonavir tablet [generics]/powder packet/solution)	Norvir tablets and oral solution are indicated in combination with other ARVs for the treatment of HIV-1 infection. Norvir oral powder is indicated in combination with other ARVs for the treatment of pediatric patients with HIV-1 infection.
Reyataz® (atazanavir capsule [generic]/oral powder)	For use in combination with other ARVs for the treatment of HIV-1 infection for patients ≥ 3 months weighing ≥ 5 kg.

* Reyataz (brand only, capsules and powder packets) and lopinavir/ritonavir (generic capsules) are not targeted in this Preferred Specialty Management Policy; ARV – Antiretroviral; HIV – Human immunodeficiency virus; PI – Protease inhibitor.

GUIDELINES

The **Department of Health and Human Services (DHHS) [January 21, 2022]** Guidelines for Adults and Adolescents with HIV address treatment-initiation in antiretroviral-naïve individuals. Antiretroviral therapy is recommended for all persons with HIV regardless of CD4 cell count.[2]

Prezcobix is not one of the recommended initial antiretroviral regimens recommended for individuals with HIV-1 who are treatment-naïve.[2] All of the recommended initial regimens contain an integrase strand-transfer inhibitor (INSTI). However, in situations where antiretroviral therapy needs to begin urgently, prior to the availability of resistance testing results, PI-based regimens are generally recommended because transmitted PI resistance is uncommon.[2] In these instances boosted Prezista may be an appropriate choice, as there is a low rate of transmitted PI resistance, it has a high barrier to resistance, and there is a low rate of treatment-emergent resistance. Additionally, because mutations are not often detected when a patient fails their first PI regimen, this class may be useful for patients at risk for intermittent therapy due to poor adherence. PIs that are recommended for use in antiretroviral-naïve patients should have proven virologic efficacy, be administered QD, have a lower pill count than older PI-based regimens, and have good tolerability. On the basis of these criteria, the Panel considers Prezcobix, Prezista + Norvir, Evotaz, or Reyataz + Norvir together with two nucleoside reverse transcriptase inhibitors (NRTIs) as PI-based regimen options in the category of "Recommended Initial Regimens in Certain Clinical Situations". Compared to other PIs, Kaletra, Lexiva + Norvir, unboosted Reyataz, and Invirase have disadvantages such as greater pill burden, lower efficacy, or increased toxicity, and thus are no longer included as options for initial therapy.

Several metabolic abnormalities, including dyslipidemia and insulin resistance, have been associated with PI use. The currently available PIs differ in their propensity to cause these metabolic complications, which also depends on the dose of Norvir used as a pharmacokinetic-enhancing agent. Large observational cohort studies found an association between some PIs (i.e., Norvir-boosted Prezista, fosamprenavir, indinavir, and Kaletra) and an increased risk of cardiovascular events; this risk was not seen with Reyataz. Another observational cohort study of predominantly male participants found a lower rate of cardiovascular events in those receiving Reyataz-containing regimens compared to those receiving other regimens. Further study is needed.

The International Antiviral Society-USA (IAS-USA) Panel (October 2020) recommendations are similar to the DHHS guidelines for recommended initial ARV regimens.[3] Prezcobix is recognized as a potential component of initial ARV therapy in patients with known or suspected pre-therapy multidrug resistance, for patients who have resistance to INSTIs, and for patients at high risk of poor adherence due to the high barrier to resistance of darunavir.

According to the **Perinatal Guidelines from the HHS Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (March 17, 2022)** all pregnant women with HIV should initiate antiretroviral therapy as early in pregnancy as possible, regardless of their HIV RNA level or CD4 T lymphocyte count.[6] In general, the recommendations for the use of ARVs in pregnant women are the same as those for women who are not pregnant. However, they may differ in some instances where regimen selection is modified based on concerns about specific drugs or limited experience with newer drugs during pregnancy. Preferred antiretroviral regimens in pregnant women are: Norvir-boosted Reyataz + two NRTIs, Norvir-boosted Prezista + two NRTIs, Triumeq® (dolutegravir/abacavir/lamivudine tablets), Tivicay® (dolutegravir tablets) + two NRTIs, or Isentress® (raltegravir tablets/chewable tablets/powder)/Isentress HD (raltegravir tablets) + two NRTIs. Kaletra is not recommended for initiation in pregnancy, except in special circumstances. However, women who conceive on a suppressive, well-tolerated regimen, including Kaletra, should continue this regimen.

According to the **DHHS Guidelines for the Use of ARV Agents in Pediatric HIV Infection (April 11, 2022)** the selection of an initial regimen should be individualized.[7] For treatment-naive children, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends initiating therapy with three drugs: a two-drug NTRI backbone plus an INSTI, a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor (PI). Similar to the adult and adolescent guidelines, pediatric guidelines classify treatments as recommended or alternative. When combined with two NRTIs, the following are preferred regimens in children: Viramune® (nevirapine tablets/oral suspension) [age < 14 days], Isentress (age < 4 weeks and weight ≥ 2 kg) [Isentress HD is only indicated for patients ≥ 40 kg], Kaletra (age ≥ 14 days to < 4 weeks), Tivicay (≥ 4 weeks and ≥ 3 kg), or Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide) [age ≥ 6 weeks and ≥ 14 kg]. Prezcobix is not among the preferred regimens for initial treatment in pediatric patients. Norvir-boosted Prezista + a two-NRTI backbone is recommended as an alternative PI-based regimen for children ≥ 3 years of age and weighing ≥ 10 kg and for adolescents ≥ 12 years of age and weighing ≥ 40 kg who are not sexually mature. Additionally, Norvir-boosted Reyataz + a two-NRTI backbone is an alternative PI-based regimen for children ≥ 3 months of age and Evotaz + a two-NRTI backbone is an alternative PI-based regimen for children weighing ≥ 35 kg.

POLICY STATEMENT

This Preferred Specialty Management program has been developed to encourage the use of Preferred Products. The program also directs the patient to try one Preferred Product prior to the approval of a Non-Preferred Product. Requests for Non-Preferred Products will also be reviewed using the exception criteria (below). All approvals are provided for 1 year.

Automation: Patients with a of one Preferred Product within the 130-day look-back period are excluded from PSM.

Preferred Products:	atazanavir capsules (generic only), ritonavir tablets (generic only), Kaletra tablets/oral solution, lopinavir/ritonavir oral solution, Prezista tablets.
Non-Preferred Product:	Prezcobix

RECOMMENDED EXCEPTION CRITERIA

Non-Preferred Product	Exception Criteria
Prezcobix	**1.** Approve for 1 year if the patient meets ONE of the following (A, B, C, or D): **A)** Patient is currently receiving Prezcobix; OR **B)** Patient has tried Evotaz (atazanavir/cobicistat tablets), Reyataz ([Brand] atazanavir capsule/oral powder), Norvir ([Brand] ritonavir tablet/oral solution/oral powder), or Tybost (cobicistat tablets); OR **C)** According to the prescriber, the patient needs to begin antiretroviral therapy urgently; OR **D)** Patient has tried one Preferred Product.

REFERENCES

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2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. January 21, 2022. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/guidelines-adult-adolescent-arv.pdf. Accessed on May 4, 2022.
3. Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV in adults. 2020 recommendations of the International Antiviral Society USA Panel. *JAMA*. 2020;324(16):1651-1669.
4. Kaletra® tablets/oral solution [prescribing information]. North Chicago, IL: AbbVie; December 2020.
5. Norvir® tablets/oral solution/oral powder [prescribing information]. North Chicago, IL: AbbVie; October 2020.
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8. Evotaz® tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; July 2020.
9. Health and Human Services Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission – a working group of the Office of AIDS Research Advisory Council (ORAC). Perinatal Guidelines: Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Transmission in the United States. Last updated March 17, 2022. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Perinatal_GL.pdf. Accessed on May 5, 2022.