PREZCOBIX®
(darunavir and cobicistat) tablets, for oral use

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PREZCOBIX® safely and effectively. See full prescribing information for PREZCOBIX.

PREZCOBIX (darunavir and cobicistat) tablets, for oral use

Initial U.S. Approval: 2015

--- RECENT MAJOR CHANGES ----------------------------------------------- 07/2020

Indication and Usage (1) 07/2020
Dosage and Administration, Recommended Dosage (2.1) 07/2020

--- INDICATIONS AND USAGE -----------------------------------------------

PREZCOBIX is a two-drug combination of darunavir, a human immunodeficiency virus (HIV-1) protease inhibitor, and cobicistat, a CYP3A inhibitor, and is indicated for the treatment of HIV-1 infection in treatment-naive and treatment-experienced adults and pediatric patients weighing at least 40 kg with no darunavir resistance-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V). (1)

--- DOSAGE AND ADMINISTRATION --------------------------------------------

Recommended dosage: One tablet taken once daily with food in adults and pediatric patients weighing at least 40 kg. (2.1)

Testing Prior to Initiation: HIV genotypic testing is recommended for antiretroviral treatment experienced patients. Assess estimated creatinine clearance in all patients prior to starting PREZCOBIX. When used with tenofovir DF: Assess urine glucose and urine protein at baseline and monitor creatinine clearance, urine glucose, and urine protein. Monitor serum phosphorus in patients with or at risk for renal impairment. (2.2)

--- DOSAGE FORMS AND STRENGTHS ------------------------------------------

Tablets: 800 mg of darunavir and 150 mg of cobicistat. (3)

--- CONTRAINDICATIONS -----------------------------------------------------

PREZCOBIX is contraindicated in patients receiving certain co-administered drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or loss of therapeutic effect. (4, 7.2)

--- WARNINGS AND PRECAUTIONS --------------------------------------------

• Drug-induced hepatitis (e.g., acute hepatitis, cytolysis), liver injury, including some fatalities can occur with PREZCOBIX. Monitor liver function before and during therapy, especially in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases. (5.1)

--- DRUG INTERACTIONS -----------------------------------------------------

• Skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms and acute generalized exanthematous pustulosis, can occur with PREZCOBIX. Discontinue treatment if severe reaction develops. (5.2)

• When PREZCOBIX is used in combination with a tenofovir disoproxil fumarate (tenofovir DF) containing regimen, cases of acute renal failure and Fanconi syndrome have been reported. (5.4)

• PREZCOBIX is not recommended in combination with other antiretroviral drugs that require pharmacokinetic boosting. (5.6)

• Monitor in patients with a known sulfonamide allergy. (5.7)

• Patients receiving PREZCOBIX may develop new onset or exacerbations of diabetes mellitus/hyperglycemia (5.8), redistribution/accumulation of body fat (5.9), and immune reconstitution syndrome. (5.10)

• Patients with hemophilia may develop increased bleeding events. (5.11)

--- USE IN SPECIFIC POPULATIONS ------------------------------------------

• Pregnancy: PREZCOBIX is not recommended during pregnancy due to substantially lower exposures of darunavir and cobicistat during pregnancy. (8.1, 12.3)

• Lactation: Breastfeeding is not recommended. (8.2)

• Pediatrics: Not recommended for pediatric patients weighing less than 40 kg. (8.4)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Products, LP at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--- CLINICAL PHARMACOLOGY -----------------------------------------------

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14.1 Clinical Trial Results in Adults with HIV-1 Infection
14.2 Clinical Trial Results in Pediatric Subjects with HIV-1 Infection

--- HOW SUPPLIED/STORAGE AND HANDLING --------------------------------

17. PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
PREZCOBIX (darunavir and cobicistat) tablets

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
PREZCOBIX® is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in treatment-naïve and treatment-experienced adults and pediatric patients weighing at least 40 kg with no darunavir resistance-associated substitutions (V11I, V32I, I54L, IS45L, IS54M, T74P, L76V, I84V, L89V).

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing
PREZCOBIX is a fixed-dose combination product containing 800 mg of darunavir and 150 mg of cobicistat. In treatment-naïve and treatment-experienced adults and pediatric patients weighing at least 40 kg with no darunavir resistance-associated substitutions, the recommended dosage of PREZCOBIX is one tablet taken once daily orally with food. Administer PREZCOBIX in conjunction with other antiretroviral agents.

2.2 Testing Prior to Initiation of PREZCOBIX
HIV Genotypic Testing
HIV genotypic testing is recommended for antiretroviral treatment-experienced patients. However, when HIV genotypic testing is not feasible, PREZCOBIX can be used in protease inhibitor naïve patients, but is not recommended in protease inhibitor-experienced patients.

Creatinine Clearance
Prior to starting PREZCOBIX, assess estimated creatinine clearance because cobicistat decreases estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function [see Warnings and Precautions (5.3)]. When co-administering PREZCOBIX with tenofovir disoproxil fumarate (tenofovir DF) assess estimated creatinine clearance, urine glucose, and urine protein at baseline [see Warnings and Precautions (5.4)].

2.3 Not Recommended in Severe Renal Impairment
PREZCOBIX co-administered with tenofovir DF is not recommended in patients who have an estimated creatinine clearance below 70 mL per minute [see Warnings and Precautions (5.4) and Adverse Reactions (6.1)].

2.4 Not Recommended in Severe Hepatic Impairment
PREZCOBIX is not recommended for use in patients with severe hepatic impairment [see Use in Specific Populations (8.8) and Clinical Pharmacology (12.3)].

2.5 Not Recommended During Pregnancy
PREZCOBIX is not recommended during pregnancy because of substantially lower exposures of darunavir and cobicistat during the second and third trimesters [see Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]. PREZCOBIX should not be initiated in pregnant individuals. An alternative regimen is recommended for those who become pregnant during therapy with PREZCOBIX.

3 DOSAGE FORMS AND STRENGTHS
PREZCOBIX is supplied as pink, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 800 mg of darunavir and 150 mg cobicistat. Each tablet is debossed with “800” on one side and “TG” on the other side.

4 CONTRAINDICATIONS
PREZCOBIX is contraindicated in patients receiving the following co-administered drugs [see Drug Interactions (7.3) and Clinical Pharmacology (12.3)].

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Anti-gout: colchicine, in patients with renal and/or hepatic impairment
- Antimycobacterial: rifampin
- Antipsychotics: lurasidone, pimozide
- Cardiac Disorders: dronedarone, ivabradine, ranolazine
- Antipsychotics: lurasidone, pimozide
- PDE-5 inhibitor: sildenafil when used for treatment of pulmonary arterial hypertension
- Sedatives/hypnotics: orally administered midazolam, triazolam

5 WARNINGS AND PRECAUTIONS
5.1 Hepatotoxicity
During the darunavir clinical development program (N=3063), where darunavir was co-administered with ritonavir 100 mg once or twice daily, severe skin reactions, accompanied by fever and/or elevations of transaminases, especially during the first several months of PREZCOBIX treatment. Evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on PREZCOBIX should prompt consideration of interruption or discontinuation of treatment.

5.2 Severe Skin Reactions
During the darunavir clinical development program (N=3063), where darunavir was co-administered with ritonavir 100 mg once or twice daily, severe skin reactions, accompanied by fever and/or elevations of transaminases in some cases, was reported in 0.4% of subjects. Stevens-Johnson Syndrome was rarely (less than 0.1%) reported during the clinical development program. During post-marketing experience toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis have been reported.

Discontinue PREZCOBIX immediately if signs or symptoms of severe skin reactions develop. These can include but are not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Mild-to-moderate rash was also reported and often occurred within the first four weeks of treatment and resolved with continued dosing.

5.3 Effects on Serum Creatinine
Cobicistat decreases estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when interpreting changes in estimated creatinine clearance in patients initiating PREZCOBIX, particularly in patients with medical conditions or receiving drugs needing monitoring with estimated creatinine clearance.

Prior to initiating therapy with PREZCOBIX, assess estimated creatinine clearance [see Dosage and Administration (2.2)]. Dosage recommendations are not available for drugs that require dosage adjustments in PREZCOBIX-treated patients with renal impairment [see Drug Interactions (7.3) and Clinical Pharmacology (12.2)]. Consider alternative medications that do not require dosage adjustments in patients with renal impairment.

Although cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function, patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg/dL from baseline should be closely monitored for renal safety.

5.4 New Onset or Worsening Renal Impairment When Used With Tenofovir Disoproxil Fumarate
Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported when cobicistat, a component of PREZCOBIX, was used in an antiretroviral regimen that contained tenofovir DF. Co-administration of PREZCOBIX and tenofovir DF is not recommended in patients who have an estimated creatinine clearance below 70 mL/min [see Dosage and Administration (2.3)].

Document urine glucose and urine protein at baseline [see Dosage and Administration (2.2)] and perform routine monitoring of estimated creatinine clearance, urine glucose, and urine protein during treatment when PREZCOBIX is used with tenofovir DF. Measure serum phosphorus in patients with or at risk for renal impairment when used with tenofovir DF.

Co-administration of PREZCOBIX and tenofovir DF in combination with concomitant or recent use of a nephrotoxic agent is not recommended.

See cobicistat full prescribing information for additional information regarding cobicistat.

5.5 Risk of Serious Adverse Reactions or Loss of Virologic Response Due to Drug Interactions
Initiation of PREZCOBIX, which inhibits CYP3A, in patients receiving medications metabolized by CYP3A, or initiation of medications metabolized by CYP3A in patients already receiving PREZCOBIX may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may respectively increase or decrease concentrations of PREZCOBIX.

Increased concentrations may lead to:

- clinically significant adverse reactions, potentially leading to severe, life threatening, or fatal events from higher exposures of concomitant medications.
- clinically significant adverse reactions from higher exposures of PREZCOBIX.

Decreased antiretroviral concentrations may lead to:

- loss of therapeutic effect of PREZCOBIX and possible development of resistance.
PREZCOBIX (darunavir and cobicistat) tablets

See Table 1 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during PREZCOBIX therapy; review concomitant medications during PREZCOBIX therapy; and monitor for the adverse reactions associated with concomitant medications [see Contraindications (4) and Drug Interactions (7)].

When used with concomitant medications, PREZCOBIX may result in different drug interactions than those observed or expected with darunavir co-administered with ritonavir. Complex or unknown mechanisms of drug interactions preclude extrapolation of drug interactions with darunavir co-administered with ritonavir to certain PREZCOBIX interactions [see Drug Interactions (7) and Clinical Pharmacology (12.3)].

5.6 Antiretrovirals Not Recommended
PREZCOBIX is not recommended in combination with other antiretroviral drugs that require pharmacokinetic boosting (i.e., another protease inhibitor or elvitegravir), because dosing recommendations for such combinations have not been established and co-administration may result in decreased plasma concentrations of the antiretroviral agents, leading to loss of therapeutic effect and development of resistance.

PREZCOBIX is not recommended in combination with products containing the individual components of PREZCOBIX (darunavir and cobicistat) or with ritonavir. For additional recommendations on use of PREZCOBIX with other antiretroviral agents, [see Drug Interactions (7)].

5.7 Sulfia Allergy
Darunavir contains a sulfonamide moiety. Monitor patients with a known sulfonamide allergy after initiating PREZCOBIX. In clinical studies with darunavir co-administered with ritonavir, the incidence and severity of rash were similar in subjects with or without a history of sulfonamide allergy.

5.8 Diabetes Mellitus/Hyperglycemia
New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in patients with HIV-1 infection receiving HIV protease inhibitor (PI) therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued PI therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between HIV PI therapy and these events have not been established.

5.9 Fat Redistribution
Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.10 Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including PREZCOBIX. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves’ disease, polymyositis, Guillain-Barré syndrome and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of antiretroviral treatment.

5.11 Hemophilia
There have been reports of increased bleeding, including spontaneous skin hematoma and hemarthrosis in patients with hemophilia type A and B treated with HIV PIs. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with HIV PIs was continued or reintroduced if treatment had been discontinued. A causal relationship between PI therapy and these episodes has not been established.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in other sections of the labeling:
- Hepatotoxicity [see Warnings and Precautions (5.1)]
- Severe skin reactions [see Warnings and Precautions (5.2)]
- Effects on serum creatinine [see Warnings and Precautions (5.3)]
- New onset or worsening renal impairment when used with tenofovir DF [see Warnings and Precautions (5.4)]
- Immune Reconstitution Syndrome [see Warnings and Precautions (5.10)]
<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV-1 antiviral agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>↔ darunavir ↔ cobicistat ↔ didanosine</td>
<td>Didanosine should be administered one hour before or two hours after PREZCOBIX (administered with food).</td>
</tr>
<tr>
<td><strong>HIV-1 antiviral agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>↓ cobicistat ↓ darunavir</td>
<td>Co-administration with efavirenz is not recommended because it may result in loss of therapeutic effect and development of resistance to darunavir.</td>
</tr>
<tr>
<td>Etravirine</td>
<td>↓ cobicistat darunavir: effect unknown</td>
<td>Co-administration with etravirine is not recommended because it may result in loss of therapeutic effect and development of resistance to darunavir.</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>↓ cobicistat darunavir: effect unknown</td>
<td>Co-administration with nevirapine is not recommended because it may result in loss of therapeutic effect and development of resistance to darunavir.</td>
</tr>
<tr>
<td><strong>HIV-1 antiviral agents: CCR5 co-receptor antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>↑ maraviroc</td>
<td>Maraviroc is a substrate of CYP3A. When co-administered with PREZCOBIX, patients should receive maraviroc 150 mg twice daily.</td>
</tr>
<tr>
<td><strong>Other agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha 1-adrenoreceptor antagonist: Alfuzosin</td>
<td>↑ alfuzosin</td>
<td>Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as hypotension.</td>
</tr>
<tr>
<td>Antibacterials: clarithromycin, erythromycin, telithromycin</td>
<td>↑ darunavir ↑ cobicistat ↑ antibacterial</td>
<td>Consider alternative antibiotics with concomitant use of PREZCOBIX.</td>
</tr>
<tr>
<td>Anticancer agents: dasatinib, nilotinib</td>
<td>↑ anticancer agent</td>
<td>A decrease in the dosage or an adjustment of the dosing interval of dasatinib or nilotinib may be necessary when co-administered with PREZCOBIX. Consult the dasatinib and nilotinib prescribing information for dosing instructions. For vincristine and vinblastine, consider temporarily withholding the cobicistat-containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when PREZCOBIX is administered concurrently with vincristine or vinblastine. If the antiretroviral regimen must be withheld for a prolonged period, consider initiating a revised regimen that does not include a CYP3A or P-gp inhibitor.</td>
</tr>
<tr>
<td>vinblastine, vincristine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 1: Established and Other Potentially Significant* Drug Interactions: Alterations in Dose or Regimen May Be Recommended (continued)

<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antifungals:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>itraconazole, isavuconazole, ketoconazole, posaconazole</td>
<td>↑ darunavir ↑ cobicistat ↑↑ trimetazidine</td>
<td>Monitor for increased darunavir or cobicistat and/or antifungal adverse reactions. Specific dosing recommendations are not available for co-administration with these antifungals. Monitor for increased itraconazole or ketoconazole adverse reactions. Co-administration with posaconazole is not recommended unless benefit/risk assessment justifies the use of voriconazole.</td>
</tr>
<tr>
<td>voriconazole</td>
<td>↔ posaconazole voriconazole: effects unknown</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-gout:</strong> colchicine</td>
<td>↑ colchicine</td>
<td>Co-administration is contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions. For patients without renal or hepatic impairment: • Treatment of gout flares – co-administration of colchicine: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. • Prophylaxis of gout flares – co-administration of colchicine: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. • Treatment of familial Mediterranean fever – co-administration of colchicine: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).</td>
</tr>
<tr>
<td><strong>Antimarial:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>artemether/ lumefantrine</td>
<td>artemether: effect unknown lumefantrine: effect unknown</td>
<td>Monitor for a potential decrease of antimalarial efficacy or potential QT prolongation.</td>
</tr>
<tr>
<td><strong>Antimycobacterials:</strong> rifampin</td>
<td>↓ rifabutin ↓ rifampin rifabutin: effects unknown rifampin: effects unknown</td>
<td>Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance. When used in combination with PREZCOBIX, the recommended dose of rifabutin is 150 mg every other day. Monitor for rifabutin-associated adverse reactions including neutropenia and uveitis. Co-administration with rifapentine is not recommended.</td>
</tr>
<tr>
<td>rifabutin</td>
<td>↑ rifabutin rifabutin: effects unknown rifabutin: effects unknown</td>
<td></td>
</tr>
<tr>
<td>rifapentine</td>
<td>↓ darunavir</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium Disorders:</strong> ranolazine</td>
<td>↑ ranolazine</td>
<td>Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.</td>
</tr>
<tr>
<td>ivabradine</td>
<td>↑ ivabradine</td>
<td></td>
</tr>
<tr>
<td><strong>β-Blockers:</strong></td>
<td>↑ beta-blockers</td>
<td>Clinical monitoring is recommended for co-administration with beta-blockers that are metabolized by CYP2D6.</td>
</tr>
<tr>
<td>e.g. carvedilol, metoprolol, timolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Calcium channel blockers:</strong></td>
<td>↑ calcium channel blockers</td>
<td>Clinical monitoring is recommended for co-administration with calcium channel blockers metabolized by CYP3A.</td>
</tr>
<tr>
<td>e.g. amiodarone, diltiazem, felodipine, nifedipine, verapamil</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Disorders:</strong> ranolazine</td>
<td>↑ ranolazine</td>
<td>Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.</td>
</tr>
<tr>
<td>ivabradine</td>
<td>↑ ivabradine</td>
<td></td>
</tr>
<tr>
<td><strong>Other antiarrhythmics</strong></td>
<td>↑ antiarrhythmics</td>
<td>Clinical monitoring is recommended upon co-administration with antiarrhythmics.</td>
</tr>
<tr>
<td>e.g. amiodarone, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dronedarone</td>
<td>↑ dronedarone</td>
<td>Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.</td>
</tr>
<tr>
<td>digoxin</td>
<td>↑ digoxin</td>
<td>When co-administering with digoxin, titrate the digoxin dose and monitor digoxin concentrations.</td>
</tr>
</tbody>
</table>

*Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.

**Adverse reactions such as cardiac arrhythmias.**

**When co-administering with PREZCOBIX, the recommended dose of rifabutin is 150 mg every other day.**

**Monitor for increased darunavir or cobicistat and/or antifungal adverse reactions.**

**Specific dosing recommendations are not available for co-administration with these antifungals.**

**Monitor for increased itraconazole or ketoconazole adverse reactions.**

**Co-administration with posaconazole is not recommended unless benefit/risk assessment justifies the use of voriconazole.**

**Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).**

**Clinical monitoring is recommended for co-administration with beta-blockers that are metabolized by CYP2D6.**

**Clinical monitoring is recommended for co-administration with calcium channel blockers metabolized by CYP3A.**

**Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.**

**Other antiarrhythmics.**

**Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.**
### Table 1: Established and Other Potentially Significant* Drug Interactions: Alterations in Dose or Regimen May Be Recommended (continued)

<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug</th>
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</tr>
</thead>
</table>
| **Systemic/Inhaled/Nasal/Ophthalmic Corticosteroids:**  
  e.g. betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone | ↓ darunavir  
  ↓ cobicistat  
  ↑ corticosteroids | Co-administration with systemic dexamethasone or other systemic corticosteroids that induce CYP3A may result in loss of therapeutic effect and development of resistance to PREZCOBIX. Consider alternative corticosteroids.  
  Co-administration with corticosteroids of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing’s syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone, prednisone and prednisolone (for which PK and/or PD are less affected by strong CYP3A inhibitors relative to other steroids) should be considered, particularly for long term use. |  |
| **Endothelin receptor antagonists:**  
  bosentan | ↓ darunavir  
  ↓ cobicistat  
  ↑ bosentan | Initiation of bosentan in patients taking PREZCOBIX: In patients who have been receiving PREZCOBIX for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability.  
  Initiation of PREZCOBIX in patients on bosentan: Discontinue use of bosentan at least 38 hours prior to initiation of PREZCOBIX. After at least 10 days following the initiation of PREZCOBIX, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.  
  Switching from darunavir co-administered with ritonavir to PREZCOBIX in patients on bosentan: Maintain bosentan dose. |  |
| **Ergot derivatives:**  
  e.g. dihydroergotamine, ergotamine, methylergonoovine | ↑ ergot derivatives | Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues. |  |
| **GI motility agent:**  
  cisapride | ↑ cisapride | Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias. |  |

### Table 1: Established and Other Potentially Significant* Drug Interactions: Alterations in Dose or Regimen May Be Recommended (continued)

<table>
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<tr>
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</tr>
</thead>
</table>
| **Hepatitis C virus (HCV): Direct-Acting Antivirals:**  
  elbasvir/grazoprevir  
  glecaprevir/pibrentasvir | ↑ elbasvir/grazoprevir  
  ↑ glecaprevir  
  ↑ pibrentasvir | Co-administration is contraindicated due to potential for the increased risk of alanine transaminase (ALT) elevations.  
  Co-administration of PREZCOBIX with glecaprevir/pibrentasvir is not recommended. |  |
| **Herbal product:**  
  St. John’s wort (Hypericum perforatum) | ↓ darunavir  
  ↓ cobicistat | Co-administration is contraindicated due to potential for reduced plasma concentrations of darunavir, which may result in loss of therapeutic effect and development of resistance. |  |
| **Hormonal contraceptives:** | | Additional or alternative (non-hormonal) forms of contraception should be considered when estrogen-containing contraceptives are co-administered with PREZCOBIX [see Use in Specific Populations (8.3)].  
  For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia.  
  No data are available to make recommendations on co-administration with other hormonal contraceptives. |  |
| **Immunosuppressants:**  
  cyclosporine, sirolimus, tacrolimus  
  immunosuppressants | ↑ immunosuppressants | These immunosuppressant agents are metabolized by CYP3A. Therapeutic drug monitoring is recommended with concomitant use. |  |
| **Immunosuppressant/neoplastic:**  
  everolimus  
  irinotecan | ↑ immunosuppressants  
  ↑ everolimus  
  ↓ irinotecan | Co-administration of everolimus and PREZCOBIX is not recommended.  
  Discontinue PREZCOBIX at least 1 week prior to starting irinotecan therapy. Do not administer PREZCOBIX with irinotecan unless there are no therapeutic alternatives. |  |
| **Inhaled beta agonist:**  
  salmeterol | ↑ salmeterol | Co-administration with salmeterol is not recommended and may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia. |  |
Table 1: Established and Other Potentially Significant* Drug Interactions: Alterations in Dose or Regimen May Be Recommended (continued)

<table>
<thead>
<tr>
<th>Concomitant Drug Name</th>
<th>Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipid Modifying Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors: lovastatin, simvastatin</td>
<td>↑ lovastatin ↑ simvastatin</td>
<td>Co-administration is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis. For atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosvastatin, start with the lowest recommended dose and titrate while monitoring for safety (e.g. myopathy). Dosage recommendations with atorvastatin or rosuvastatin are as follows: • atorvastatin dosage should not exceed 20 mg/day • rosuvastatin dosage should not exceed 20 mg/day Co-administration is contraindicated due to potential for markedly increased transaminases associated with increased plasma concentrations of lomitapide.</td>
</tr>
<tr>
<td>atorvastatin, fluvastatin, pitavastatin, pravastatin, rosvastatin</td>
<td>↑ atorvastatin ↑ fluvastatin ↑ pravastatin ↑ rosuvastatin</td>
<td></td>
</tr>
<tr>
<td>Other lipid modifying agents: lomitapide</td>
<td>↑ lomitapide</td>
<td></td>
</tr>
<tr>
<td><strong>Narcotic analgesics metabolized by CYP3A:</strong> e.g. fentanyl, oxycodone</td>
<td>↑ fentanyl ↑ oxycodone</td>
<td>Careful monitoring of therapeutic effects and adverse reactions associated with CYP3A-metabolized narcotic analgesics (including potentially fatal respiratory depression) is recommended with co-administration. A dose decrease may be needed for tramadol with concomitant use.</td>
</tr>
<tr>
<td>tramadol</td>
<td>↑ tramadol</td>
<td></td>
</tr>
<tr>
<td><strong>Narcotic analgesics for treatment of opioid dependence:</strong> buprenorphine, buprenorphine/naloxone, methadone</td>
<td></td>
<td>Initiation of buprenorphine, buprenorphine/naloxone or methadone in patients taking PREZCOBIX: Carefully titrate the dose of buprenorphine, buprenorphine/naloxone or methadone to the desired effect; use the lowest feasible initial or maintenance dose. Initiation of PREZCOBIX in patients taking buprenorphine, buprenorphine/naloxone or methadone: A dose adjustment for buprenorphine, buprenorphine/naloxone or methadone may be needed. Monitor clinical signs and symptoms.</td>
</tr>
<tr>
<td>buprenorphine or buprenorphine/naloxone: effects unknown methadone: effects unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid Antagonist naloxegol</td>
<td>↑ naloxegol</td>
<td>Co-administration of PREZCOBIX and naloxegol is contraindicated due to potential for precipitating opioid withdrawal symptoms.</td>
</tr>
<tr>
<td><strong>Platelet aggregation inhibitor:</strong> ticagrelor</td>
<td>↑ ticagrelor</td>
<td>Co-administration of PREZCOBIX and ticagrelor is not recommended.</td>
</tr>
</tbody>
</table>
PREZCOBIX (darunavir and cobicistat) tablets

Table 1: Established and Other Potentially Significant* Drug Interactions: Alterations in Dose or Regimen May Be Recommended (continued)

<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedatives/hypnotics: orally administered midazolam, triazolam</td>
<td>↑ midazolam ↑ triazolam</td>
<td>Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. Triazolam and orally administered midazolam are extensively metabolized by CYP3A. Co-administration of triazolam or orally administered midazolam with PREZCOBIX may cause large increases in the concentrations of these benzodiazepines.</td>
</tr>
</tbody>
</table>

metabolized by CYP3A: e.g. buspirone, diazepam, estazolam, zolpidem | ↑ sedatives/hypnotics | With concomitant use, titration is recommended with sedatives/hypnotics metabolized by CYP3A and a lower dose of the sedatives/hypnotics should be considered with monitoring for increased and prolonged effects or adverse reactions. |

parenterally administered midazolam | | Co-administration of parenteral midazolam should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for parenteral midazolam should be considered, especially if more than a single dose of midazolam is administered. |

Urinary antispasmodics | | |

fesoterodine | ↑ fesoterodine | When fesoterodine is co-administered with PREZCOBIX, do not exceed a fesoterodine dose of 4 mg once daily. |

solifenacin | ↑ solifenacin | When solifenacin is co-administered with PREZCOBIX, do not exceed a solifenacin dose of 5 mg once daily. |

* this table is not all inclusive

7.4 Drugs without Clinically Significant Interactions with PREZCOBIX

Clinically relevant drug-drug interactions have not been observed or are not anticipated with concomitant use of darunavir and cobicistat with rifilpine, dolutegravir, raltegravir, abacavir, emtricitabine, emtricitabine/tenofovir alafenamide, tenofovir DF; lamivudine, stavudine, zidovudine, or acid modifying medicines (antacids, H2-receptor antagonists, proton pump inhibitors).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to PREZCOBIX during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) 1-800-258-4823.

Risk Summary

There are insufficient data with PREZCOBIX in pregnant individuals from the APR to inform a drug-associated risk of pregnancy outcomes. Available data from the APR show no difference in rate of overall birth defects for darunavir compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) (see Data). The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk of major birth defects and miscarriage for the indicated population is unknown.

In animal reproduction studies, no adverse developmental effects were observed when the components of PREZCOBIX were administered separately at darunavir exposures less than 1 (mice and rabbits) and 3-times (rats), and at cobicistat exposures of 1.6 (rats) and 3.8 (rabbits). Exposure to darunavir and cobicistat at these exposures was lower (less than 1-fold) compared to those obtained in humans at the recommended daily dose of these components in PREZCOBIX (see Data). No adverse developmental effects were seen when cobicistat was administered to rats through lactation at cobicistat exposures up to 1.2 times the human exposure at the recommended therapeutic dose.

PREZCOBIX should not be initiated in pregnant individuals. An alternative regimen is recommended for individuals who become pregnant during therapy with PREZCOBIX.

Data

Human Data

Darunavir/Cobicistat: PREZCOBIX in combination with a background regimen was evaluated in a clinical trial of 7 pregnant individuals taking PREZCOBIX prior to enrollment and who were willing to remain on PREZCOBIX throughout the study. The study period included the second and third trimesters, and through 12 weeks postpartum. Six pregnant individuals completed the trial. Exposure to darunavir and cobicistat as part of an antiretroviral regimen was substantially lower during the second and third trimesters of pregnancy compared with postpartum (see Clinical Pharmacology (12.3)). One out of 6 pregnant individuals who completed the study experienced virologic failure with HIV-1 RNA >1,000 copies/mL from the third trimester visit through the postpartum period. Five pregnant individuals had sustained virologic response (HIV RNA <50 copies/mL) throughout the study period. There are no clinical data on the virologic response when PREZCOBIX is initiated during pregnancy.

There were no new clinically relevant safety findings compared with the known safety profile of PREZCOBIX in adults with HIV-1 infection.

Darunavir: Based on prospective reports to the APR of 679 live births following exposure to darunavir-containing regimens during pregnancy (including 425 exposed in the first trimester and 254 exposed in the second/third trimester), there was no difference in rate of overall birth defects for darunavir compared with the background rate for major birth defects in a U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.1% (95% CI: 1.0% to 4.0%) with first trimester exposure to darunavir-containing regimens and 2.4% (95% CI: 0.9% to 5.1%) with second/third trimester exposure to darunavir-containing regimens.

Cobicistat: Insufficient numbers of pregnancies with exposure to cobicistat have been reported to the APR to estimate the rate of birth defects.

Animal Data

Darunavir: Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice (doses up to 1000 mg/kg from gestation day (GD) 8-15 with darunavir alone) and rats (doses up to 1000 mg/kg from GD 7-19 in the presence or absence of ritonavir) as well as in rabbits (doses up to 125 mg/kg/day on GD 6-17). Increases in post-implantation loss and decreased fetal weights were observed at a maternal toxic dose of 125 mg/kg/day. No malformations were noted at doses up to 125 mg/kg/day. Systemic exposures (AUC) at 50 mg/kg/day in pregnant females were 1.6 times higher than human exposures at the recommended daily dose of cobicistat. In pregnant rabbits, cobicistat was administered orally at doses up to 100 mg/kg/day during GD 7-20. No maternal or embryo/fetal effects were noted at the highest dose of 100 mg/kg/day. Systemic exposures (AUC) at 100 mg/kg/day were 3.8 times higher than human exposures at the recommended daily dose of cobicistat.

In a pre/postnatal developmental study in rats, cobicistat was administered orally at doses up to 75 mg/kg from GD 6 to postnatal day 20, 21, or 22. At doses of 75 mg/kg/day, no maternal or developmental toxicity was noted. Systemic exposures (AUC) at this dose were 1.2 times the human exposures at the recommended daily dose of cobicistat.
PREZCOBIX (darunavir and cobicistat) tablets

8.2 Lactation

Risk Summary
The Centers for Disease Control and Prevention recommend that HIV infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV.

There are no data on the presence of darunavir or cobicistat in human milk, the effects on the breastfed infant, or the effects on milk production. Darunavir and cobicistat are present in the milk of lactating rats (see Data). Because of the potential for (1) HIV transmission in HIV-negative infants, (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in breastfed infants, instruct mothers not to breastfeed if they are receiving PREZCOBIX.

Data

Animal Data
Darunavir: Studies in rats (with darunavir alone or with ritonavir) have demonstrated that darunavir is excreted in milk. In the rat pre- and postnatal development study, a reduction in pup body weight gain was observed due to exposure of pups to drug substances via milk. The maximal maternal plasma exposures achieved with darunavir (up to 1000 mg/kg with ritonavir) were approximately 50% of those obtained in humans at the recommended clinical dose of darunavir with ritonavir.

Cobicistat: During the pre/postnatal developmental toxicology study at doses up to 75 mg/kg/day, mean cobicistat milk to plasma ratio of up to 1.9 was measured 2 hours after administration to rats on lactation day 10.

8.3 Females and Males of Reproductive Potential

Contraception

Additional or alternative (non-hormonal) forms of contraception should be considered when estrogen-containing contraceptives are co-administered with PREZCOBIX. For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia. No data are available to make recommendations on co-administration with other hormonal contraceptives (see Drug Interactions [13]).

8.4 Pediatric Use

The safety and effectiveness of PREZCOBIX for the treatment of HIV-1 infection in pediatric patients weighing at least 40 kg was established through a trial with components of PREZCOBIX. Use of PREZCOBIX in this group is supported by evidence from adequate and well-controlled studies in adults with additional pharmacodynamic, safety, and virologic data from a study of components of PREZCOBIX (Trial GS-US-216-0128) in pediatric subjects with HIV-1 infection aged 12 to less than 18 years (see Adverse Reactions [6.1], Clinical Pharmacology [12.3], and Clinical Studies [14.2]).

The safety and effectiveness of PREZCOBIX have not been established in pediatric patients weighing less than 40 kg. Darunavir, a component of PREZCOBIX, is not recommended in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir.

Juvenile Animal Toxicity Data
Darunavir: In a juvenile toxicity study where rats were directly dosed with darunavir (up to 1000 mg/kg), deaths occurred from post-natal day 5 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicokinetic study, when dosing was initiated on post-natal day 22 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) 2 times the human plasma exposure levels.

8.5 Geriatric Use

Clinical trials of PREZCOBIX did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of PREZCOBIX in elderly patients, reflecting the greater frequency of decreased hepatic function, and of concomitant disease or other drug therapy (see Clinical Pharmacology [12.3]).

8.6 Hepatic Impairment

No clinical trials were conducted with darunavir co-administered with cobicistat in hepatically impaired subjects and the effect of hepatic impairment on darunavir exposure when co-administered with cobicistat has not been evaluated. Based on the recommendations for darunavir co-administered with ritonavir, a dose adjustment for patients with mild or moderate hepatic impairment is not necessary. No pharmacokinetic or safety data are available regarding the use of darunavir in subjects with severe hepatic impairment. Therefore, PREZCOBIX is not recommended for use in patients with severe hepatic impairment (see Clinical Pharmacology [12.3]).

8.7 Renal Impairment

A renal impairment trial was not conducted for darunavir co-administered with cobicistat (see Clinical Pharmacology [12.3]). Cobicistat has been shown to decrease estimated creatinine clearance without affecting actual renal glomerular function. Therefore, the recommendations are not available for drugs that require dosage adjustment for renal impairment when used in combination with PREZCOBIX (see Warnings and Precautions [5.3] and Clinical Pharmacology [12.12]).

10 OVERDOSE

Human experience of acute overdose with PREZCOBIX is limited. No specific antidote is available for overdose with PREZCOBIX. Treatment of overdose with PREZCOBIX consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Since both darunavir and cobicistat are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

11 DESCRIPTION

PREZCOBIX is a fixed-dose combination tablet containing darunavir and cobicistat. Darunavir is an inhibitor of the human immunodeficiency virus (HIV-1) protease. Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family.

PREZCOBIX tablets are for oral administration. Each tablet contains darunavir ethanolate equivalent to 800 mg of darunavir and 150 mg of cobicistat. The tablets include the following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, magnesium stearate, and silicon dioxide. The tablets are film-coated with a coating material containing iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide.

Darunavir: Darunavir, in the form of darunavir ethanolate, has the following chemical name: [(1S,2R,3S)-3-[(4-aminophenyl)sulfonyl]l-2-methylpropyl]amino]-1,2-hydroxy-1-phenylmethylyl-[propyl]-carbamic acid (3R,3aS,6aR)-hexahydrofuran[2,3-b]furan-3-y1 ester monohydrate. Its molecular formula is C23H31N2O5 • H2O and its molecular weight is 593.73. Darunavir ethanolate has the following structural formula:

Cobicistat: Cobicistat is adsorbed onto silicon dioxide. The chemical name for cobicistat is 1,3-thiazol-5-ylmethyl[[(2S,5R,5-S)(2S-[((2-methylpropyl)carbamoyl]amino)-4-(morpholin-4-yl)butanoyl]amino]-1,6-dihydropyridine-2-yl)][carbamate. It has a molecular formula of C47H54N4O12 and a molecular weight of 776.0. It has the following structural formula:
for subjects with normal renal function or mild-to-moderate renal impairment 7 days after cobicistat was discontinued. The actual glomerular filtration rate, as determined by the clearance of probe drug iohexol, was not altered from baseline following treatment of cobicistat among subjects with normal renal function and mild-to-moderate renal impairment, indicating that cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in eGFR$_{CG}$, without affecting the actual glomerular filtration rate.

### 12.3 Pharmacokinetics

The pharmacokinetics of darunavir co-administered with cobicistat (150 mg) have been evaluated in healthy adult subjects and in HIV-1 infected subjects. Darunavir is primarily metabolized by CYP3A. Cobicistat inhibits CYP3A, thereby increasing the plasma concentrations of darunavir.

Under fed (525 total kcal, 171 kcal from fat, 268 kcal from carbohydrates, 96 kcal from protein) and fasted conditions in healthy subjects, the 90% confidence intervals when comparing darunavir exposure between PREZCOBIX and darunavir 800 mg co-administered with cobicistat 150 mg as single entities were within 80-125%.

Darunavir exposure when comparing darunavir co-administered with cobicistat (as single entities) to darunavir co-administered with ritonavir was evaluated in a relative bioavailability trial [see cobicistat full prescribing information]. Table 2 displays the population pharmacokinetic estimates of darunavir after oral administration of darunavir 800 mg co-administered with ritonavir 100 mg once daily (based on sparse sampling in 335 subjects in Trial TMC114-C211 and 280 subjects in Trial TMC114-C229) and darunavir 800 mg co-administered with cobicistat 150 mg once daily as single entities (based on sparse sampling in 298 subjects in Trial GS-US-216-0130) to HIV-1 infected subjects.

**Table 2: Population Pharmacokinetic Estimates of Darunavir as Darunavir 800 mg Co-administered with Ritonavir 100 mg Once Daily (Trial TMC114-C211, 48 Week Analysis and Trial TMC114-C229, 48 Week Analysis) and Darunavir 800 mg Co-administered with Cobicistat 150 mg Once Daily (Trial GS-US-216-1230, 24 Week Analysis)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trial TMC114-C211 (treatment-naive)</th>
<th>Trial TMC114-C229 (treatment-experienced)</th>
<th>Trial GS-US-216-0130 (treatment-naive and experienced)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{24h}$ (ng·h/mL)</td>
<td>93026 ± 27050</td>
<td>93334 ± 28626</td>
<td>100152 ± 32042</td>
</tr>
<tr>
<td>Mean ± Standard Deviation</td>
<td>(45000-219240)</td>
<td>(45456-236920)</td>
<td>(34500-224000)</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>87584 (45000-219240)</td>
<td>87788 (45456-236920)</td>
<td>96900 (34500-224000)</td>
</tr>
<tr>
<td>C$_{0}$ (ng/mL)</td>
<td>2282 ± 1168</td>
<td>2160 ± 1201</td>
<td>2043 ± 1257</td>
</tr>
<tr>
<td>Mean ± Standard Deviation</td>
<td>(368-7242)</td>
<td>(184-7881)</td>
<td>(70-6890)</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>2041 (368-7242)</td>
<td>1896 (184-7881)</td>
<td>1875 (70-6890)</td>
</tr>
</tbody>
</table>

N=number of subjects with data

**Absorption and Bioavailability**

In healthy subjects, under fed conditions, when single doses of the darunavir and cobicistat fixed dose combination tablet were administered, the maximum plasma concentration was achieved within approximately 4 to 4.5 hours for darunavir and approximately 4 to 5 hours for cobicistat.

**Effects of Food on Oral Absorption**

When compared to fasted conditions, administration of PREZCOBIX to healthy adult subjects with a high-fat meal (965 total kcal: 129 kcal from protein, 236 kcal from carbohydrates and 800 kcal from fat) resulted in a 70% increase in AUC$_{24h}$ and a 127% increase in C$_{max}$ for darunavir. Cobicistat exposures were not affected from carbohydrates and 600 kcal from fat) resulted in a 70% increase in AUC (0-inf) when compared to fasted conditions, administration of PREZCOBIX to healthy adult subjects with a high-fat meal (965 total kcal: 129 kcal from protein, 236 kcal from carbohydrates and 800 kcal from fat).

**Distribution**

**Darunavir**: Darunavir is approximately 95% bound to plasma proteins. Darunavir binds primarily to plasma alpha 1-acid glycoprotein (AAG).

**Cobicistat**: Cobicistat is 97-98% bound to human plasma proteins and the mean blood-to-plasma ratio was approximately 0.5.
PREZCOBIX (darunavir and cobicistat) tablets

Race
Darunavir: Population pharmacokinetic analysis of darunavir in HIV-1 infected subjects taking darunavir co-administered with ritonavir indicated that race had no apparent effect on the exposure to darunavir.

Cobicistat: Population pharmacokinetic analysis of cobicistat in HIV-1 infected subjects indicated that race had no clinically relevant effect on the exposure of cobicistat.

Geriatric Patients
Darunavir: In subjects with HIV-1 infection taking darunavir co-administered with ritonavir, population pharmacokinetic analysis showed no considerable differences in darunavir pharmacokinetics for ages 18 to 75 years compared to ages greater than or equal to 65 years (n=12) [see Use in Specific Populations (8.5)].

Cobicistat: Insufficient data are available to determine whether potential differences exist in the pharmacokinetics of cobicistat in geriatric (65 years of age and older) subjects compared to younger subjects.

Pediatric Patients Weighing at Least 40 kg
Available pharmacokinetic data for the different components of PREZCOBIX indicate that there were no clinically relevant differences in exposure between adults and pediatric subjects weighing at least 40 kg.

Darunavir and cobicistat In pediatric subjects aged 12 to less than 18 years, weighing at least 40 kg who received darunavir 800 mg co-administered with cobicistat 150 mg (n=7), geometric mean darunavir Cmax values were similar between adults and pediatric subjects. Geometric mean darunavir AUC24h and C24h values were 15% and 32% lower, with geometric mean ratios of 0.85 (90% CI: 0.64, 1.13) and 0.68 (90% CI: 0.30, 1.15) in pediatric subjects relative to adults, respectively. These differences were not considered clinically significant. Geometric mean cobicistat AUC24h, Cmax, and C24h values were comparable in pediatric subjects and adults (Table 3).

Table 3: Multiple-Dose PK Parameters of Darunavir and Cobicistat Following Administration of Darunavir with Cobicistat in HIV-1 Infected Adults and Pediatric Subjects Weighing at least 40 kg

<table>
<thead>
<tr>
<th>Parameter Geometric mean (CV%)</th>
<th>Darunavir</th>
<th>Cobicistat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Subjectsa</td>
<td>N=7</td>
<td>N=7</td>
</tr>
<tr>
<td>AUC24h (mcg.hr/mL)</td>
<td>77.22 (29.5)</td>
<td>8.33 (34.9)</td>
</tr>
<tr>
<td>Cmax (mcg/mL)</td>
<td>7.32 (21.7)</td>
<td>1.10 (20.0)</td>
</tr>
<tr>
<td>C24h (mcg/mL)</td>
<td>0.68 (81.6)</td>
<td>0.02 (123.9)c</td>
</tr>
<tr>
<td>Adultsb</td>
<td>N=21</td>
<td>N=21</td>
</tr>
<tr>
<td>AUC24h (mcg.hr/mL)</td>
<td>90.56 (45.3)</td>
<td>7.69 (43.9)</td>
</tr>
<tr>
<td>Cmax (mcg/mL)</td>
<td>8.34 (33.3)</td>
<td>1.04 (35.3)</td>
</tr>
<tr>
<td>C24h (mcg/mL)</td>
<td>1.00 (108.0)</td>
<td>0.02 (135.1)c</td>
</tr>
</tbody>
</table>

CV = Coefficient of Variation; mcg = microgram
a From intensive PK analysis of trial GS-US-216-0128, where subjects with HIV-1 infection were administered darunavir 800 mg and cobicistat 150 mg once daily with 2 NRTIs
b N=5; Data from two subjects who had undetectable cobicistat C24h concentrations were excluded from summary statistics
c From intensive PK analysis of trial GS-US-299-0102 where subjects with HIV-1 infection were administered darunavir/cobicistat/emtricitabine/tenofovir alafenamide

Pregnancy and Postpartum
The exposure to total and unbound darunavir boosted with cobicistat after intake of PREZCOBIX as part of an antiretroviral regimen was substantially lower during the second and third trimesters of pregnancy compared with 6-12 weeks postpartum (see Table 4 and Figure 1).

Table 4: Pharmacokinetic Results of Total Darunavir after Administration of PREZCOBIX Once Daily as Part of an Antiretroviral Regimen, During the 2nd and 3rd Trimester of Pregnancy, the 3rd Trimester of Pregnancy, and Postpartum

<table>
<thead>
<tr>
<th>Pharmacokinetics of total darunavir (mean ± SD)</th>
<th>2nd trimester of pregnancy N=7</th>
<th>3rd trimester of pregnancy N=6</th>
<th>Postpartum (6-12 weeks) N=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, ng/mL</td>
<td>4340 ± 1616</td>
<td>4910 ± 970</td>
<td>7918 ± 2199</td>
</tr>
<tr>
<td>AUC24h, ng.h/mL</td>
<td>47233 ± 19058</td>
<td>47991 ± 9879</td>
<td>99613 ± 34862</td>
</tr>
<tr>
<td>Cmin, ng/mL</td>
<td>168 ± 149</td>
<td>184 ± 99</td>
<td>1538 ± 1344</td>
</tr>
</tbody>
</table>

Legend: 90% CI: 90% confidence interval; GMR: geometric mean ratio (i.e. second or third trimester / postpartum). Solid vertical line: ratio of 1.0; dotted vertical lines: reference lines of 0.8 and 1.25.

Drug Interactions
Based on in vitro data, cobicistat is not expected to induce CYP1A2 or CYP2B6 and based on in vivo data, cobicistat is not expected to induce CYP3A to a clinically significant extent. The induction effect of cobicistat on CYP2C9, CYP2C19, or UGT1A1 is unknown, but is expected to be low based on CYP3A in vitro induction data [see Drug Interactions (7)].

12.4 Microbiology
Mechanism of Action
Darunavir: Darunavir is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV-1 encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles.

Cobicistat: Cobicistat is a selective, mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates.

Antiviral Activity
Darunavir: Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells, and human monocytes/macrophages with median EC50 values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity in cell culture against a broad panel of HIV-1 group M (A, B, C, D, E, F, G), and group O primary isolates with EC50 values ranging...
Darunavir and cobicistat tablets

Cobicistat does not inhibit recombinant HIV-1 protease in a biochemical assay and has no detectable antiviral activity in cell culture against HIV-1. The antiviral activity in cell culture of approved HIV-1 antiretroviral drugs was not antagonized by cobicistat.

Resistance

Cell Culture

Darunavir-resistant HIV-1 isolates with a decreased susceptibility to darunavir have been selected in cell culture and obtained from subjects treated with darunavir co-administered with ritonavir. Darunavir-resistant virus derived in cell culture from wild-type HIV-1 had 21- to 88-fold decreased susceptibility to darunavir and developed 2 to 4 of the following amino acid substitutions S32D, R41E/T, K50, H69Q, K70E, T74S, V77I, or 185V in the protease. Selection in cell culture of darunavir-resistant HIV-1 from nine HIV-1 strains harboring multiple PI resistance-associated substitutions resulted in the overall emergence of 22 mutations in the protease gene, coding for amino acid substitutions L10F, V11I, I35V, L51I, V68C, L80V, V82A, Y181C, and Q82R, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were the most prevalent. These darunavir-resistant viruses had at least eight protease substitutions and exhibited 50- to 64-fold decreases in susceptibility with final EC50 values ranging from 125 nm to 346 nm.

Clinical Studies

The resistance profile of PREZCOBIX is driven by darunavir. Cobicistat does not select any HIV resistance substitutions, due to its lack of antiviral activity. For the clinical resistance profile of darunavir, refer to the darunavir full prescribing information.

Cross-resistance

Cross-resistance among PIs has been observed. Darunavir has a less than 10-fold increased susceptibility to darunavir in cell culture from wild-type HIV-1 with 21- to 88-fold decreased susceptibility to darunavir and developed 2 to 4 of the following amino acid substitutions S32D, R41E/T, K50, H69Q, K70E, T74S, V77I, or 185V in the protease. Selection in cell culture of darunavir-resistant HIV-1 from nine HIV-1 strains harboring multiple PI resistance-associated substitutions resulted in the overall emergence of 22 mutations in the protease gene, coding for amino acid substitutions L10F, V11I, I35V, L51I, V68C, L80V, V82A, Y181C, and Q82R, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were the most prevalent. These darunavir-resistant viruses had at least eight protease substitutions and exhibited 50- to 64-fold decreases in susceptibility with final EC50 values ranging from 125 nm to 346 nm.

Baseline Genotype/Phenotype and Virologic Outcome Analyses

Baseline International AIDS Society (IAS)-defined PI resistance substitutions confer reduced virologic response to darunavir. Please refer to the “Baseline Genotype/Phenotype and Virologic Outcome Analyses” section in the darunavir full prescribing information.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Darunavir: Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. A dose-related increase in the incidence of hepatocellular adenomas and carcinomas was observed in males and females of both species and an increase in multicellular cell adenomas was observed in male rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to darunavir (based on AUC) were between 0.4- and 1.3-fold (male and female) and 0.7-fold (male) and 1-fold (female) of exposures observed in humans at the recommended 150 mg daily dose.

PREZCOBIX (darunavir and cobicistat) tablets

PREZCOBIX (darunavir and cobicistat) tablets, 800/150 mg, are supplied as pink, oval-shaped, film-coated tablets debossed with “800” on one side and “TG” on the other side. PREFECOBIX is packaged in bottles of 30 tablets (NDC 59676-575-30).

Storage: Store at 20-25°C (between 68-77°F); with excursions permitted to 15°-30°C (59°-86°F). [see USP Controlled Room Temperature]. Keep PREZCOBIX and all medicines out of reach of children.

17 PATIENT COUNSELING INFORMATION

Inform patients that skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, could potentially occur with PREZCOBIX.告知患者可能出现严重皮肤反应，包括Stevens-Johnson Syndrome，药物性皮炎，系统性表现，以及毒性表皮坏死症。

Severe Skin Reactions

Inform patients that skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, could potentially occur with PREZCOBIX. Inform patients to contact their healthcare provider immediately if signs or symptoms of severe skin reactions develop, including but not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, and/or conjunctivitis. [see Warnings and Precautions (5.1)].
PREZCOBIX (darunavir and cobicistat) tablets

Renal Impairment
Inform patients that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported when cobicistat is used in combination with a tenofovir DF-containing regimen [see Warnings and Precautions (5.4)].

Pregnancy
Advise patients that PREZCOBIX is not recommended during pregnancy and to alert their healthcare provider if they get pregnant while taking PREZCOBIX [see Use in Specific Populations (8.1)]. Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant individuals exposed to PREZCOBIX [see Use in Specific Populations (8.1)].

Lactation
Instruct individuals with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk [see Use in Specific Populations (8.2)].

Drug Interactions
PREZCOBIX may interact with many drugs; therefore, inform patients of the potential serious drug interactions with PREZCOBIX, and that some drugs are contraindicated with PREZCOBIX and other drugs may require dosage adjustment. Advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John’s wort.

Immune Reconstitution Syndrome
Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started [see Warnings and Precautions (5.10)].

Fat Redistribution
Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including PREZCOBIX and that the cause and long-term health effects of these conditions are not known at this time [see Warnings and Precautions (5.9)].

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Janssen Ortho LLC, Gurabo, PR 00778
Manufactured for:
Janssen Therapeutics, Division of Janssen Products, LP, Titusville NJ 08560
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What is the most important information I should know about PREZCOBIX?

- **PREZCOBIX may cause liver problems.** Some people taking PREZCOBIX may develop liver problems which may be life-threatening. Your healthcare provider should do blood tests before and during your treatment with PREZCOBIX. If you have chronic hepatitis B or C infection, your healthcare provider should check your blood tests more often because you have an increased chance of developing liver problems. Tell your healthcare provider if you have any of the below signs and symptoms of liver problems.

  o dark (tea colored) urine
  o yellowing of your skin or whites of your eyes
  o pale colored stools (bowel movements)
  o nausea

  o vomiting
  o pain or tenderness on your right side below your ribs
  o loss of appetite

  ° dark (tea colored) urine
  ° yellowing of your skin or whites of your eyes
  ° pale colored stools (bowel movements)

- **PREZCOBIX may cause severe or life-threatening skin reactions or rash.** Sometimes these skin reactions and skin rashes can become severe and require treatment in a hospital. Call your healthcare provider right away if you develop a rash. **Stop taking PREZCOBIX** and call your healthcare provider right away if you develop any skin changes with symptoms below:

  o fever
  o tiredness
  o muscle or joint pain
  o blisters or skin lesions
  o mouth sores or ulcers
  o red or inflamed eyes, like “pink eye” (conjunctivitis)

  ° fever
  ° tiredness
  ° muscle or joint pain

- **PREZCOBIX when taken with certain other medicines can cause new or worse kidney problems, including kidney failure.** Your healthcare provider should check your kidneys before you start and while you are taking PREZCOBIX. See “What are the possible side effects of PREZCOBIX?” for more information about side effects.

What is PREZCOBIX?

PREZCOBIX is a prescription medicine that is used with other HIV-1 medicines to treat HIV-1 infection in adults and in children who weigh at least 88 pounds (40 kg).

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

PREZCOBIX contains the prescription medicines darunavir and cobicistat.

It is not known if PREZCOBIX is safe and effective in children weighing less than 88 pounds (40 kg).

Do not take PREZCOBIX with any medicine that contains:

- alfuzosin
- carbamazepine
- cisapride
- colchicine, if you have liver or kidney problems
- dronedarone
- elbasvir and grazoprevir
- ergot-containing medicines:
  - dihydroergotamine
  - ergotamine tartrate
  - methylergonovine
- ivabradine
- lomitapide
- lovastatin
- lurasidone
- midazolam, when taken by mouth
- naloxegol
- phenobarbital
- phenytoin
- pimozide
- ranolazine
- rifampin
- sildenafil, when used for the treatment of pulmonary arterial hypertension (PAH)
- simvastatin
- St. John’s wort (Hypericum perforatum)
- triazolam

Serious problems can happen if you take any of these medicines with PREZCOBIX.
Before taking PREZCOBIX, tell your healthcare provider about all your medical conditions, including if you:

• have liver problems, including hepatitis B or hepatitis C
• have kidney problems
• are allergic to sulfa (sulfonamide)
• have diabetes
• have hemophilia
• are pregnant or plan to become pregnant.
  • It is not known if PREZCOBIX will harm your unborn baby.
• PREZCOBIX should not be used during pregnancy because the PREZCOBIX levels in your blood may be lower during pregnancy and may not control your HIV-1.
• Tell your healthcare provider right away if you become pregnant during treatment with PREZCOBIX.
• Your healthcare provider will prescribe different medicines if you become pregnant during treatment with PREZCOBIX.
• Hormonal forms of birth control, such as injections, vaginal rings or implants, contraceptive patches, and some birth control pills may not work during treatment with PREZCOBIX. Talk to your healthcare provider about forms of birth control that may be used during treatment with PREZCOBIX.
• Pregnancy Exposure Registry: There is a pregnancy exposure registry for people who take HIV-1 medicines during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
• are breastfeeding or plan to breastfeed. Do not breastfeed if you take PREZCOBIX.
  ° You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  ° It is not known if PREZCOBIX can pass into your breast milk.
  ° Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines interact with PREZCOBIX. Keep a list of your medicines to show your healthcare provider and pharmacist.
• You can ask your healthcare provider or pharmacist for a list of medicines that interact with PREZCOBIX.
• Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take PREZCOBIX with other medicines.

How should I take PREZCOBIX?
• Take PREZCOBIX exactly as your healthcare provider tells you.
• Do not change your dose or stop taking PREZCOBIX without talking to your healthcare provider.
• Take PREZCOBIX 1 time a day with food.
• Do not miss a dose of PREZCOBIX.
• If you take too much PREZCOBIX, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of PREZCOBIX?
PREZCOBIX may cause serious side effects, including:
• See “What is the most important information I should know about PREZCOBIX?”
• Diabetes and high blood sugar (hyperglycemia). Some people who take protease inhibitors including PREZCOBIX can get high blood sugar, develop diabetes, or your diabetes can get worse. Tell your healthcare provider if you notice an increase in thirst or urinate often while taking PREZCOBIX.
• Changes in body fat can happen in people who take HIV-1 medications. The changes may include an increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
• Changes in your immune system (Immune Reconstitution Syndrome) can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after starting your HIV-1 medicine.
• Increased bleeding for hemophiliacs. Some people with hemophilia have increased bleeding with protease inhibitors including PREZCOBIX.

The most common side effects of darunavir, one of the medicines in PREZCOBIX, include:
• diarrhea
• nausea
• rash
• headache
• stomach-area (abdominal) pain
• vomiting

These are not all of the possible side effects of PREZCOBIX. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
**How should I store PREZCOBIX?**

- Store PREZCOBIX tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep PREZCOBIX and all medicines out of reach of children.

**General information about the safe and effective use of PREZCOBIX.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use PREZCOBIX for a condition for which it was not prescribed. Do not give PREZCOBIX to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about PREZCOBIX that is written for health professionals.

**What are the ingredients in PREZCOBIX?**

**Active ingredients:** darunavir and cobicistat

**Inactive ingredients:** colloidal silicon dioxide, crospovidone, hypromellose, magnesium stearate, and silicified microcrystalline cellulose.

The tablets are film-coated with a coating material containing iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide.

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