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----------

Dosage and Administration (2.5) 06/2018

----------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-naïve and treatment-experienced adults 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. (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, cytolytic hepatitis), 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)
- 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)

----------ADVERSE REACTIONS----------

- The most common adverse reactions to darunavir, a component of PREZCOBIX (incidence greater than or equal to 5%) of at least moderate severity (greater than or equal to Grade 2) were diarrhea, nausea, rash, headache, abdominal pain, and vomiting. (6.1)

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*.

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

- Co-administration of PREZCOBIX with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of darunavir or cobicistat. Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.6, 7, 12.3)

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

- Pregnancy: PREZCOBIX is not recommended in pregnant women due to substantially lower exposures of darunavir and cobicistat during pregnancy. (8.1, 12.3)
- Lactation: Women infected with HIV-1 should be instructed not to breastfeed due to the potential for HIV transmission. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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 with no darunavir resistance-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

PREZCOBIX is a fixed-dose combination product containing 800 mg of darunavir and 150 mg of cobicistat. In treatment-naïve and treatment-experienced adults 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 (8.6) and Clinical Pharmacology (12.3)]*.

2.5 Not Recommended During Pregnancy

PREZCOBIX is not recommended for use in pregnant women because of substantially lower exposures of darunavir and cobicistat during pregnancy *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

PREZCOBIX should not be initiated in pregnant women. An alternative regimen is recommended for women 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
- Antianginal: ranolazine
- Antiarrhythmic: dronedarone
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Anti-gout: colchicine, in patients with renal/and or hepatic impairment
- Antimycobacterial: rifampin
- Antipsychotics: lurasidone, pimozide
- Ergot derivatives, e.g. dihydroergotamine, ergotamine, methylergonovine
- GI motility agent: cisapride
- Herbal product: St. John's wort (*Hypericum perforatum*)
- Hepatitis C direct acting antiviral: elbasvir/grazoprevir
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- 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, drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) was reported in 0.5% of subjects. Patients with pre-existing liver

dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse reactions.

Post-marketing cases of liver injury, including some fatalities, have also been reported with darunavir co-administered with ritonavir. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications, having co-morbidities including hepatitis B or C co-infection, and/or developing immune reconstitution syndrome. A causal relationship with darunavir co-administered with ritonavir has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with PREZCOBIX and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment 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.

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 Sulfa 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 HIV infected patients 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, and Guillain-Barré syndrome) 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 hematomas 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)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During the darunavir clinical development program, where darunavir was co-administered with ritonavir 100 mg once or twice daily, the most common clinical adverse reactions (incidence greater than or equal to 5%) of at least moderate intensity (greater than or equal to Grade 2) were diarrhea, nausea, rash, headache, abdominal pain, and vomiting. See the darunavir full prescribing information for additional information on adverse reactions reported with darunavir co-administered with ritonavir. See cobicistat full prescribing information for clinical trial information on adverse reactions reported with cobicistat.

One single arm clinical trial was conducted with darunavir and cobicistat administered as single entities in 313 HIV-infected subjects. Adverse reactions evaluated through Week 24 did not

differ substantially from those reported in clinical trials with darunavir co-administered with ritonavir.

6.2 Postmarketing Experience

The following events have been identified during post-approval use of darunavir. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Metabolism and Nutrition Disorders:

Redistribution of body fat

Musculoskeletal and Connective Tissue Disorders

Rhabdomyolysis (associated with co-administration with HMG-CoA reductase inhibitors)

Skin and Subcutaneous Tissue Disorders

Toxic epidermal necrolysis, acute generalized exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

7.1 Potential for PREZCOBIX to Affect Other Drugs

Darunavir co-administered with cobicistat is an inhibitor of CYP3A and CYP2D6. Cobicistat inhibits the following transporters: P-glycoprotein (P-gp), BCRP, MATE1, OATP1B1 and OATP1B3. Therefore, co-administration of PREZCOBIX with drugs that are primarily metabolized by CYP3A and/or CYP2D6 or are substrates of P-gp, BCRP, MATE1, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and can be associated with adverse events (see Table 1).

7.2 Potential for Other Drugs to Affect PREZCOBIX

Darunavir is metabolized by CYP3A. Cobicistat is metabolized by CYP3A, and to a minor extent, by CYP2D6. Co-administration of PREZCOBIX and drugs that induce CYP3A activity are expected to increase the clearance of darunavir and cobicistat, resulting in lowered plasma concentrations of darunavir and cobicistat which may lead to loss of therapeutic effect and development of resistance. Co-administration of PREZCOBIX and other drugs that inhibit CYP3A may result in increased plasma concentrations of darunavir and cobicistat (see Table 1).

7.3 Established and Other Potentially Significant Drug Interactions

Table 1 provides dosing recommendations for expected clinically relevant interactions with PREZCOBIX (this table is not all inclusive). These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of therapeutic effect.

Table 1: Established and Other Potentially Significant* Drug Interactions: Alterations in Dose or Regimen May Be Recommended		
Concomitant Drug Class: Drug Name	**Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug**	**Clinical Comment**
HIV-1 antiviral agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
didanosine	↔ darunavir ↔ cobicistat ↔ didanosine	Didanosine should be administered one hour before or two hours after PREZCOBIX (administered with food).
HIV-1 antiviral agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
efavirenz	↓ cobicistat ↓ darunavir	Co-administration with efavirenz is not recommended because it may result in loss of therapeutic effect and development of resistance to darunavir.
etravirine	↓ cobicistat darunavir: effect unknown	Co-administration with etravirine is not recommended because it may result in loss of therapeutic effect and development of resistance to darunavir.
nevirapine	↓ cobicistat darunavir: effect unknown	Co-administration with nevirapine is not recommended because it may result in loss of therapeutic effect and development of resistance to darunavir.
HIV-1 antiviral agents: CCR5 co-receptor antagonists		
maraviroc	↑ maraviroc	Maraviroc is a substrate of CYP3A. When co-administered with PREZCOBIX, patients should receive maraviroc 150 mg twice daily.
Other agents		
Alpha 1-adrenoreceptor antagonist: alfuzosin	↑ alfuzosin	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as hypotension.
Antianginal: ranolazine	↑ ranolazine	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
Antiarrhythmics: dronedarone	↑ dronedarone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
e.g. amiodarone, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↑ antiarrhythmics	Clinical monitoring is recommended upon co-administration with antiarrhythmics.
digoxin	↑ digoxin	When co-administering with digoxin, titrate the digoxin dose and monitor digoxin concentrations.

Antibacterials: clarithromycin, erythromycin, telithromycin	↑ darunavir ↑ cobicistat ↑ antibacterial	Consider alternative antibiotics with concomitant use of PREZCOBIX.
Anticancer agents: dasatinib, nilotinib	↑ anticancer agent	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.
vinblastine, vincristine		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.
Anticoagulants: apixaban	↑ anticoagulant	Concomitant use of apixaban is not recommended.
dabigatran etexilate		Concomitant use with dabigatran etexilate is not recommended in specific renal impairment groups (depending on the indication). Please see the dabigatran US prescribing information for specific recommendations.
rivaroxaban		Co-administration with rivaroxaban is not recommended.
warfarin	warfarin: effect unknown	Monitor the international normalized ratio (INR) when co-administering with warfarin.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ 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.
<u>Anticonvulsants with CYP3A induction effects that are NOT contraindicated:</u> e.g. eslicarbazepine, oxcarbazepine	↓ cobicistat darunavir: effect unknown	Consider alternative anticonvulsant or antiretroviral therapy to avoid potential changes in exposures. If co-administration is necessary, monitor for lack or loss of virologic response.
<u>Anticonvulsants that are metabolized by CYP3A:</u> e.g. clonazepam	↑ clonazepam	Clinical monitoring of anticonvulsants is recommended.
Antidepressants: <u>Selective Serotonin Reuptake Inhibitors (SSRIs):</u> e.g. paroxetine, sertraline	SSRIs: effects unknown	When co-administering with SSRIs, TCAs, or trazodone, careful dose titration of the antidepressant to the desired effect, including using the lowest feasible initial or maintenance dose, and monitoring for antidepressant response are recommended.

Tricyclic Antidepressants (TCAs): e.g. amitriptyline, desipramine, imipramine, nortriptyline Other antidepressants: trazodone	↑ TCAs ↑ trazodone	
Antifungals: itraconazole, ketoconazole, posaconazole voriconazole	↑ darunavir ↑ cobicistat ↑ itraconazole ↑ ketoconazole ↔ posaconazole voriconazole: effects unknown	Monitor for increased darunavir or cobicistat adverse reactions. Specific dosing recommendations are not available for co-administration with itraconazole or ketoconazole. Monitor for increased itraconazole or ketoconazole adverse reactions. Co-administration with voriconazole is not recommended unless benefit/risk assessment justifies the use of voriconazole.
Anti-gout: colchicine	↑ colchicine	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).
Antimalarial: artemether/lumefantrine	artemether: effect unknown lumefantrine: effect unknown	Monitor for a potential decrease of antimalarial efficacy or potential QT prolongation.
Antimycobacterials: rifampin rifabutin	↓ darunavir ↓ cobicistat ↑ rifabutin cobicistat: effects unknown	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. When used in combination with PREZCOBIX, the recommended dose of rifabutin is 150 mg every other day. Monitor for rifabutin-associated adverse

	darunavir: effects unknown	reactions including neutropenia and uveitis.
rifapentine	↓ darunavir	Co-administration with rifapentine is not recommended.
Antipsychotics: lurasidone	↑ lurasidone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
pimozide	↑ pimozide	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
e.g. perphenazine, risperidone, thioridazine	↑ antipsychotic	A decrease in the dose of antipsychotics that are metabolized by CYP3A or CYP2D6 may be needed when co-administered with PREZCOBIX.
quetiapine	↑ quetiapine	Initiation of PREZCOBIX in patients taking quetiapine: Consider alternative antiretroviral therapy to avoid increases in quetiapine exposure. If co-administration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine- associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. Initiation of quetiapine in patients taking PREZCOBIX: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
β-Blockers: e.g. carvedilol, metoprolol, timolol	↑ beta-blockers	Clinical monitoring is recommended for co-administration with beta-blockers that are metabolized by CYP2D6.
Calcium channel blockers: e.g. amlodipine, diltiazem, felodipine, nifedipine, verapamil	↑ calcium channel blockers	Clinical monitoring is recommended for co-administration with calcium channel blockers metabolized by CYP3A.
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 36 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, methylergonovine	↑ 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.
Hepatitis C virus (HCV): Direct-Acting Antivirals: elbasvir/grazoprevir	↑ elbasvir/grazoprevir	Co-administration is contraindicated due to potential for the increased risk of alanine transaminase (ALT) elevations.
simeprevir	darunavir: effects unknown ↑ simeprevir	No drug interaction data are available. Co-administration with simeprevir 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.
HMG-CoA reductase inhibitors: lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis.
e.g. atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin	↑ atorvastatin ↑ fluvastatin ↑ pravastatin ↑ rosuvastatin pitavastatin: effect unknown	For atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin, 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
Hormonal contraceptives: drospirenone/ethinylestradiol other progestin/estrogen contraceptives	↑ drospirenone ↓ ethinylestradiol progestin: effects unknown estrogen: effects unknown	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. Additional or alternative (non-hormonal) forms of contraception should be considered.
Immunosuppressants: cyclosporine, sirolimus, tacrolimus **Immunosuppressant /neoplastic:** everolimus	↑ immunosuppressants	These immunosuppressant agents are metabolized by CYP3A. Therapeutic drug monitoring is recommended with concomitant use. Co-administration of everolimus and PREZCOBIX is not recommended.
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.
Narcotic analgesics metabolized by CYP3A: e.g. fentanyl, oxycodone tramadol	↑ fentanyl ↑ oxycodone ↑ tramadol	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.
Narcotic analgesic for treatment of opioid dependence: buprenorphine, buprenorphine/naloxone, methadone	buprenorphine or buprenorphine/ naloxone: effects unknown methadone: effects unknown	<u>Initiation of buprenorphine, buprenorphine/naloxone or methadone in patients taking PREZCOBIX</u>: Carefully titrate the dose of buprenorphine, buprenorphine/naloxone or methadone to the desired effect; use the lowest feasible initial or maintenance dose. <u>Initiation of PREZCOBIX in patients taking buprenorphine, buprenorphine/naloxone or methadone</u>: A dose adjustment for buprenorphine, buprenorphine/naloxone or methadone may be needed. Monitor clinical signs and symptoms.
Phosphodiesterase PDE-5 inhibitors: e.g. avanafil, sildenafil, tadalafil, vardenafil	↑ PDE-5 inhibitors	Co-administration with avanafil is not recommended because a safe and effective avanafil dosage regimen has not been established.

		Co-administration with PDE-5 inhibitors may result in an increase in PDE-5 inhibitor-associated adverse reactions including hypotension, syncope, visual disturbances and priapism. Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH): Co-administration with sildenafil used for PAH is contraindicated due to potential for sildenafil associated adverse reactions (which include visual disturbances, hypotension, prolonged erection, and syncope). The following dose adjustments are recommended for use of tadalafil with PREZCOBIX: • *Initiation of tadalafil in patients taking PREZCOBIX*: In patients receiving PREZCOBIX for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. • *Initiation of PREZCOBIX in patients taking tadalafil*: Avoid use of tadalafil during the initiation of PREZCOBIX. Stop tadalafil at least 24 hours prior to starting PREZCOBIX. After at least one week following the initiation of PREZCOBIX, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. • *Patients switching from darunavir co-administered with ritonavir to PREZCOBIX*: Maintain tadalafil dose. Use of PDE-5 inhibitors for erectile dysfunction: Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE-5 inhibitor-associated adverse reactions.
Platelet aggregation inhibitor: **ticagrelor**	↑ ticagrelor	Co-administration of PREZCOBIX and ticagrelor is not recommended.
Sedatives/hypnotics: orally administered midazolam, triazolam metabolized by CYP3A: e.g. buspirone, diazepam, estazolam, zolpidem	↑ midazolam ↑ triazolam ↑ sedatives/hypnotics	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. 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. 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.
parenterally administered midazolam		
* 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 rilpivirine, dolutegravir, raltegravir, abacavir, emtricitabine, emtricitabine/tenofovir alafenamide, tenofovir DF, lamivudine, stavudine, zidovudine, or acid modifying medications (antacids, H_2-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 women exposed to PREZCOBIX during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) 1-800-258-4263.

Risk Summary

There are insufficient data with PREZCOBIX in pregnant women 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 APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks gestation.

The rate of miscarriage is not reported in the APR. 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 1.6 (rats) and 3.8 (rabbits) times human exposures 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.

Clinical Considerations

Not Recommended During Pregnancy

PREZCOBIX is not recommended for use in pregnant women because of substantially lower exposures of darunavir and cobicistat during pregnancy *(see Data) and [see Clinical Pharmacology (12.3)]*.

PREZCOBIX should not be initiated in pregnant women. An alternative regimen is recommended for women 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 women 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 women 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 women 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 women 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 HIV-1-infected adults.

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) 6-15 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 1000 mg/kg/day from GD 8-20 with darunavir alone). In these studies, darunavir exposures (based on AUC) were higher in rats (3-fold), whereas in mice and rabbits, exposures were lower (less than 1-fold) compared to those obtained in humans at the recommended clinical dose of darunavir co-administered with ritonavir.

Cobicistat: Cobicistat was administered orally to pregnant rats at 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, neither maternal nor developmental toxicity was noted. Systemic exposures (AUC) at this dose were 1.2 times the human exposures at the recommended daily dose of cobicistat.

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.

8.4 Pediatric Use

Safety, effectiveness, and pharmacokinetics of PREZCOBIX in pediatric patients less than 18 years of age have not been established. 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 toxicology study, when dosing was initiated on post-natal day 23 (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. Dosing 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 (12.2)]*.

10 OVERDOSAGE

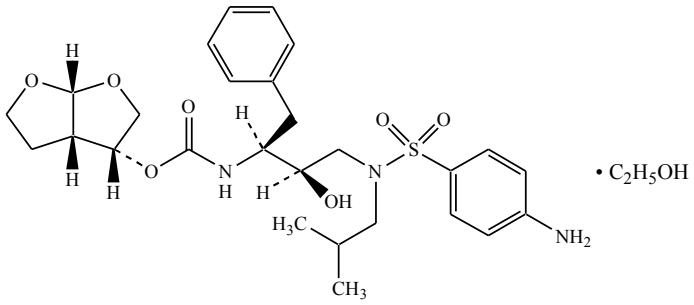
Human experience of acute overdose with PREZCOBIX is limited. No specific antidote is available for overdose with PREZCOBIX. Treatment of overdose with PREZCOBIX consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Since both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

11 DESCRIPTION

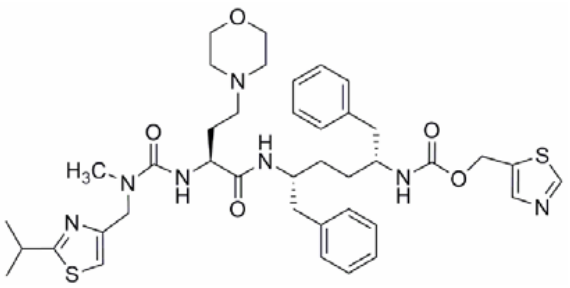
PREZCOBIX is a fixed-dose combination tablet containing darunavir and cobicistat. Darunavir is an inhibitor of the human immunodeficiency virus (HIV-1) protease. Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family.

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 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.

Darunavir: Darunavir, in the form of darunavir ethanolate, has the following chemical name: [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester monoethanolate. Its molecular formula is $C_{27}H_{37}N_3O_7S \bullet C_2H_5OH$ 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[(2*R*,5*R*)-5-{[(2*S*)2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate. It has a molecular formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.0. It has the following structural formula:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PREZCOBIX is a fixed-dose combination of an HIV-1 antiviral drug, darunavir and a CYP3A inhibitor, cobicistat *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Separate thorough QT trials have been conducted for darunavir co-administered with ritonavir and for cobicistat. The effect of darunavir co-administered with cobicistat on the QT interval has not been evaluated.

Darunavir: In a thorough QT/QTc study in 40 healthy subjects, darunavir doses (co-administered with 100 mg ritonavir) of approximately 2 times the recommended darunavir dose did not affect the QT/QTc interval.

Cobicistat: The effect of a single dose of cobicistat 250 mg and 400 mg (approximately 1.7 and 2.7 times the recommended dose) on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) four-period crossover thorough QT trial in 48 healthy subjects. In this trial, no significant QTc prolongation effect of cobicistat was detected. The dose of 400 mg cobicistat is expected to provide information on a high exposure clinical scenario. Prolongation of the PR interval was noted in subjects receiving cobicistat in the same trial. The maximum mean (95% upper confidence bound) difference in PR from placebo after baseline-correction was 9.5 (12.1) msec for 250 mg and 20.2 (22.8) msec for 400 mg of cobicistat.

Effects on Serum Creatinine

Cobicistat: The effect of cobicistat on serum creatinine was investigated in a trial in subjects with normal renal function (eGFR ≥ 80 mL/min, N=12) and mild-to-moderate renal impairment (eGFR 50-79 mL/min, N=18). A statistically significant decrease in the estimated glomerular filtration rate, calculated by Cockcroft-Gault method ($eGFR_{CG}$) from baseline, was observed

after 7 days of treatment with cobicistat 150 mg among subjects with normal renal function (-9.9 ± 13.1 mL/min) and mild-to-moderate renal impairment (-11.9 ± 7.0 mL/min). No statistically significant changes in $eGFR_{CG}$ were observed compared to baseline 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 (535 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 administered 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-216-130, 24 Week Analysis)

Parameter	Trial TMC114-C211 (treatment-naïve) Darunavir 800 mg co-administered with ritonavir 100 mg once daily N=335	Trial TMC114-C229 (treatment-experienced) Darunavir 800 mg co-administered with ritonavir 100 mg once daily N=280	Trial GS-US-216-0130 (treatment-naïve and experienced) Darunavir 800 mg co-administered with cobicistat 150 mg once daily N=298
AUC_{24h} (ng·h/mL)			
Mean ± Standard Deviation	93026 ± 27050	93334 ± 28626	100152 ± 32042
Median (Range)	87854 (45000-219240)	87788 (45456-236920)	96900 (34500-224000)
C_{0h} (ng/mL)			
Mean ± Standard Deviation	2282 ± 1168	2160 ± 1201	2043 ± 1257
Median (Range)	2041 (368-7242)	1896 (184-7881)	1875 (70-6890)

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 600 kcal from fat) resulted in a 70% increase in $AUC_{(0\text{-inf})}$ and a 127% increase in C_{max} for darunavir. Cobicistat exposures were not affected by food. PREZCOBIX should be taken with food.

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.

Metabolism

Darunavir: *In vitro* experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by CYP enzymes, primarily by CYP3A. A mass balance trial in healthy subjects showed that after single dose administration of 400 mg ^{14}C-darunavir co-administered with 100 mg ritonavir, the majority of the radioactivity in the plasma was due to darunavir. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 90% less than the activity of darunavir against wild-type HIV-1.

Cobicistat: Cobicistat is metabolized by CYP3A and to a minor extent by CYP2D6 enzymes and does not undergo glucuronidation.

Elimination

Darunavir: A mass balance trial in healthy subjects showed that after single dose administration of 400 mg ^{14}C-darunavir co-administered with 100 mg ritonavir, approximately 79.5% and 13.9% of the administered dose of ^{14}C-darunavir was recovered in the feces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively.

When single doses of the darunavir and cobicistat fixed dose combination tablet were administered, the terminal elimination half-life of darunavir was approximately 7 hours under fed conditions.

Cobicistat: When single doses of the darunavir and cobicistat fixed dose combination tablet were administered, the terminal elimination half-life of cobicistat was approximately 4 hours under

fed conditions. With single dose administration of ^{14}C-cobicistat after multiple dosing of cobicistat for six days, the mean percent of the administered dose excreted in feces and urine was 86.2% and 8.2%, respectively.

Specific Populations

Hepatic Impairment

Darunavir: Darunavir is primarily metabolized by the liver. The steady-state pharmacokinetic parameters of darunavir were similar after multiple dose co-administration of darunavir 600 mg co-administered with ritonavir 100 mg twice daily to subjects with normal hepatic function (n=16), mild hepatic impairment (Child-Pugh Class A, n=8), and moderate hepatic impairment (Child-Pugh Class B, n=8). The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been evaluated *[see Use in Specific Populations (8.6)]*.

Cobicistat: Cobicistat is primarily metabolized by the liver. A trial evaluating the pharmacokinetics of cobicistat was performed in non-HIV-1 infected subjects with moderate hepatic impairment. No clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with moderate hepatic impairment (Child-Pugh Class B) and healthy subjects. The effect of severe hepatic impairment on the pharmacokinetics of cobicistat has not been evaluated *[see Use in Specific Populations (8.6)]*.

Hepatitis B or Hepatitis C Virus Co-Infection

Darunavir: In HIV-infected subjects taking darunavir co-administered with ritonavir, the 48 week analysis of the data from clinical studies in HIV-1 infected subjects indicated that hepatitis B and/or hepatitis C virus co-infection status had no apparent effect on the exposure of darunavir.

The effect of hepatitis B and/or C virus infection on the pharmacokinetics of PREZCOBIX have not been evaluated.

Renal Impairment

Darunavir: Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-1 infected subjects with moderate renal impairment taking darunavir co-administered with ritonavir (creatinine clearance between 30-60 mL/min, n=20). There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease taking darunavir co-adminstered with either ritonavir or cobicistat *[see Use in Specific Populations (8.7)]*.

Cobicistat: A trial of the pharmacokinetics of cobicistat was performed in non-HIV infected subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min). No clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects *[see Use in Special Populations (8.7)]*.

Gender

Darunavir: In HIV-infected subjects taking darunavir co-administered with ritonavir, population pharmacokinetic analysis showed higher mean darunavir exposure in HIV-1 infected females compared to males. This difference is not clinically relevant.

Cobicistat: No clinically relevant pharmacokinetic differences have been observed between men and women for cobicistat.

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 HIV-infected subjects 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

The pharmacokinetics of PREZCOBIX in pediatric subjects have not been established.

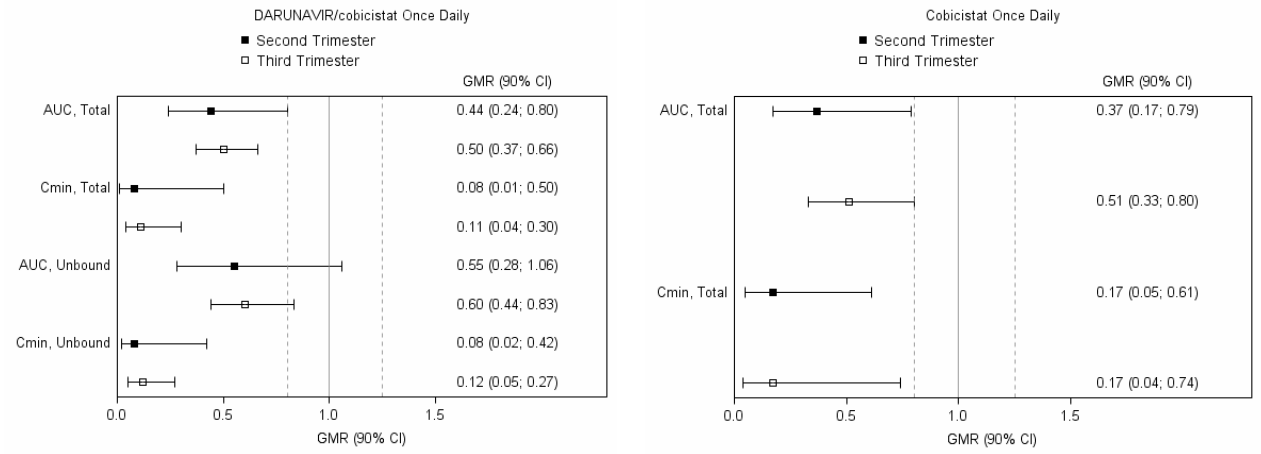
Pregnancy and Postpartum

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 3 and Figure 1).

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

Pharmacokinetics of total darunavir (mean ± SD)	**2nd Trimester of pregnancy N=7**	**3rd Trimester of pregnancy N=6**	**Postpartum (6-12 weeks) N=6**
C_{max}, ng/mL	4340 ± 1616	4910 ± 970	7918 ± 2199
AUC_{24h}, ng.h/mL	47293 ± 19058	47991 ± 9879	99613 ± 34862
C_{min}, ng/mL	168 ± 149	184 ± 99	1538 ± 1344

Figure 1: Pharmacokinetic Results (Within-Subject Comparison) of Total and Unbound Darunavir and Total Cobicistat After Administration of PREZCOBIX at 800/150 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd and 3rd Trimester of Pregnancy Compared to Postpartum



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 MDR1 or, in general, 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 EC_{50} 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 EC_{50} values ranging from less than 0.1 to 4.3 nM. The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum. Darunavir did not show antagonism when studied in combination with the HIV protease inhibitors (PIs) amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir, the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine, the NNRTIs delavirdine, efavirenz, etravirine, rilpivirine, or nevirapine, and the fusion inhibitor enfuvirtide.

Cobicistat: 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: 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 S37D, R41E/T, K55Q, H69Q, K70E, T74S, V77I, or I85V 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, I13V, I15V, G16E, L23I, V32I, L33F, S37N, M46I, I47V, I50V, F53L, L63P, A71V, G73S, L76V, V82I, I84V, T91A/S, and Q92R, 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 641-fold decreases in darunavir susceptibility with final EC_{50} values ranging from 125 nM to 3461 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 decreased susceptibility in cell culture against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and/or tipranavir showing that viruses resistant to these PIs remain susceptible to darunavir. A less than 10-fold decreased susceptibility was observed for the other PIs in 26% to 96% of these PI resistant clinical isolates [nelfinavir (26%), ritonavir (34%), lopinavir (46%), indinavir (57%), atazanavir (59%), saquinavir (64%), amprenavir (70%), and tipranavir (96%)].

Cross-resistance between darunavir and nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, fusion inhibitors, CCR5 co-receptor antagonists, or integrase strand transfer inhibitors is unlikely because the viral targets are different.

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 thyroid follicular 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 0.7-fold (mice) and 0.7- and 1-fold (rats) of exposures observed in humans at the recommended therapeutic doses (darunavir 600 mg co-administered with ritonavir 100 mg twice daily or darunavir 800 mg co-administered with ritonavir 100 mg once daily).

Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes, and *in vivo* micronucleus test in mice.

Cobicistat: In a long-term carcinogenicity study in mice, no drug-related increases in tumor incidence were observed at doses up to 50 and 100 mg/kg/day in males and females, respectively. Cobicistat exposures at these doses were approximately 7 (male) and 16 (females) times, respectively, the human systemic exposure at the therapeutic daily dose. In a long-term carcinogenicity study of cobicistat in rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses of 25 and 50 mg/kg/day in males, and at 30 mg/kg/day in females. The follicular cell findings are considered to be rat-specific, secondary to hepatic microsomal enzyme induction and thyroid hormone imbalance, and are not relevant for humans. At the highest doses tested in the rat carcinogenicity study, systemic exposures were approximately 2 times the human systemic exposure at the therapeutic daily dose.

Cobicistat was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

Impairment of Fertility

Darunavir: No effects on fertility or early embryonic development were observed with darunavir in rats.

Cobicistat: Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 4-fold higher than human exposures at the recommended 150 mg daily dose.

Fertility was normal in the offspring of rats exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 1.2-fold higher than human exposures at the recommended 150 mg daily dose.

14 CLINICAL STUDIES

The efficacy of PREZCOBIX is based on efficacy demonstrated in clinical trials of darunavir co-administered with ritonavir *[see darunavir full prescribing information]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

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.

PREZCOBIX 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]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Instructions for Use

Advise patients to take PREZCOBIX with food every day on a regular dosing schedule, as missed doses can result in development of resistance. Inform patients not to alter the dose of PREZCOBIX or discontinue therapy with PREZCOBIX without consulting their physician *[see Dosage and Administration (2.2)]*.

Hepatotoxicity

Inform patients that drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) and liver injury, including some fatalities, could potentially occur with PREZCOBIX. Advise patients to contact their healthcare provider immediately if signs and symptoms of liver problems develop *[see Warnings and Precautions (5.1)]*.

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. Advise 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 (5.2)]*.

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 in pregnant women 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 women exposed to PREZCOBIX *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct women 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)]*.

Manufactured by:
Janssen Ortho LLC, Gurabo, PR 00778

Manufactured for:
Janssen Therapeutics, Division of Janssen Products, LP, Titusville NJ 08560

PATIENT INFORMATION
PREZCOBIX® (prez-koe-bix)
(darunavir and cobicistat)
tablets

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.
  - dark (tea colored) urine
  - yellowing of your skin or whites of your eyes
  - pale colored stools (bowel movements)
  - nausea
  - vomiting
  - pain or tenderness on your right side below your ribs
  - loss of appetite
- **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:
  - fever
  - tiredness
  - muscle or joint pain
  - blisters or skin lesions
  - mouth sores or ulcers
  - red or inflamed eyes, like “pink eye” (conjunctivitis)
- **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 HIV-1 (Human Immunodeficiency Virus 1) medicine used with other antiretroviral medicines to treat HIV-1 infection in adults. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

PREZCOBIX contains the prescription medicines darunavir and cobicistat.

It is not known if PREZCOBIX is safe and effective in children under 18 years of age.

Who should not take PREZCOBIX?

Do not take PREZCOBIX with any of the following medicines:

- alfuzosin
- carbamazepine
- cisapride
- colchicine, if you have liver or kidney problems
- dronedarone
- elbasvir and grazoprevir
- ergot-containing medicines:
  - dihydroergotamine
  - ergotamine tartrate
  - methylergonovine
- lovastatin or a product that contains lovastatin
- lurasidone
- midazolam, when taken by mouth
- phenobarbital
- phenytoin
- pimozide
- ranolazine
- rifampin
- sildenafil, when used for the treatment of pulmonary arterial hypertension (PAH)
- simvastatin or a product that contains simvastatin

- St. John's wort (*Hypericum perforatum*), or a product that contains St. John's wort
- 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
- have any other medical condition
- are pregnant or plan to become pregnant.
  - It is not known if PREZCOBIX will harm your unborn baby.
  - PREZCOBIX should not be used in pregnant women because you may not have enough PREZCOBIX in your body during pregnancy.
  - Tell your healthcare provider if you become pregnant while taking PREZCOBIX. Your healthcare provider will prescribe different medicines if you become pregnant while taking PREZCOBIX.
  - **Pregnancy Registry**: There is a pregnancy registry for women who take antiretroviral 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 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
- headache
- stomach-area (abdominal) pain

- rash
- 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.

Manufactured by: Janssen Ortho LLC, Gurabo, PR 00778
Manufactured for: Janssen Therapeutics, Division of Janssen Products, LP, Titusville NJ 08560

For more information call 1-800-526-7736.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 06/2018

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