Brand Name	Prezcobix
Active Ingredient(s)	darunavir, cobicistat
Strength	800-150 mg
Dosage Form	tablet
Inactive Ingredients	colloidal silicon dioxide, crospovidone, hypromellose, magnesium stearate, and silicified microcrystalline cellulose. The coating contains iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide.
NDC	59676-575-30
DIN	02426501
Canadian Distributor	Janssen Inc. 19 Green Belt Drive, Toronto, Ontario, Canada M3C 1L9
NDA Number	NDA205395
US Distributor (NDA Holder)	Janssen Products LP 800 Ridgeview Dr Horsham, PA, 19044
Manufacturer (Final Packager)	Janssen Ortho LLC. Gurabo, PR 00778 USA
API Manufacturer	Not available
Relationship to Sponsor	The Sponsor may have or have had agreements with the U.S. manufacturer for rebates. The Sponsor has no relationship with the foreign manufacturer.

Current FDA-approved Package Insert

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----------

Contraindications (4) 04/2022

----------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 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, 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 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)

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

Revised: 03/2023

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 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).

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 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 (8.6) 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

Darunavir and cobicistat are both inhibitors of the cytochrome P450 3A (CYP3A) isoform. PREZCOBIX should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life threatening events (narrow therapeutic index). Darunavir and cobicistat are both substrates of the cytochrome P450 3A (CYP3A) isoform. Co-administration of PREZCOBIX with CYP3A inducers may lead to lower exposures of darunavir and cobicistat and potential loss of efficacy of darunavir and possible resistance. Examples of drugs that are contraindicated for co-administration with PREZCOBIX *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]* are listed below.

- 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
- Ergot derivatives, e.g. dihydroergotamine, ergotamine, methylergonovine
- Herbal product: St. John's wort (*Hypericum perforatum*)
- Hepatitis C direct acting antiviral: elbasvir/grazoprevir
- Lipid modifying agents: lomitapide, lovastatin, simvastatin
- Opioid Antagonist: naloxegol
- 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.

PREZCOBIX (darunavir and cobicistat) tablets

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 and reduce plasma concentrations of active metabolite(s) formed by CYP3A. Initiation of medications that inhibit or induce CYP3A may respectively increase or decrease concentrations of PREZCOBIX.

These interactions 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.
- loss of therapeutic effect of the concomitant medications from lower exposures of active metabolite(s).
- loss of therapeutic effect of PREZCOBIX and possible development of resistance from lower exposures of PREZCOBIX.

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 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 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)]*
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.10)]*

PREZCOBIX (darunavir and cobicistat) tablets

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.

Clinical Trials in Adults

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 subjects with HIV-1 infection. Adverse reactions evaluated through Week 24 did not differ substantially from those reported in clinical trials with darunavir co-administered with ritonavir.

Clinical Trials in Pediatric Patients

No clinical trials with PREZCOBIX were performed in pediatric patients. However, the safety of the components of PREZCOBIX, darunavir and cobicistat, co-administered with two nucleoside reverse transcriptase inhibitors, was evaluated in pediatric subjects of 12 to less than 18 years of age with HIV-1 infection through clinical trial GS-US-216-0128 (virologically-suppressed, N=7 with weight ≥40 kg) through Week 48. Safety analyses of this trial in these pediatric subjects did not identify new safety concerns compared to the known safety profile of PREZCOBIX in adult subjects *[see Clinical Studies (14.2)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of darunavir. Because these reactions 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)

Renal and Urinary Disorders

Crystal nephropathy, crystalluria

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. Co-administration of PREZCOBIX with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect (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. The table includes examples of potentially significant interactions but is not all inclusive, and therefore the label of each drug that is co-administered with PREZCOBIX should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regard to co-administration. For the list of examples of contraindicated drugs, *[see Contraindications (4)]*.

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

Concomitant Drug Class: Drug Name Examples	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.
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.

PREZCOBIX (darunavir and cobicistat) tablets

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Anticoagulants: Direct Oral Anticoagulants (DOACs) apixaban	↑ apixaban	Due to potentially increased bleeding risk, dosing recommendations for co-administration of apixaban with PREZCOBIX depend on the apixaban dose. Refer to apixaban dosing instructions for co-administration with P-gp and strong CYP3A inhibitors in apixaban prescribing information.
rivaroxaban	↑ rivaroxaban	Co-administration of rivaroxaban with PREZCOBIX is not recommended because it may lead to an increased bleeding risk.
dabigatran etexilate edoxaban	↑ dabigatran ↑ edoxaban	Refer to the dabigatran etexilate or edoxaban prescribing information for recommendations regarding co-administration. The specific recommendations are based on indication, renal function, and effect of the co-administered P-gp inhibitors on the concentration of dabigatran or edoxaban. Clinical monitoring is recommended when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate and edoxaban, is co-administered with PREZCOBIX.
Other Anticoagulants: 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.
Anticonvulsants with CYP3A induction effects that are NOT contraindicated: 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.
Anticonvulsants that are metabolized by CYP3A: e.g. clonazepam	↑ clonazepam	Clinical monitoring of anticonvulsants is recommended.
Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs): 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	↑ TCAs	
Other antidepressants: trazodone	↑ trazodone	

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Antifungals: itraconazole, isavuconazole, ketoconazole, posaconazole	↑ darunavir ↑ cobicistat	Monitor for increased darunavir or cobicistat and/or antifungal adverse reactions.
	↑ itraconazole ↑ ketoconazole ↑ isavuconazole	Specific dosing recommendations are not available for co-administration with these antifungals. Monitor for increased itraconazole or ketoconazole adverse reactions.
voriconazole	↔ posaconazole voriconazole: effects unknown	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	↓ darunavir ↓ cobicistat	Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance.
rifabutin	↑ rifabutin cobicistat: effects unknown darunavir: effects unknown	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.
rifapentine	↓ darunavir	Co-administration with rifapentine is not recommended.

PREZCOBIX (darunavir and cobicistat) tablets

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
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.
Cardiac Disorders: ranolazine, ivabradine	↑ ranolazine ↑ ivabradine	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
dronedarone	↑ dronedarone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Other antiarrhythmics 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.

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Corticosteroids: dexamethasone (systemic)	↓ darunavir ↓ cobicistat	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.
Corticosteroids primarily metabolized by CYP3A: e.g. betamethasone budesonide ciclesonide fluticasone methylprednisolone mometasone triamcinolone	↑ corticosteroids	Co-administration with corticosteroids (all routes of administration) 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.

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
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.
glecaprevir/ pibrentasvir	↑ glecaprevir ↑ pibrentasvir	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)]*.
drospirenone/ ethinylestradiol	↑ drospirenone ↓ ethinylestradiol	For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia.
Other progestin/ estrogen contraceptives	progestin: effects unknown estrogen: effects unknown	No data are available to make recommendations on co-administration with other hormonal contraceptives.
Immunosuppressants: cyclosporine, sirolimus, tacrolimus	↑ immunosuppressants	These immunosuppressant agents are metabolized by CYP3A. Therapeutic drug monitoring is recommended with concomitant use
Immunosuppressant/ neoplastic: everolimus	↑immunosuppressants	Co-administration of everolimus and PREZCOBIX is not recommended.
irinotecan		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)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Lipid Modifying Agents		
HMG-CoA reductase inhibitors: lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis.
atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin	↑ atorvastatin ↑ fluvastatin ↑ pravastatin ↑ rosuvastatin	For atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin, start with the lowest recommended dose and titrate while monitoring for safety (e.g. myopathy).
	pitavastatin: effect unknown	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
Other lipid modifying agents: lomitapide	↑ lomitapide	Co-administration is contraindicated due to potential for markedly increased transaminases associated with increased plasma concentrations of lomitapide.
Narcotic analgesics metabolized by CYP3A: e.g. fentanyl, oxycodone	↑ fentanyl ↑ oxycodone	Careful monitoring of therapeutic effects and adverse reactions associated with CYP3A-metabolized narcotic analgesics (including potentially fatal respiratory depression) is recommended with co-administration.
tramadol	↑ tramadol	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	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.
Opioid Antagonist naloxegol	↑ naloxegol	Co-administration of PREZCOBIX and naloxegol is contraindicated due to potential for precipitating opioid withdrawal symptoms.

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
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.

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Platelet aggregation inhibitor: ticagrelor	↑ ticagrelor	Co-administration of PREZCOBIX and ticagrelor is not recommended.
clopidogrel	↓ clopidogrel active metabolite	Co-administration of PREZCOBIX with clopidogrel is not recommended due to the potential reduction of the antiplatelet activity of clopidogrel.
prasugrel	↔ prasugrel active metabolite	No dose adjustment is needed when prasugrel is co-administered with PREZCOBIX.
Sedatives/hypnotics: orally administered midazolam, triazolam	↑ midazolam ↑ triazolam	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.
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 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).

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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) 1-800-258-4263.

Risk Summary

PREZCOBIX is not recommended during pregnancy because of substantially lower exposures of darunavir and cobicistat during the second and third trimesters *[see Dosage and Administration (2.5)]*. A study evaluating the pharmacokinetics of antiretrovirals during pregnancy demonstrated substantially lower exposures of darunavir and cobicistat in the second and third trimesters compared to the post-partum period *(see Data)* and *[see Clinical Pharmacology (12.3)]*.

Prospective pregnancy data from the APR are not sufficient to adequately assess the risk of birth defects or miscarriage. However, available data from the APR show no statistically significant difference in the overall risk of major birth defects for darunavir and cobicistat 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 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 during pregnancy 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 individuals. An alternative regimen is recommended for individuals who become pregnant during therapy with PREZCOBIX.

Data

Human Data

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.

Prospective reports from the APR of overall major birth defects in pregnancies exposed to the components of PREZCOBIX are compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. Limitations of using an external comparator include differences in methodology and populations, as well as confounding due to the underlying disease.

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 over 980 exposures to darunavir-containing regimens during pregnancy resulting in live births (including over 660 exposed in the first trimester and over 320 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.6% (95% CI: 2.3% to 5.3%) with first trimester exposure to darunavir-containing regimens and 2.5% (95% CI: 1.1% to 4.8%) with second/third trimester exposure to darunavir-containing regimens.

Cobicistat: Based on prospective reports to the APR of over 570 exposures to cobicistat-containing regimens during pregnancy resulting in live births (including over 480 exposed in the first trimester and over 80 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.7% (95% CI: 2.2% to 5.7%) and 1.1% (95% CI: 0.0% to 6.2%) with first and second/third trimester, respectively, to cobicistat-containing regimens.

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.

8.3 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 (7.3)].*

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 pharmacokinetic, 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 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)].*

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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

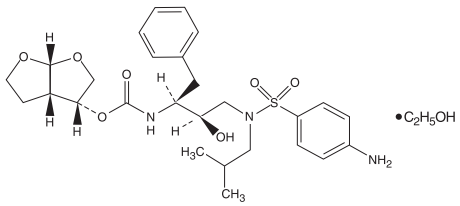
Human experience of acute overdose with PREZCOBIX is limited. No specific antidote is available for overdose with PREZCOBIX. Treatment of overdose with PREZCOBIX consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Since both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

11 DESCRIPTION

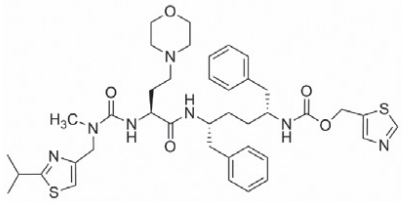
PREZCOBIX® is a fixed-dose combination tablet containing darunavir and cobicistat. Darunavir is an inhibitor of the human immunodeficiency virus (HIV-1) protease. Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family.

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.

PREZCOBIX (darunavir and cobicistat) tablets

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 subjects with HIV-1 infection 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 subjects with HIV-1 infection 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 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 C_{max} values were similar between adults and pediatric subjects. Geometric mean darunavir AUC_{24h} and C_{24h} 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, 1.55) in pediatric subjects relative to adults, respectively. These differences were not considered clinically significant. Geometric mean cobicistat AUC_{24h}, C_{max}, and C_{24h} 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[a]

Parameter Geometric mean (CV%)	Darunavir	Cobicistat
Pediatric Subjects[a]	N=7	N=7
AUC_{24h} (mcg.hr/mL)	77.22 (29.5)	8.33 (34.9)
C_{max} (mcg/mL)	7.32 (21.7)	1.10 (20.0)
C_{24h} (mcg/mL)	0.68 (91.6)	0.02 (123.9)[b]
Adults[c]	N=21	N=21
AUC_{24h} (mcg.hr/mL)	90.56 (45.3)	7.69 (43.9)
C_{max} (mcg/mL)	8.34 (33.3)	1.04 (35.3)
C_{24h} (mcg/mL)	1.00 (108.0)	0.02 (135.1)[d]

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 C_{24h} 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

[d] N=18

Pregnancy and Postpartum

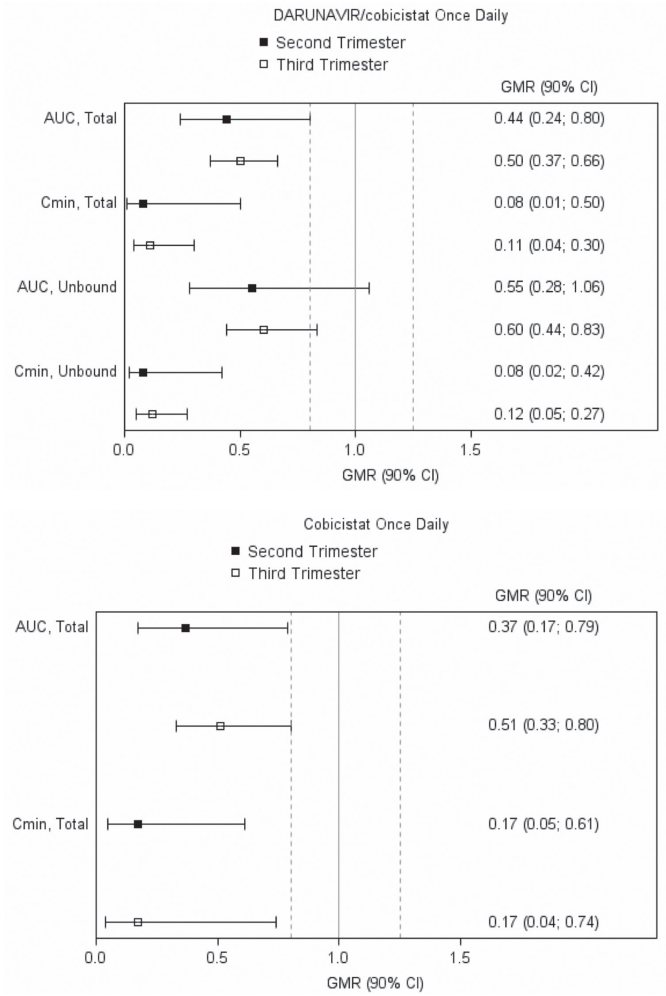
The exposure to total and unbound darunavir boosted with cobicistat after intake of PREZCOBIX as part of an antiretroviral regimen was substantially lower during the second and third trimesters of pregnancy compared with 6-12 weeks postpartum (see Table 4 and Figure 1).

PREZCOBIX (darunavir and cobicistat) tablets

Table 4: 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

Darunavir is metabolized by CYP3A. Cobicistat is metabolized by CYP3A and, to a minor extent, by CYP2D6. Darunavir co-administered with cobicistat is an inhibitor of CYP3A and CYP2D6. Cobicistat inhibits the following transporters: P-gp, BCRP, MATE1, OATP1B1, and OATP1B3. 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)]*.

A drug-drug interaction study between darunavir/cobicistat and dabigatran etexilate was conducted in healthy participants. The effects of darunavir on co-administration with dabigatran etexilate are summarized in Table 5.

Table 5: Drug Interactions: Pharmacokinetic Parameters for Co-Administered Drugs in the Presence of darunavir/cobicistat

	Dose/Schedule				LS Mean ratio (90% CI) of co-administered drug pharmacokinetic parameters with/without darunavir no effect =1.00		
Co-administered drug	Co-administered drug	Darunavir/ cobicistat	N	PK	C_{max}	AUC	C_{min}
Dabigatran etexilate	150 mg	800/150 mg single dose	14	↑	2.64 (2.29-3.05)	2.64 (2.32-3.00)	-
		800/150 mg q.d.[a]	14	↑	1.99 (1.72-2.30)	1.88 (1.65-2.13)	-

N = number of subjects with data
q.d. = once daily
[a] 800/150 mg q.d. for 14 days before co-administered with dabigatran etexilate.

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.

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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

14.1 Clinical Trial Results in Adults with HIV-1 Infection

The efficacy of PREZCOBIX in adults with HIV-1 infection is based on efficacy demonstrated in clinical trials of darunavir co-administered with ritonavir *[see darunavir full prescribing information]*.

14.2 Clinical Trial Results in Pediatric Subjects with HIV-1 Infection

Trial GS-US-216-0128 was a Phase 2/3 multicenter, open-label trial to evaluate the pharmacokinetics, safety, and efficacy of darunavir co-administered with cobicistat in adolescents aged 12 years and older with HIV-1 infection who were virolgically suppressed and had a baseline estimated creatinine clearance ≥90 mL/min/1.73 m². Subjects were on a stable antiretroviral regimen (for at least 3 months), consisting of darunavir administered with ritonavir, combined with 2 NRTIs. These subjects (N=7) were switched from ritonavir to cobicistat 150 mg once daily and continued darunavir and 2 NRTIs.

The median age of subjects was 14 years (range 12-16 years), median weight was 60 kg (range 45-78 kg), and 43% were male. At baseline, all subjects had plasma HIV-1 RNA <50 copies/mL. At Week 48, 86% (6/7) of subjects remained suppressed (HIV-1 RNA <50 copies/mL), and 1 subject had missing data. From a median baseline CD4+ cell count and CD4+% of 1,117 cells/mm^3 (range 658 to 2,416 cells/mm^3) and 45% (range 28% to 56%), respectively, the median change from baseline in CD4+ cell count and CD4+% at Week 48 was -342 cells/mm^3 (range -1,389 to 219 cells/mm^3) and -6% (range -12% to 5%), respectively. All 6 subjects with available data had CD4+ cell counts above 800 cells/mm^3 at Week 48.

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]*.

Keep PREZCOBIX and all medicines out of reach of children.

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 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)]*.

Manufactured for:
Janssen Products, LP, Horsham PA 19044, USA

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 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
- 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. This is not a complete list of medicines. Therefore, tell your healthcare provider about **all** medicines you take.

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, topical creams, 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.

Manufactured for: Janssen Products, LP, Horsham PA 19044, USA

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 03/2023

cp-51114v18

Proposed Package Insert

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----------

Contraindications (4) 04/2022

----------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 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, 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 LifeScience Logistics at 1-855-738-6171 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 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)

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

Revised: 03/2023

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 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).

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 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 (8.6) 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

Darunavir and cobicistat are both inhibitors of the cytochrome P450 3A (CYP3A) isoform. PREZCOBIX should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life threatening events (narrow therapeutic index). Darunavir and cobicistat are both substrates of the cytochrome P450 3A (CYP3A) isoform. Co-administration of PREZCOBIX with CYP3A inducers may lead to lower exposures of darunavir and cobicistat and potential loss of efficacy of darunavir and possible resistance. Examples of drugs that are contraindicated for co-administration with PREZCOBIX *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]* are listed below.

- 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
- Ergot derivatives, e.g. dihydroergotamine, ergotamine, methylergonovine
- Herbal product: St. John's wort (*Hypericum perforatum*)
- Hepatitis C direct acting antiviral: elbasvir/grazoprevir
- Lipid modifying agents: lomitapide, lovastatin, simvastatin
- Opioid Antagonist: naloxegol
- 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.

PREZCOBIX (darunavir and cobicistat) tablets

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 and reduce plasma concentrations of active metabolite(s) formed by CYP3A. Initiation of medications that inhibit or induce CYP3A may respectively increase or decrease concentrations of PREZCOBIX.

These interactions 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.
- loss of therapeutic effect of the concomitant medications from lower exposures of active metabolite(s).
- loss of therapeutic effect of PREZCOBIX and possible development of resistance from lower exposures of PREZCOBIX.

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 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 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)]*
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.10)]*

PREZCOBIX (darunavir and cobicistat) tablets

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.

Clinical Trials in Adults

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 subjects with HIV-1 infection. Adverse reactions evaluated through Week 24 did not differ substantially from those reported in clinical trials with darunavir co-administered with ritonavir.

Clinical Trials in Pediatric Patients

No clinical trials with PREZCOBIX were performed in pediatric patients. However, the safety of the components of PREZCOBIX, darunavir and cobicistat, co-administered with two nucleoside reverse transcriptase inhibitors, was evaluated in pediatric subjects of 12 to less than 18 years of age with HIV-1 infection through clinical trial GS-US-216-0128 (virologically-suppressed, N=7 with weight ≥40 kg) through Week 48. Safety analyses of this trial in these pediatric subjects did not identify new safety concerns compared to the known safety profile of PREZCOBIX in adult subjects *[see Clinical Studies (14.2)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of darunavir. Because these reactions 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)

Renal and Urinary Disorders

Crystal nephropathy, crystalluria

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. Co-administration of PREZCOBIX with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect (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. The table includes examples of potentially significant interactions but is not all inclusive, and therefore the label of each drug that is co-administered with PREZCOBIX should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regard to co-administration. For the list of examples of contraindicated drugs, *[see Contraindications (4)]*.

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

Concomitant Drug Class: Drug Name Examples	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.
Antibacterials: clarithromycin, erythromycin, telithromycin	↑ darunavir ↑ cobicistat ↑ antibacterial	Consider alternative antibiotics with concomitant use of PREZCOBIX.
Anticancer agents: dasatinib, nilotinib vinblastine, vincristine	↑ 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. 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.

PREZCOBIX (darunavir and cobicistat) tablets

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Anticoagulants: Direct Oral Anticoagulants (DOACs) apixaban	↑ apixaban	Due to potentially increased bleeding risk, dosing recommendations for co-administration of apixaban with PREZCOBIX depend on the apixaban dose. Refer to apixaban dosing instructions for co-administration with P-gp and strong CYP3A inhibitors in apixaban prescribing information.
rivaroxaban	↑ rivaroxaban	Co-administration of rivaroxaban with PREZCOBIX is not recommended because it may lead to an increased bleeding risk.
dabigatran etexilate edoxaban	↑ dabigatran ↑ edoxaban	Refer to the dabigatran etexilate or edoxaban prescribing information for recommendations regarding co-administration. The specific recommendations are based on indication, renal function, and effect of the co-administered P-gp inhibitors on the concentration of dabigatran or edoxaban. Clinical monitoring is recommended when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate and edoxaban, is co-administered with PREZCOBIX.
Other Anticoagulants: 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.
Anticonvulsants with CYP3A induction effects that are NOT contraindicated: 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.
Anticonvulsants that are metabolized by CYP3A: e.g. clonazepam	↑ clonazepam	Clinical monitoring of anticonvulsants is recommended.
Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs): 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	↑ TCAs	
Other antidepressants: trazodone	↑ trazodone	

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Antifungals: itraconazole, isavuconazole, ketoconazole, posaconazole	↑ darunavir ↑ cobicistat	Monitor for increased darunavir or cobicistat and/or antifungal adverse reactions.
	↑ itraconazole ↑ ketoconazole ↑ isavuconazole	Specific dosing recommendations are not available for co-administration with these antifungals. Monitor for increased itraconazole or ketoconazole adverse reactions.
voriconazole	↔ posaconazole voriconazole: effects unknown	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	↓ darunavir ↓ cobicistat	Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance.
rifabutin	↑ rifabutin cobicistat: effects unknown darunavir: effects unknown	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.
rifapentine	↓ darunavir	Co-administration with rifapentine is not recommended.

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
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.
Cardiac Disorders: ranolazine, ivabradine	↑ ranolazine ↑ ivabradine	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
dronedarone	↑ dronedarone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Other antiarrhythmics 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.

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Corticosteroids: dexamethasone (systemic)	↓ darunavir ↓ cobicistat	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.
Corticosteroids primarily metabolized by CYP3A: e.g. betamethasone budesonide ciclesonide fluticasone methylprednisolone mometasone triamcinolone	↑ corticosteroids	Co-administration with corticosteroids (all routes of administration) 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.

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
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.
glecaprevir/ pibrentasvir	↑ glecaprevir ↑ pibrentasvir	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)]*.
drospirenone/ ethinylestradiol	↑ drospirenone ↓ ethinylestradiol	For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia.
Other progestin/ estrogen contraceptives	progestin: effects unknown estrogen: effects unknown	No data are available to make recommendations on co-administration with other hormonal contraceptives.
Immunosuppressants: cyclosporine, sirolimus, tacrolimus	↑ immunosuppressants	These immunosuppressant agents are metabolized by CYP3A. Therapeutic drug monitoring is recommended with concomitant use
Immunosuppressant/ neoplastic: everolimus	↑immunosuppressants	Co-administration of everolimus and PREZCOBIX is not recommended.
irinotecan		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)

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Lipid Modifying Agents		
HMG-CoA reductase inhibitors: lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis.
atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin	↑ atorvastatin ↑ fluvastatin ↑ pravastatin ↑ rosuvastatin	For atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin, start with the lowest recommended dose and titrate while monitoring for safety (e.g. myopathy).
	pitavastatin: effect unknown	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
Other lipid modifying agents: lomitapide	↑ lomitapide	Co-administration is contraindicated due to potential for markedly increased transaminases associated with increased plasma concentrations of lomitapide.
Narcotic analgesics metabolized by CYP3A: e.g. fentanyl, oxycodone	↑ fentanyl ↑ oxycodone	Careful monitoring of therapeutic effects and adverse reactions associated with CYP3A-metabolized narcotic analgesics (including potentially fatal respiratory depression) is recommended with co-administration.
tramadol	↑ tramadol	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	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.
Opioid Antagonist naloxegol	↑ naloxegol	Co-administration of PREZCOBIX and naloxegol is contraindicated due to potential for precipitating opioid withdrawal symptoms.

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
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.

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

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Platelet aggregation inhibitor: ticagrelor	↑ ticagrelor	Co-administration of PREZCOBIX and ticagrelor is not recommended.
clopidogrel	↓ clopidogrel active metabolite	Co-administration of PREZCOBIX with clopidogrel is not recommended due to the potential reduction of the antiplatelet activity of clopidogrel.
prasugrel	↔ prasugrel active metabolite	No dose adjustment is needed when prasugrel is co-administered with PREZCOBIX.
Sedatives/hypnotics: orally administered midazolam, triazolam	↑ midazolam ↑ triazolam	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.
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 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).

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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) 1-800-258-4263.

Risk Summary

PREZCOBIX is not recommended during pregnancy because of substantially lower exposures of darunavir and cobicistat during the second and third trimesters *[see Dosage and Administration (2.5)]*. A study evaluating the pharmacokinetics of antiretrovirals during pregnancy demonstrated substantially lower exposures of darunavir and cobicistat in the second and third trimesters compared to the post-partum period *(see Data)* and *[see Clinical Pharmacology (12.3)]*.

Prospective pregnancy data from the APR are not sufficient to adequately assess the risk of birth defects or miscarriage. However, available data from the APR show no statistically significant difference in the overall risk of major birth defects for darunavir and cobicistat 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 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 during pregnancy 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 individuals. An alternative regimen is recommended for individuals who become pregnant during therapy with PREZCOBIX.

Data

Human Data

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.

Prospective reports from the APR of overall major birth defects in pregnancies exposed to the components of PREZCOBIX are compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. Limitations of using an external comparator include differences in methodology and populations, as well as confounding due to the underlying disease.

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 over 980 exposures to darunavir-containing regimens during pregnancy resulting in live births (including over 660 exposed in the first trimester and over 320 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.6% (95% CI: 2.3% to 5.3%) with first trimester exposure to darunavir-containing regimens and 2.5% (95% CI: 1.1% to 4.8%) with second/third trimester exposure to darunavir-containing regimens.

Cobicistat: Based on prospective reports to the APR of over 570 exposures to cobicistat-containing regimens during pregnancy resulting in live births (including over 480 exposed in the first trimester and over 80 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.7% (95% CI: 2.2% to 5.7%) and 1.1% (95% CI: 0.0% to 6.2%) with first and second/third trimester, respectively, to cobicistat-containing regimens.

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.

8.3 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 (7.3)].*

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 pharmacokinetic, 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 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)].*

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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

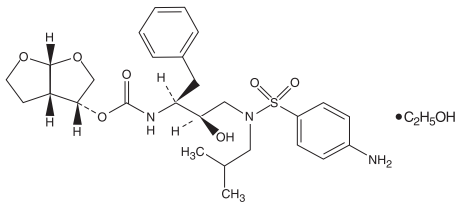
Human experience of acute overdose with PREZCOBIX is limited. No specific antidote is available for overdose with PREZCOBIX. Treatment of overdose with PREZCOBIX consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Since both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

11 DESCRIPTION

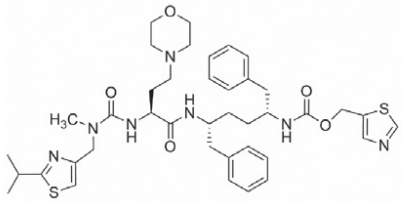
PREZCOBIX® is a fixed-dose combination tablet containing darunavir and cobicistat. Darunavir is an inhibitor of the human immunodeficiency virus (HIV-1) protease. Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family.

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.

PREZCOBIX (darunavir and cobicistat) tablets

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 subjects with HIV-1 infection 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 subjects with HIV-1 infection 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 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 C_{max} values were similar between adults and pediatric subjects. Geometric mean darunavir AUC_{24h} and C_{24h} 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, 1.55) in pediatric subjects relative to adults, respectively. These differences were not considered clinically significant. Geometric mean cobicistat AUC_{24h}, C_{max}, and C_{24h} 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[a]

Parameter Geometric mean (CV%)	Darunavir	Cobicistat
Pediatric Subjects[a]	N=7	N=7
AUC_{24h} (mcg.hr/mL)	77.22 (29.5)	8.33 (34.9)
C_{max} (mcg/mL)	7.32 (21.7)	1.10 (20.0)
C_{24h} (mcg/mL)	0.68 (91.6)	0.02 (123.9)[b]
Adults[c]	N=21	N=21
AUC_{24h} (mcg.hr/mL)	90.56 (45.3)	7.69 (43.9)
C_{max} (mcg/mL)	8.34 (33.3)	1.04 (35.3)
C_{24h} (mcg/mL)	1.00 (108.0)	0.02 (135.1)[d]

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 C_{24h} 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

[d] N=18

Pregnancy and Postpartum

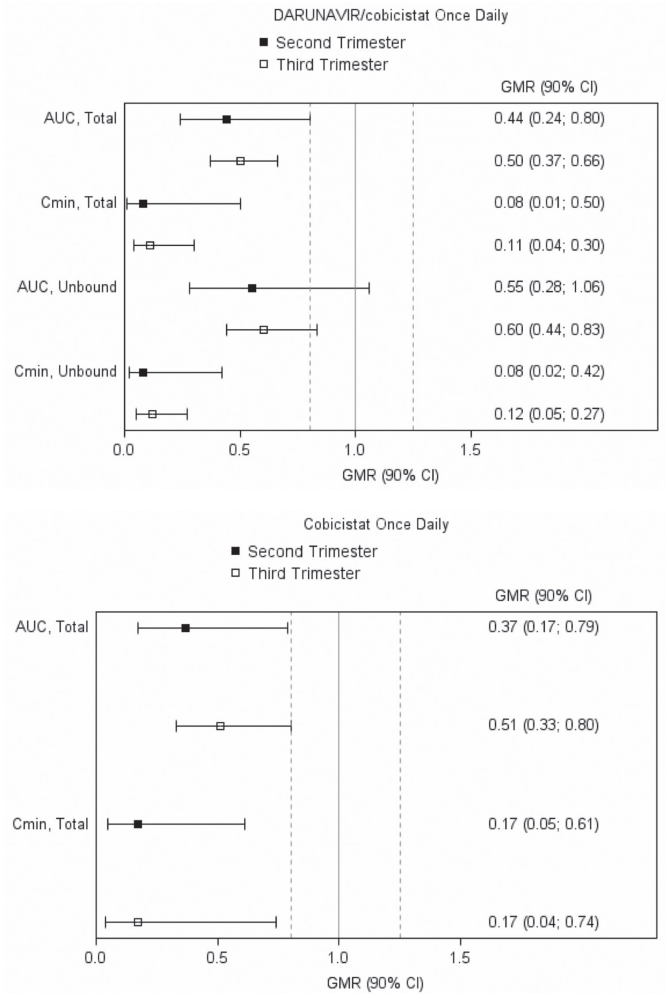
The exposure to total and unbound darunavir boosted with cobicistat after intake of PREZCOBIX as part of an antiretroviral regimen was substantially lower during the second and third trimesters of pregnancy compared with 6-12 weeks postpartum (see Table 4 and Figure 1).

PREZCOBIX (darunavir and cobicistat) tablets

Table 4: 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

Darunavir is metabolized by CYP3A. Cobicistat is metabolized by CYP3A and, to a minor extent, by CYP2D6. Darunavir co-administered with cobicistat is an inhibitor of CYP3A and CYP2D6. Cobicistat inhibits the following transporters: P-gp, BCRP, MATE1, OATP1B1, and OATP1B3. 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)]*.

A drug-drug interaction study between darunavir/cobicistat and dabigatran etexilate was conducted in healthy participants. The effects of darunavir on co-administration with dabigatran etexilate are summarized in Table 5.

Table 5: Drug Interactions: Pharmacokinetic Parameters for Co-Administered Drugs in the Presence of darunavir/cobicistat

					LS Mean ratio (90% CI) of co-administered drug pharmacokinetic parameters with/without darunavir no effect =1.00		
	Dose/Schedule						
Co-administered drug	Co-administered drug	Darunavir/ cobicistat	N	PK	C_{max}	AUC	C_{min}
Dabigatran etexilate	150 mg	800/150 mg single dose	14	↑	2.64 (2.29-3.05)	2.64 (2.32-3.00)	-
		800/150 mg q.d.[a]	14	↑	1.99 (1.72-2.30)	1.88 (1.65-2.13)	-

N = number of subjects with data
q.d. = once daily
[a] 800/150 mg q.d. for 14 days before co-administered with dabigatran etexilate.

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

14.1 Clinical Trial Results in Adults with HIV-1 Infection

The efficacy of PREZCOBIX in adults with HIV-1 infection is based on efficacy demonstrated in clinical trials of darunavir co-administered with ritonavir *[see darunavir full prescribing information]*.

14.2 Clinical Trial Results in Pediatric Subjects with HIV-1 Infection

Trial GS-US-216-0128 was a Phase 2/3 multicenter, open-label trial to evaluate the pharmacokinetics, safety, and efficacy of darunavir co-administered with cobicistat in adolescents aged 12 years and older with HIV-1 infection who were virolgically suppressed and had a baseline estimated creatinine clearance ≥90 mL/min/1.73 m^2. Subjects were on a stable antiretroviral regimen (for at least 3 months), consisting of darunavir administered with ritonavir, combined with 2 NRTIs. These subjects (N=7) were switched from ritonavir to cobicistat 150 mg once daily and continued darunavir and 2 NRTIs.

The median age of subjects was 14 years (range 12-16 years), median weight was 60 kg (range 45-78 kg), and 43% were male. At baseline, all subjects had plasma HIV-1 RNA <50 copies/mL. At Week 48, 86% (6/7) of subjects remained suppressed (HIV-1 RNA <50 copies/mL), and 1 subject had missing data. From a median baseline CD4+ cell count and CD4+% of 1,117 cells/mm^3 (range 658 to 2,416 cells/mm^3) and 45% (range 28% to 56%), respectively, the median change from baseline in CD4+ cell count and CD4+% at Week 48 was -342 cells/mm^3 (range -1,389 to 219 cells/mm^3) and -6% (range -12% to 5%), respectively. All 6 subjects with available data had CD4+ cell counts above 800 cells/mm^3 at Week 48.

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 42067-210-30).

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.

This drug was imported from Canada without the authorization of Janssen Products, LP under the State of Florida Section 804 Importation Program. Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

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 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)]*.

Manufactured for:
Janssen Products, LP, Horsham PA 19044, USA

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 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
- 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. This is not a complete list of medicines. Therefore, tell your healthcare provider about **all** medicines you take.

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, topical creams, 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.

Manufactured for: Janssen Products, LP, Horsham PA 19044, USA

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 03/2023

cp-51114v18

This drug was imported from Canada without the authorization of Janssen Products, LP under the State of Florida Section 804 Importation Program.
Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

Annotated Label Comparisons

PI Comparisons FDA VS. FLCPDIP
Differences
Updated information Adverse Reactions Contact
How Supplied/Storage and Handling added SIP804 language
Patient Information added SIP804 language
Listed new NDC #
Added Importation language & Importer name & address
Listed only drug strength purchased for program

FDA

----------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*.

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]*.

Keep PREZCOBIX and all medicines out of reach of children.

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 Products, LP, Horsham PA 19044

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 10/2022

FLSIP

----------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 LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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 42067-210-30).
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.

This drug was imported from Canada without the authorization of Janssen Products, LP under the State of Florida Section 804 Importation Program.
Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

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 for: Janssen Products, LP, Horsham PA 19044, USA

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 03/2023

cp-51114v18

This drug was imported from Canada without the authorization of Janssen Products, LP under the State of Florida Section 804 Importation Program.
Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

Proposed Package Label

Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.

Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	LSL Proprietary Name	LSL Generic Name	FLSIP Strength	LSL NDC	LSL Relabeler Name	Applicant Holder Name	Applicant Holder Address	FLSIP Active Ingredients
3/31/2023	Prezcobix	Darunavir-cobicistat	800-150	59676-575-30	205395	Janssen Products, LP	Horsham PA 19044	Darunavir-cobicistat	Aug-23	Prezcobix	Darunavir-cobicistat	800-150	42067-210-30	LifeScience Logistics, LLC	Janssen Products, LP,	Horsham PA 19044	Darunavir-cobicistat

Canadian to FDA Drug Comparison

Comparisons
Canada to FDA

Active Ingredient	Canadian Submission Number	Canadian Proprietary Name	Canadian Generic Name	DIN	Date Labeling Approved	Company Name	Address	Canadian Strength	Dosage Form	# of active Ingred.	Canadian Ingredients	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	US Ingredients	Comments for FDA
COBICISTAT,DARUNAVIR (DARUNAVIR ETHANOLATE)	268359	Prezcobix	Darunavir-cobicistat	02426501	Revision: March 3, 2023	JANSSEN INC	19 Green Belt Drive Toronto Ontario Canada M3C 1L9	150-800 mg	Oral Tablet, Once daily	2	COBICISTAT,DARUNAVIR (DARUNAVIR ETHANOLATE)	Prezcobix	Darunavir-cobicistat	150-800 mg	59676-575-30	NDA205395	Janssen Products, LP, Horsham PA 19044	Darunavir-cobicistat	n/a

Canadian Monograph

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]PREZCOBIX®

darunavir (as darunavir ethanolate)/cobicistat

film-coated tablets (800 mg/150 mg)

Human Immunodeficiency Virus (HIV) Protease Inhibitor

Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9

www.janssen.com/canada

Date of Initial Authorization:
June 18, 2014

Date of Revision:
March 3, 2023

Submission Control Number: 268359

RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	08/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PREZCOBIX® (darunavir/cobicistat), a fixed dose combination of darunavir and cobicistat, is indicated in combination with other antiretroviral agents for the treatment of HIV infection in treatment-naïve and in treatment-experienced adult patients without DRV RAMS.

For a description of the clinical data and dosing in support of this indication, refer to **4 DOSAGE AND ADMINISTRATION** and **14 CLINICAL TRIALS**.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

The safety and efficacy of PREZCOBIX® have not been established in pediatric patients (see **4 DOSAGE AND ADMINISTRATION** and **7 WARNINGS AND PRECAUTIONS**).

1.2 Geriatrics

Geriatrics (≥65 years of age)
Clinical studies 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, renal or cardiac function and of concomitant disease or other drug therapy (see **4 DOSAGE AND ADMINISTRATION** and **7 WARNINGS AND PRECAUTIONS**, and **10 CLINICAL PHARMACOLOGY**).

2 CONTRAINDICATIONS

PREZCOBIX® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

PREZCOBIX® is contraindicated in patients with severe (Child-Pugh Class C) hepatic insufficiency.

Administration of PREZCOBIX® is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). Darunavir and cobicistat are both substrates of the CYP3A isoform. Co-administration of PREZCOBIX® is contraindicated with potent CYP3A inducers as it may lead to lower exposures of darunavir and cobicistat and potential loss of efficacy of darunavir and possible resistance. Drugs that are contraindicated with PREZCOBIX® are listed in Table 1 (also see **9.4 Drug-Drug Interactions**, Table 4).

Table 1: Drugs that are Contraindicated with PREZCOBIX®

Drug Class	Drugs within Class that are Contraindicated with PREZCOBIX®
Alpha 1-Adrenoreceptor Antagonist	alfuzosin
Antiarrhythmics/Antianginals	amiodarone, dronedarone, ivabradine, lidocaine (systemic)
Direct Oral Anti-coagulants (DOACs)	apixaban, dabigatran, rivaroxaban
Anti-convulsants	carbamezepine, phenobarbital, phenytoin
Anti-gout	colchicine (in patients with renal and/or hepatic impairment)
Antimycobacterial	rifampin
Antivirals (Hepatitis C virus [HCV] direct-acting antivirals)	elbasvir/grazoprevir
Ergot Derivatives	dihydroergotamine, ergonovine, ergotamine
Herbal Products	St. John's wort (*Hypericum perforatum*)
HMG-CoA Reductase Inhibitors / Other lipid modifying agents	lovastatin, simvastatin lomitapide
Inhaled Beta Agonist	salmeterol
Neuroleptics	lurasidone, pimozide
Opioid Antagonist	naloxegol
PDE-5 Inhibitor	sildenafil (for treatment of pulmonary arterial hypertension)
Platelet Aggregation Inhibitor	ticagrelor
Sedatives/Hypnotics	triazolam

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

PREZCOBIX® consists of the HIV protease inhibitor darunavir and the pharmacokinetic enhancer cobicistat.

After therapy with PREZCOBIX® has been initiated, patients should not alter the dosage or discontinue therapy without instruction of their healthcare provider. If discontinuation of therapy with the components of PREZCOBIX® is indicated, dose modification of darunavir is necessary, or patients are unable to swallow the PREZCOBIX® tablet, separate pharmaceutical forms of darunavir and cobicistat are available. Please refer to the respective prescribing information for proper use of the products.

4.2 Recommended Dose and Dosage Adjustment

Adults

The recommended oral dosing regimen of PREZCOBIX® for antiretroviral treatment-naïve patients and antiretroviral treatment-experienced patients with no darunavir-resistance associated mutations (DRV-RAMS V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) is one tablet taken once daily with food. The type of food does not affect exposure

to PREZCOBIX® (see **9.5 Drug-Food Interactions**, **Effects of Food on Oral Absorption** and **10.3 Pharmacokinetics**).

Genotypic testing is recommended for all antiretroviral (ART) treatment-experienced patients prior to initiation of therapy. When genotypic testing is not feasible and darunavir treatment is considered:

- PREZCOBIX® is recommended in protease inhibitor-naive patients only.
- PREZCOBIX® is not recommended in protease inhibitor-experienced patients. PREZISTA® should be used instead of PREZCOBIX®. Refer to PREZISTA® Product Monograph for dosing recommendations.

Pediatric Patients
Health Canada has not authorized an indication for pediatric use.

Geriatric Patients
Insufficient data are available on which to make dose recommendations for patients 65 years of age and older. In general, caution should be exercised in the administration and monitoring of PREZCOBIX® in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy (see **1 INDICATIONS**, **7 WARNINGS AND PRECAUTIONS** and **10 CLINICAL PHARMACOLOGY**).

Pregnancy and postpartum
PREZCOBIX® is not recommended for use during pregnancy because of substantially lower exposures of darunavir and cobicistat during pregnancy.

Therapy with PREZCOBIX® should not be initiated during pregnancy, and women who become pregnant during therapy with PREZCOBIX® should be switched to an alternative regimen (see **7.1.1 Pregnant Women**).

Hepatic Impairment
There are no pharmacokinetic data regarding the use of PREZCOBIX® in patients with hepatic impairment. The safety and efficacy of PREZCOBIX® have not been established in patients with severe hepatic insufficiency (see **2 CONTRAINDICATIONS**).

Darunavir and cobicistat are metabolized by the liver. Studies with darunavir/ritonavir and with cobicistat as a single agent suggest no dose adjustment is required in patients with mild or moderate hepatic impairment (see **10.3 Pharmacokinetics**).

Renal Impairment
No dose adjustment is required in patients with renal impairment. PREZCOBIX® should not be initiated as part of a regimen containing emtricitabine, lamivudine, tenofovir disoproxil fumarate or adefovir in patients who have an estimated creatinine clearance below 70 mL/min since dose adjustment of these drugs is required below 50 mL/min and such dose adjustments have not been established in combination with PREZCOBIX® (see **7 WARNINGS AND PRECAUTIONS**, **Renal** and **10.3 Pharmacokinetics**).

4.4 Administration

PREZCOBIX® should be swallowed whole without breaking or crushing to ensure administration of the entire dose.

Dosing with Didanosine
As it is recommended that didanosine be administered on an empty stomach, didanosine should be administered at least one hour before or two hours after PREZCOBIX® (administered with food).

4.5 Missed Dose

If a dose of PREZCOBIX® is missed by less than 12 hours, the missed dose should be taken as soon as possible. If the dose of PREZCOBIX® was missed by more than 12 hours, the next dose should be taken at the next regularly scheduled time. Doses should be taken with food and should not be doubled.

5 OVERDOSAGE

Human experience of acute overdose with PREZCOBIX® is limited. Single doses up to 3,200 mg of the oral solution of darunavir alone and up to 1,600 mg of the tablet formulation of darunavir co-administered with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

Limited clinical experience with cobicistat is available at doses higher than the therapeutic dose. In two studies, a single dose of cobicistat 400 mg was administered to a total of 60 healthy subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

There is no specific antidote 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 darunavir and cobicistat are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substances.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	film-coated tablet / 800 mg darunavir (as darunavir ethanolate) / 150 mg cobicistat	silicified microcrystalline cellulose, crospovidone, hypromellose, and magnesium stearate. The tablet film coating contains OPADRY® II Pink (polyethylene glycol, polyvinyl alcohol - partially hydrolyzed, talc, titanium dioxide, iron oxide red, iron oxide black).

Description

PREZCOBIX® Tablets

PREZCOBIX®(darunavir/cobicistat) 800/150-mg tablets are supplied as pink, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 800 mg of darunavir per tablet and 150 mg cobicistat. Each tablet is debossed with “800” on one side and “TG” on the other side. Each bottle contains 30 tablets.

7 WARNINGS AND PRECAUTIONS

General

PREZCOBIX® is not a cure for HIV-1 infection or AIDS. Patients receiving darunavir/cobicistat or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV-1 infection.

PREZCOBIX® therapy has not been shown to reduce the risk of transmission of HIV-1 to others.

PREZCOBIX® should not be used concurrently with products or regimens containing ritonavir or cobicistat and PREZCOBIX® should not be used in combination with the individual components of PREZCOBIX® (darunavir or cobicistat).

PREZCOBIX® should not be used in combination with another antiretroviral that requires pharmacokinetic boosting (e.g., atazanavir, indinavir, lopinavir, saquinavir).

Caution should be exercised when administering PREZCOBIX® to patients who have been previously treated with a protease inhibitor-based regimen. Genotypic testing is recommended, however, when genotypic testing is not feasible, PREZCOBIX® is recommended in protease inhibitor-naïve patients only (see **10.3 Pharmacokinetics**).

Due to inhibition of CYP3A by PREZCOBIX®, co-administration of PREZCOBIX® with quetiapine may results in increased quetiapine concentrations. Serious and life-threatening quetiapine-related adverse reactions have been reported with CYP3A inhibitors. PREZCOBIX® should not be used in combination with quetiapine (see **9 DRUG INTERACTIONS**). Monitoring and dose reductions may be required if necessary.

Carcinogenesis and Mutagenesis

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. A dose-related increase in the incidence of hepatocellular adenomas and carcinomas were observed in males and females of both species as well as an increase in thyroid follicular cell adenomas in male rats. These findings are considered to be of limited relevance to humans. Based on AUC measurements, exposure to darunavir at the dose levels studied was below or approximately equivalent to exposure in humans at the recommended therapeutic dose (see **16 NON-CLINICAL TOXICOLOGY**, **Carcinogenicity** and **Genotoxicity**).

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 (see **16 NON-CLINICAL TOXICOLOGY**, **Carcinogenicity** and **Genotoxicity**).

Refer to **16 NON-CLINICAL TOXICOLOGY**, **Carcinogenicity** and **Genotoxicity** for information regarding cobicistat.

Endocrine and Metabolism

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving 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 PI therapy and these events have not been established.

Lipid Elevations

Treatment with darunavir has resulted in increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiating PREZCOBIX® therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See Table 4 and Table 5 for additional information on potential drug interactions with PREZCOBIX® and HMG-CoA reductase inhibitors /other lipid modifying agents.

Hematologic

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established; however, the frequency of bleeding episodes should be closely monitored in patients on PREZCOBIX®.

Hepatic/Biliary/Pancreatic

Hepatic Impairment

There are no pharmacokinetic data regarding the use of PREZCOBIX® in patients with hepatic impairment. Pharmacokinetic data in patients with mild or moderate hepatic impairment is available for darunavir and cobicistat separately.

PREZCOBIX® is contraindicated in patients with severe hepatic insufficiency (Child-Pugh Class C) (see **2 CONTRAINDICATIONS**). Patients with mild or moderate hepatic impairment (Child-Pugh Class A or B, respectively) should be closely monitored.

Refer to the TYBOST and PREZISTA® Product Monographs for additional information.

Hepatotoxicity
Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with darunavir/ritonavir. During the darunavir clinical development program (n=3,063), hepatitis has been reported in 0.5% of patients receiving combination therapy with darunavir/ritonavir.

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

Patients Co-infected with Hepatitis B and/or Hepatitis C Virus
Patients with chronic hepatitis B and/or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. Limited information is available on the use of PREZCOBIX® in patients co-infected with hepatitis B and/or C virus.

With darunavir/ritonavir, the incidence of adverse events or clinical chemistry abnormalities, except for increased hepatic enzymes, was comparable in patients co-infected with hepatitis B or C virus and patients who were not co-infected. Patients co-infected with hepatitis B or C virus receiving darunavir/ritonavir were more likely to have baseline and treatment-emergent hepatic transaminase elevations than those without chronic viral hepatitis. Patients with chronic hepatitis B and/or C co-infection should be monitored appropriately.

Patients with pre-existing liver dysfunction including chronic hepatitis B or C have an increased frequency of liver function abnormalities during combination antiretroviral therapy. Appropriate monitoring should be conducted prior to initiating therapy with PREZCOBIX® and increased monitoring should be considered in patients with elevated baseline transaminase levels, active hepatitis B and/or C and in patients with underlying liver disease, 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 and hepatomegaly) in patients on PREZCOBIX®, should prompt consideration to interrupt or discontinue treatment.

Pancreatic
Pancreatitis has been observed in patients receiving darunavir/ritonavir therapy, including those who developed marked triglyceride elevations. Although a causal relationship to darunavir has not been established, marked triglyceride elevation is a risk factor for development of pancreatitis (see **7 WARNINGS AND PRECAUTIONS**, **Lipid Elevations**). Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during PREZCOBIX® therapy.

Immune

Immune Reconstitution Inflammatory Syndrome
During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium complex* (MAC), *cytomegalovirus* (CMV) infection, *Pneumocystis jirovecii pneumonia* (PCP), and tuberculosis (TB), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, autoimmune hepatitis, 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 treatment.

Renal

Effects on Serum Creatinine

Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-infected patients with moderate renal impairment (CrCL 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. Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. An increase in serum creatinine due to cobicistat's inhibitory effect generally does not exceed 0.4 mg per dL from baseline. This effect should be considered when interpreting changes in creatinine clearance in patients initiating PREZCOBIX® particularly when co-administered with a drug that has dosing adjustment recommendations guided by estimated creatinine clearance. Dosing recommendations are not available for drugs that require dosing adjustment for renal impairment with the use of cobicistat (see **4.2 Recommended Dose and Dosage Adjustment**). Consider alternative medications that do not require dosing adjustments.

Prior to initiating therapy with PREZCOBIX®, assess estimated creatinine clearance. 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 per dL from baseline should be closely monitored for renal safety.

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 is used in an antiretroviral regimen that contains tenofovir disoproxil fumarate (tenofovir DF).

- Do not initiate cobicistat as part of a regimen containing tenofovir DF in patients who have an estimated creatinine clearance below 70 mL/min because dose adjustment of tenofovir DF is required below 50 mL/min and such dose adjustments have not been established for co-administration with cobicistat.
- Document urine glucose and urine protein at baseline and perform routine monitoring of estimated creatinine clearance, urine glucose, and urine protein during treatment when cobicistat is used with tenofovir DF.
- Measure serum phosphorus in patients with or at risk for renal impairment.
- Avoid use of cobicistat with tenofovir DF in combination with concomitant or recent use of a nephrotoxic agent.

Since the renal clearance of darunavir and cobicistat is limited, a decrease in total body clearance of darunavir and cobicistat is not expected in patients with renal impairment. As darunavir and cobicistat are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis (see **4 DOSAGE AND ADMINISTRATION** and **10.3 Pharmacokinetics**, **Special Populations and Conditions**, **Renal Insufficiency**).

Sensitivity/Resistance
Darunavir contains a sulfonamide moiety. PREZCOBIX® (darunavir/cobicistat) should be used with caution in patients with a known sulfonamide allergy. The potential for cross-sensitivity between drugs in the sulfonamide class and darunavir is unknown. In clinical studies with darunavir/ritonavir, the incidence and severity of rash was similar in patients with or without a history of sulphonamide allergy.

Skin

Severe Skin Reactions
During the clinical development program (n=3,063), where darunavir was co-administered with low dose ritonavir, severe skin reactions, which may be accompanied by fever and/or elevations of transaminases, have been reported in 0.4% of patients. Stevens-Johnson Syndrome was rarely (<0.1%) reported; and during post-marketing experience toxic epidermal necrolysis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and acute generalized exanthematous pustulosis have been reported very rarely (<0.01%). 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.

Rash (all grades, regardless of causality) occurred in 10.3% of patients treated with darunavir/ritonavir (see **8 ADVERSE REACTIONS**). Rash was mostly mild-to-moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. The discontinuation rate due to rash in patients using darunavir/ritonavir was 0.5%.

Rash occurred more commonly in treatment-experienced patients receiving regimens containing darunavir/ritonavir + raltegravir compared to subjects receiving darunavir/ritonavir without raltegravir or raltegravir without darunavir/ritonavir. However, rash that was considered drug related occurred at similar rates for all three groups. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash.

In a single-arm trial investigating darunavir 800 mg once daily in combination with cobicistat 150 mg once daily and other antiretrovirals, 15.7% of patients experienced rash, and 2.2% discontinued treatment due to rash. Rash was mostly mild-to-moderate, often occurring within the first four weeks of treatment and resolving with continued dosing (see **8 ADVERSE REACTIONS**).

7.1 Special Populations

7.1.1 Pregnant Women

PREZCOBIX® is not recommended for use during pregnancy because of substantially lower exposures of darunavir and cobicistat during pregnancy. PREZCOBIX® should not be initiated in pregnant women. An alternative regimen is recommended for women who become pregnant during therapy with PREZCOBIX®.

PREZCOBIX® in combination with a background regimen was evaluated in a clinical trial of 7 pregnant women during the second and third trimesters, and postpartum (6-12 weeks). The pharmacokinetic data demonstrate that exposure to darunavir boosted with cobicistat was substantially lower during pregnancy compared with postpartum (see **10.3 Pharmacokinetics**, **Special Populations and Conditions, Pregnancy and Breast-feeding**).

There are no clinical data on the virologic response when PREZCOBIX is initiated during pregnancy.

At clinically relevant exposures of darunavir and cobicistat, animal studies do not indicate direct or indirect harmful effects with respect to developmental or reproductive toxicity and fertility. However, due to limited bioavailability and/or dosing limitations with darunavir, animal exposures (based on AUC) were only 50% (mice and rats) and 5% (rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir (see **16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicity**).

Antiretroviral Pregnancy Registry: *To monitor maternal-fetal outcomes of pregnant women exposed to PREZCOBIX®, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.*

7.1.2 Breast-feeding

HIV-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether darunavir, cobicistat or their metabolites are excreted in human milk. Animal studies have demonstrated that darunavir and cobicistat are excreted in milk. Because of both the potential for HIV transmission and the potential for serious adverse events in nursing infants, mothers should be instructed not to breast-feed if they are receiving PREZCOBIX® (see **16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicity**).

7.1.3 Pediatrics

Pediatrics (<18 years of age)
PREZCOBIX® is not indicated in pediatric patients <18 years of age. The safety and efficacy of PREZCOBIX® have not been established in pediatric patients. In pre-clinical studies of darunavir, toxicity and mortality were observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1,000 mg/kg) up to days 23 to 26 of age (see **10.3 Pharmacokinetics, Special Populations and Conditions, Pediatrics** and **16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicity**).

7.1.4 Geriatrics

Geriatrics (≥65 years of age)
Clinical studies 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, renal or cardiac function and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The overall safety profile of PREZCOBIX® is based on all available clinical data from the Phase 3 single-arm trial (GS-US-216-0130) and on all available clinical trial and post-marketing data on darunavir/ritonavir and cobicistat in combination with other antiretroviral agents and is consistent with the data presented below.

ADRs to darunavir/ ritonavir or to cobicistat are considered ADRs to PREZCOBIX® unless otherwise specified.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse Drug Reactions in Trials with Darunavir/Cobicistat 800/150 mg q.d.
The safety of darunavir in combination with cobicistat has been evaluated in a Phase 3 single-arm trial (GS-US-216-0130), in which 295 treatment-naïve patients and 18 treatment-experienced patients received darunavir 800 mg once daily in combination with cobicistat 150 mg once daily as single agents and other antiretrovirals for at least 48 weeks. The mean exposure in 313 patients treated with darunavir/cobicistat was 58.4 weeks.

The majority of the ADRs reported during treatment with darunavir/cobicistat in GS-US-216-0130 were mild in severity. The most frequent (≥5%) ADRs to darunavir/cobicistat that were moderate to severe (Grade 2 to 4) were diarrhea and rash. The most frequent (≥1%) ADR that was severe (Grade 3 or 4) was drug hypersensitivity. All other Grade 3 or 4 ADRs were reported in less than 1% of the patients; 3.8% of the patients discontinued treatment due to ADRs.

ADRs of Grades 2 to 4 severity reported in GS-US-216-0130, considered ADRs to PREZCOBIX® are presented in Table 2 below.

Table 2: Adverse Drug Reactions of At Least Moderate Intensity (≥Grade 2) Reported in ≥1% of HIV-1-Infected, Antiretroviral Treatment-Naïve and Treatment-Experienced Adult Patients Who Received darunavir/cobicistat 800/150 mg q.d. (Open-Label Study GS-US-216-0130; Week 48 Analyses)

	darunavir/cobicistat **800 mg/150 mg q.d. + OBR** **N=313**
Gastrointestinal Disorders	
Abdominal Pain	1.3%
Diarrhea	5.4%
Flatulence	1.0%
Nausea	3.5%
Vomiting	1.9%

	darunavir/cobicistat 800 mg/150 mg q.d. + OBR N=313
Hepatobiliary Disorders	
Hepatic Enzyme Increased	1.0%
Immune System Disorders	
Drug Hypersensitivity	1.9%
Nervous System Disorders	
Headache	2.9%
Skin and Subcutaneous Tissue Disorders	
Rash[1]	5.4%

N=total number of subjects with data; OBR=optimized background regimen

[1]Grouped term 'rash' included the preferred terms dermatitis allergic, drug eruption, erythema, rash, rash erythematous, rash generalized, rash macular, rash macula-papular, rash papular, rash pruritic, skin reaction, urticaria papular

Adverse Drug Reactions in Trials with Darunavir/Ritonavir 800/100 mg q.d.

The safety assessment is based on all safety data from two randomized, controlled, open-label Phase 3 trials: TMC114-C211 in antiretroviral treatment-naïve HIV-1-infected adult patients comparing darunavir/ritonavir 800/100 mg q.d. versus the comparator in antiretroviral treatment-naïve HIV-1-infected adult patients and TMC114-C229 comparing darunavir/ritonavir 800/100 mg q.d. to darunavir/ritonavir 600/100 mg b.i.d. in treatment-experienced HIV-1 infected patients with screening genotype resistance test showing no darunavir resistance associated mutations. Additional ADRs identified in other clinical trials are also included. The majority of the ADRs reported during treatment with darunavir/ritonavir 800/100 mg q.d. were mild in severity.

ADRs to darunavir/ritonavir 800/100 mg q.d. of at least moderate intensity (≥Grade 2) in HIV-1-infected adult patients occurring in ≥1% of patients included abdominal pain, anorexia, diarrhea, headache, nausea, pruritis, rash, urticaria and vomiting.

Serious ADRs

The following serious ADRs of at least moderate intensity (≥Grade 2) occurred in the Phase 2b studies and Phase 3 studies with darunavir/ritonavir: abdominal pain, acute hepatitis, acute pancreatitis, anorexia, asthenia, diabetes mellitus, diarrhea, fatigue, headache, hepatic enzyme increased, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, immune reconstitution inflammatory syndrome, low density lipoprotein increased, nausea, pancreatic enzyme increased, rash, Stevens-Johnson Syndrome and vomiting.

Refer to the TYBOST and PREZISTA® Product Monographs for additional information.

8.3 Less Common Clinical Trial Adverse Reactions

Adverse Drug Reactions in Trials with Darunavir/Cobicistat 800/150 mg q.d.:
Less Common Clinical Trial Adverse Drug Reactions (<1%)
Adverse drug reactions occurring in less than 1% of patients receiving darunavir/cobicistat considered at least possibly related to treatment and of at least moderate intensity are listed below by body system:

Gastrointestinal Disorders: dyspepsia

General Disorders and Administration Site Conditions: fatigue

Immune System Disorders: immune reconstitution inflammatory syndrome

Metabolism and Nutrition Disorders: diabetes mellitus, hypercholesterolemia, hypertriglyceridemia

Musculoskeletal and Connective Tissue Disorders: myalgia

Psychiatric Disorders: abnormal dreams

Skin and Subcutaneous Tissue Disorders: pruritus

Adverse Drug Reactions in Trials with Darunavir/Ritonavir 800/100 mg q.d.:
Less common ADRs of at least moderate intensity (≥Grade 2) in HIV-1-infected adult patients occurring in <1% of patients included abdominal distension, abnormal dreams, acute hepatitis, acute pancreatitis, angioedema, asthenia, diabetes mellitus, dyspepsia, flatulence, fatigue, gynecomastia, (drug) hypersensitivity, immune reconstitution inflammatory syndrome, lipodystrophy (lipohypertrophy, lipodystrophy, lipoatrophy) myalgia, osteonecrosis, pruritus, Stevens-Johnson Syndrome, and urticaria.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Adverse Drug Reactions in Trials with Darunavir/Cobicistat 800/150 mg q.d.:

Abnormal Clinical Chemistry Findings
The percentages of antiretroviral treatment-naïve and treatment-experienced HIV-1-infected adult patients treated with darunavir/cobicistat 800/150 mg q.d. with Grade 2 to 4 laboratory abnormalities, with a term considered an ADR, are presented in Table 3.

Table 3: Grade 2 to 4 Laboratory Abnormalities, Observed in Antiretroviral Treatment-Naïve and Treatment-Experienced HIV-1-Infected Adult Patients (Open-Label Study GS-US-216-0130; Week 48 Analyses)

Laboratory Parameter Preferred Term	Limit	darunavir/cobicistat 800 mg/150 mg q.d. + OBR N=313
Biochemistry		
Pancreatic Amylase		
Grade 2	>1.5 to ≤2.0 x ULN	6.5%
Grade 3	>2.0 to ≤5.0 x ULN	2.6%
Lipase		
Grade 2	>1.5 to ≤3.0 x ULN	3.9%
Grade 3	>3.0 to ≤5.0 x ULN	1.0%
Grade 4	>5.0 x ULN	1.3%
Creatinine		
Grade 2	1.4-1.8 ULN	3.2%
Total Cholesterol		
Grade 2	240-300 mg/dL	10.6%
Grade 3	>300 mg/dL	1.0%
Glucose		
Grade 2	251-500 mg/dL	6.5%
LDL Cholesterol		
Grade 2	160-190 mg/dL	10.9%
Grade 3	≥191 mg/dL	4.8%
Triglycerides		
Grade 2	500-750 mg/dL	1.4%
Grade 3	751-1,200 mg/dL	1.4%
ALT		
Grade 2	>2.5 to ≤5.0 x ULN	3.2%
Grade 3	>5.0 to ≤10.0 x ULN	1.9%
Grade 4	>10.0 x ULN	1.0%
ALP		
Grade 2	>2.5 to ≤5.0 x ULN	1.0%
AST		
Grade 2	>2.5 to ≤5.0 x ULN	6.1%
Grade 3	>5.0 to ≤10.0 x ULN	2.3%
Grade 4	>10.0 x ULN	0.6%

N=total number of subjects with data; OBR=optimized background regimen
The number of subjects with data can vary per laboratory parameter, but the % reflects the true percentage of observed abnormalities.

Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. An increase in serum creatinine due to cobicistat's inhibitory effect generally does not exceed 0.4 mg per dL from baseline. In the Phase 3 single-arm trial (GS-US-216-0130), a decrease in the estimated glomerular filtration rate based on creatinine clearance, as estimated by the Cockcroft-Gault formula ($eGFR_{CG}$), was noted at Week 2, which remained stable through Week 48. The mean ± SD $eGFR_{CG}$ change from baseline was -9.6 ± 13.66 mL/min at Week 2, and -11.5 ± 15.47 mL/min at Week 24, and -9.6mL/min at Week 48.

Adverse Drug Reactions in Trials with Darunavir/Ritonavir 800/100 mg q.d.:
Grade 2 to 4 laboratory abnormalities, with a term considered an ADR included increased ALP, ALT, AST, glucose, hyperbilirubinemia, LDL cholesterol, total cholesterol, pancreatic amylase, pancreatic lipase, and triglycerides.

8.5 Post-Market Adverse Reactions

Post-Market Adverse Drug Reactions
In addition to adverse events identified in clinical trials, the following post-marketing events have been included due to their seriousness, frequency of reporting, potential causal association with darunavir/ritonavir, or a combination of these factors. Because they are reported spontaneously from a population of unknown size, estimates of incidence cannot be made.

Blood and Lymphatic System Disorders: anemia, pancytopenia, thrombocytopenia and neutropenia

Cardiac Disorders: bradycardia, myocarditis

Eye Disorders: eye swelling, uveitis, maculopathy, blurred vision

Gastrointestinal Disorders: pancreatitis, pancreatitis relapsing, rectal hemorrhage, gastritis

Hepatobiliary Disorders: bile duct obstruction, hepatic cirrhosis, hepatic failure, hepatitis, hepatotoxicity, jaundice

Infections and Infestations: clostridial infection, cryptosporidiosis infection, cytomegalovirus encephalitis, hepatitis B, esophageal candidiasis, progressive multifocal leukoencephalopathy, sepsis

Investigations: blood alkaline phosphatase increased, blood bilirubin increased, abnormal liver function test

Immune System Disorders: drug hypersensitivity, immune reconstitution inflammatory syndrome, autoimmune disorders such as Graves' disease and autoimmune hepatitis

Injury, Poisoning and Procedural Complications: drug toxicity

Metabolism and Nutrition Disorders: dehydration, hyperkalemia, metabolic acidosis

Musculoskeletal and Connective Tissue Disorders: myositis, osteonecrosis, rhabdomyolysis, sensation of heaviness, arthritis, bone pain, pain in extremities, arthropathy

Neoplasms Benign, Malignant and Unspecified: diffuse large B-cell neoplasm, malignant hepatic neoplasm, lymphoma

Nervous System Disorders: altered state of consciousness, cerebrovascular accident, dizziness, facial palsy, grand mal convulsion, ischemic cerebral infarction, nervous system disorder, neuromyopathy, petit mal epilepsy

Psychiatric Disorders: completed suicide, anxiety, depression

Renal and Urinary Disorders: acute renal failure, hematuria, renal tubular necrosis, creatinine renal decreased, GFR decreased, renal failure, proteinuria, crystal nephropathy

Respiratory, Thoracic and Mediastinal Disorders: acute respiratory distress syndrome, pharyngeal lesion, pneumothorax, respiratory failure, pulmonary edema, epistaxis

Skin and Subcutaneous Tissue Disorders: angioedema, rash, swelling face, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, acute generalized exanthematous pustulosis, DRESS (Drug Rash with Eosinophilia and Systemic Symptoms)

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Darunavir and cobicistat are both inhibitors of the cytochrome P450 3A4 (CYP3A4) isoform. PREZCOBIX® should not be co-administered with medicinal products that are highly dependent on CYP3A4 for clearance, and for which increased plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). Examples include alfuzosin, amiodarone, apixaban, colchicine (in patients with renal and/or hepatic impairment), dabigatran, dronedarone, elbasvir/grazoprevir, the ergot alkaloids (e.g., ergotamine, dihydroergotamine, ergonovine), lidocaine (systemic), ivabradine, lomitapide, lovastatin, lurasidone, naloxegol, pimozide, rivaroxaban, salmeterol, sildenafil (when used for the treatment of pulmonary arterial hypertension), simvastatin, ticagrelor and triazolam (see **2 CONTRAINDICATIONS**).
- Cobicistat inhibits OATP1B transporters. PREZCOBIX® should not be co-administrated with medicinal products that are substrates of these transporters and for which, when co-administered with PREZCOBIX®, a significant increase in plasma concentrations may occur. These medicinal products include elbasvir/grazoprevir.
- Rifampin and St John's Wort (*Hypericum perforatum*), carbamezepine, phenytoin and phenobarbital are potent inducers of CYP450 metabolism. PREZCOBIX® should not be used in combination with these products as this may cause significant decreases in darunavir plasma concentrations. This may result in a loss of therapeutic effect of PREZCOBIX® and development of resistance (see **2 CONTRAINDICATIONS**).

9.2 Drug Interactions Overview

Darunavir is an inhibitor of the cytochrome P450 isoform CYP3A4. Cobicistat is a weak inhibitor of CYP2D6 and strong inhibitor of CYP3A4. Cobicistat is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19. Cobicistat is not expected to induce CYP1A2, CYP3A4, CYP2C9, CYP2C19, uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), or multidrug resistance protein 1 (MDR1). The transporters cobicistat inhibits include p-glycoprotein (P-gp), BCRP, MATE1, OATP1B1 and OATP1B3. Thus, co-administration of PREZCOBIX® with drugs that are primarily metabolized by CYP3A, 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 adverse events (see **2 CONTRAINDICATIONS** and **9.4 Drug-Drug Interactions**, Table 4 and Table 5). Co-administration of PREZCOBIX® with drugs that have active metabolite(s) formed by CYP3A may

result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect (see **9.4 Drug-Drug Interactions**, Table 5).

Darunavir and cobicistat are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to lower plasma concentrations of darunavir and cobicistat. Co-administration with strong inducers of CYP3A could potentially lead to loss of efficacy of darunavir and possible development of resistance (see **2 CONTRAINDICATIONS** and **9.4 Drug-Drug Interactions**, Table 4 and Table 5). Co-administration of PREZCOBIX® and other medicinal products that inhibit CYP3A may increase plasma concentrations of darunavir and cobicistat.

PREZCOBIX® should not be used in combination with another antiretroviral that requires pharmacokinetic boosting (e.g., atazanavir, indinavir, lopinavir, saquinavir). PREZCOBIX® should not be used concurrently with products or regimens containing darunavir, ritonavir or cobicistat. PREZCOBIX® should not be used in combination with the individual components of PREZCOBIX® (darunavir or cobicistat).

The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as pharmacokinetic enhancer, therefore there may be different recommendations for the use of darunavir with concomitant medicines. In the table below, it is specified when recommendations for PREZCOBIX® differ from those for darunavir boosted with low dose ritonavir. Refer to the product information for PREZISTA® (darunavir) for further information.

Refer to the TYBOST and PREZISTA® Product Monographs for additional information.

9.4 Drug-Drug Interactions

No drug interaction studies have been performed using PREZCOBIX®. As PREZCOBIX® contains darunavir and cobicistat, interactions that have been identified with darunavir (in combination with low-dose ritonavir) and with cobicistat determine the interactions that may occur with PREZCOBIX®. Interaction studies with darunavir/ritonavir and with cobicistat have only been performed in adults (see **9 DRUG INTERACTIONS**).

As PREZCOBIX® contains darunavir and cobicistat, interactions that have been identified with darunavir (in combination with low-dose ritonavir) and with cobicistat determine the interactions that may occur with PREZCOBIX®. Interaction studies with darunavir/ritonavir and with cobicistat have only been performed in adults.

Drugs that are contraindicated for co-administration with PREZCOBIX® are included in Table 4. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

The below list of examples of drug-drug interactions is not comprehensive and therefore the label of each drug that is co-administered with PREZCOBIX® should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

The drugs listed in this Table are based on either drug interactions case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interactions (i.e., those identified as contraindicated).

Table 4: Drugs that are CONTRAINDICATED with PREZCOBIX®

Drug Class: Drug Name	Clinical Comment
Alpha 1-Adrenoreceptor Antagonists: alfuzosin	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as hypotension.
Antiarrhythmics/Antianginals: amiodarone dronedarone ivabradine lidocaine (systemic)	CONTRAINDICATED: Concentrations of bepredil, dronedarone, ivabradine, lidocaine (systemic), and amiodarone may be increased when co-administered with PREZCOBIX® due to inhibition of CYP3A and/or CYP2D6.
Direct Oral Anticoagulants DOACs): apixaban dabigatran rivaroxaban	CONTRAINDICATED: Concentrations of apixaban, dabigatran or rivaroxaban may be increased when co-administered with PREZCOBIX® (inhibition of CYP3A and/or P-glycoprotein).
Anti-convulsants: carbamezepine phenobarbital phenytoin	CONTRAINDICATED: due to potential in loss of therapeutic effect and development of resistance.
Anti-gout: colchicine	Concomitant use of PREZCOBIX® with colchicine may increase concentrations of colchicine (inhibition of CYP3A). Refer to colchicine product information for dosing recommendations. CONTRAINDICATED: Patients with renal or hepatic impairment should not be given colchicine with PREZCOBIX®.
Antimycobacterials: rifampin	CONTRAINDICATED: Rifampin is a potent inducer of CYP450 metabolism. PREZCOBIX® should not be used in combination with rifampin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect of PREZCOBIX® and development of resistance.
Antivirals (Hepatitis C Virus [HCV] direct-acting antivirals)**:** elbasvir/grazoprevir	CONTRAINDICATED: Concentrations of grazoprevir may be increased when co-administered with PREZCOBIX® due to inhibition of OATP1B and CYP3A.
Ergot Derivatives: dihydroergotamine ergonovine ergotamine	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.
Herbal Products: St. John's wort (*Hypericum perforatum*)	CONTRAINDICATED: PREZCOBIX® should not be used concomitantly with products containing St. John's wort (*Hypericum perforatum)* because co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect and development of resistance.

Drug Class: Drug Name	Clinical Comment
HMG-CoA Reductase Inhibitors: lovastatin simvastatin **Other Lipid modifying agents:** lomitapide	CONTRAINDICATED: HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, which are highly dependent on CYP3A4 metabolism, are expected to have markedly increased plasma concentrations when co-administered with PREZCOBIX®. Increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Concomitant use of PREZCOBIX® with lovastatin or simvastatin is not recommended. For information regarding atorvastatin and pravastatin see Table 5. PREZCOBIX® is expected to increase the exposure of lomitapide when co-administered.
Inhaled Beta Agonist: salmeterol	CONTRAINDICATED as the combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Neuroleptics: lurasidone pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Opioid Antagonist: naloxegol	CONTRAINDICATED: Concomitant use of naloxegol and PREZCOBIX® may increase the exposure to naloxegol (inhibition of CYP3A).
PDE-5 Inhibitors: sildenafil (for treatment of pulmonary arterial hypertension)	CONTRAINDICATED: A safe and effective dose of the PDE-5 inhibitors for the treatment of pulmonary arterial hypertension has not been established when co-administered with PREZCOBIX®. There is an increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope).
Platelet Aggregation Inhibitors: ticagrelor	CONTRAINDICATED: Based on theoretical considerations co-administration of PREZCOBIX® with ticagrelor may increase concentrations of the anticoagulant (CYP3A and/or P-glycoprotein inhibition). Concomitant administration of PREZCOBIX® with ticagrelor is contraindicated.
Sedatives/Hypnotics: triazolam	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Established and other potentially significant drug interactions with PREZCOBIX® are included in Table 5. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 5: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
delavirdine	↑ darunavir ↑ cobicistat ↑ delavirdine	Co-administration of PREZCOBIX® and delavirdine may increase darunavir, cobicistat and/or delavirdine concentrations (inhibition of CYP3A). The appropriate dose of PREZCOBIX® and delavirdine has not been established. The combination of PREZCOBIX® and delavirdine is not recommended.
efavirenz	↓ darunavir ↓ cobicistat ↑ efavirenz	Co-administration of PREZCOBIX® with efavirenz may decrease darunavir and/or cobicistat concentrations (induction of CYP3A) which may result in loss of therapeutic effect and development of resistance. Co-administration of PREZCOBIX® with efavirenz is not recommended. The recommendation is different from ritonavir-boosted darunavir. Consult the PREZISTA® Product Monograph for further details.
etravirine	↔ darunavir ↓ cobicistat ↓ etravirine	Co-administration of PREZCOBIX® with etravirine may decrease darunavir and/or cobicistat concentrations (induction of CYP3A) which may result in loss of therapeutic effect and development of resistance. Co-administration of PREZCOBIX® with etravirine is not recommended. The recommendation is different from ritonavir-boosted darunavir. Consult the PREZISTA® Product Monograph for further details.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
nevirapine	↔ darunavir ↓ cobicistat ↑ nevirapine	Co-administration of PREZCOBIX® with nevirapine may decrease darunavir and/or cobicistat concentrations (induction of CYP3A) which may result in loss of therapeutic effect and development of resistance. Nevirapine concentrations may be increased when co-administered with PREZCOBIX®. Co-administration of PREZCOBIX® with nevirapine is not recommended. The recommendation is different from ritonavir-boosted darunavir. Consult the PREZISTA® Product Monograph for further details.
rilpivirine	↔ darunavir ↔ cobicistat ↑ rilpivirine	Co-administration of PREZCOBIX® with rilpivirine may increase concentrations of rilpivirine (inhibition of CYP3A). The increase in rilpivirine is not expected to be clinically relevant and no dose adjustment of rilpivirine is needed when co-administered with PREZCOBIX®.
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
didanosine	↔ darunavir ↔ cobicistat ↔ didanosine	PREZCOBIX® and didanosine can be used without dose adjustments. As it is recommended that didanosine be administered on an empty stomach, didanosine should be administered one hour before or two hours after PREZCOBIX® (administered with food).
tenofovir disoproxil fumarate	↔ darunavir ↔ cobicistat ↑ tenofovir	Co-administration of PREZCOBIX® with tenofovir disoproxil fumarate may increase concentrations of tenofovir (inhibition of P-glycoprotein). The increase in tenofovir is not expected to be clinically relevant and no dose adjustment of tenofovir disoproxil fumarate is needed.
HIV-Antiviral Agents: CCR5 Antagonist		
maraviroc	↑ maraviroc	Co-administration of PREZCOBIX® with maraviroc may increase concentrations of maraviroc (inhibition of CYP3A). When used in combination with PREZCOBIX®, the recommended dose of maraviroc is 150 mg twice daily.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
HIV-1 Antiviral Agents: Integrase Strand Transfer Inhibitors		
dolutegravir	↔ darunavir ↔ cobicistat ↔ dolutegravir	Darunavir/rtv (600/100 mg b.i.d.) did not have a clinically relevant effect on dolutegravir exposure and the same is anticipated for cobicistat-boosted darunavir. Using cross-study comparisons to historical pharmacokinetic data, dolutegravir had no clinically significant effect on the pharmacokinetics of darunavir. PREZCOBIX® and dolutegravir can be used concomitantly without dose adjustment.
elvitegravir	↔ darunavir	The pharmacokinetics and dosing recommendations for darunavir with elvitegravir/cobicistat have not been established. Therefore, co-administration of PREZCOBIX® with elvitegravir is not recommended.
raltegravir	↓ darunavir	Some clinical studies suggest raltegravir may cause a modest decrease in darunavir plasma. At present the effect of raltegravir on darunavir concentrations does not appear to be clinically relevant. PREZCOBIX® and raltegravir can be used concomitantly without dose adjustments.
HIV-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
ritonavir	↑ darunavir	PREZCOBIX® should not be used concurrently with products or regimens containing ritonavir.
atazanavir indinavir lopinavir/ritonavir saquinavir	↔ darunavir ↔ atazanavir ↑ indinavir ↑ darunavir ↓ darunavir ↓ darunavir	PREZCOBIX® should not be used in combination with another antiretroviral that requires pharmacokinetic boosting.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Other Agents		
Antacids: aluminium/magnesium, hydroxide, calcium carbonate	↔ darunavir ↔ cobicistat	PREZCOBIX® and antacids can be used concomitantly without dose adjustment.
Antiarrhythmics/Antianginals: digoxin disopyramide flecainide mexiletine propafenone	↑ digoxin ↑ antiarrhythmics/antianginals	Co-administration of PREZCOBIX® with digoxin may increase concentrations of digoxin (inhibition of p-glycoprotein). The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect. Co-administration of PREZCOBIX® with disopyramide, flecainide, mexiletine or propafenoe may increase concentrations of the antiarrhythmic (inhibition of CYP3A). Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics/antianginals when co-administered with PREZCOBIX®.
Anticancer Agents: dasatinib nilotinib vinblastine vincristine everolimus, irinotecan	↑ anticancer agent	Co-administration of PREZCOBIX® with these anticancer agents may increase concentrations of the anticancer agent (inhibition of CYP3A), resulting in the potential for increased adverse events usually associated with these agents. Clinical monitoring is recommended when coadministering PREZCOBIX® with these anticancer agents. Concomitant use of everolimus or irinotecan and PREZCOBIX® is not recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Direct Oral Anticoagulants (DOACs): dabigatran edoxaban	↑ dabigatran ↑ edoxaban	DOACs are primarily metabolized by CYP3A4 and/or transported by P-gp. Co-administration with PREZCOBIX® may result in increased plasma concentrations of the DOAC, which may lead to an increased bleeding risk. The results of a drug-drug interaction study, between darunavir/cobicistat 800/150 mg and dabigatran 150 mg in healthy participants showed a 2.6-fold increase in dabigatran plasma AUC after single dosing of darunavir/cobicistat, and a 1.9-fold increase in dabigatran plasma AUC after repeated dosing of darunavir/cobicistat. The study demonstrated a 2.6-fold increase in dabigatran plasma C_{max} after single dosing of darunavir/cobicistat and a 2.0-fold increase in dabigatran plasma C_{max} after repeated dosing of darunavir/cobicistat. Use of dabigatran is contraindicated (see Table 4). Clinical monitoring is required when edoxaban, which is not affected by CYP3A4 but is transported by P-gp, is co-administered with PREZCOBIX®. A dose reduction of edoxaban may be needed. The combination of darunavir/cobicistat and edoxaban is not recommended in subjects with severe renal impairment.
warfarin	effect on warfarin unknown	Warfarin concentrations may be affected when co-administered with PREZCOBIX®. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with PREZCOBIX®.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Anticonvulsants: oxcarbazepine	↓ darunavir ↓ cobicistat	Co-administration of PREZCOBIX® with oxcarbazepine may decrease darunavir and/or cobicistat concentrations (induction of CYP3A), which may result in loss of therapeutic effect to darunavir and development of resistance. Co-administration of PREZCOBIX® with oxcarbezepine is not recommended. Alternative anticonvulsants should be considered.
clonazepam, ethosuximide	↑clonazepam ↑ ethosuximide	Co-administration of PREZCOBIX® with clonazepam or ethosuximide may increase concentrations of the anticonvulsant (inhibition of CYP3A). Clinical monitoring is recommended when coadministering PREZCOBIX® with these anticonvulsants.
Anti-infectives: ketolide or macrolide antibiotics clarithromycin erythromycin	↔ darunavir ↑ cobicistat ↑ anti-infective	Co-administration of PREZCOBIX® with these antibacterials may increase concentrations of darunavir, cobicistat, or the antibacterial (inhibition of CYP3A). PREZCOBIX® and clarithromycin can be used without dose adjustment in patients with normal renal function; for patients with renal impairment, consult the prescribing information for clarithromycin for the recommended dosage.
Antiemetics: domperidone	↑ domperidone	Use with caution: monitor for domperidone adverse reactions.
Antifungals: fluconazole ketoconazole itraconazole	↑ darunavir ↑ cobicistat ↑ antifungal	Co-administration of PREZCOBIX® with these antifungals may increase concentrations of darunavir, cobicistat, and/or the antifungal (inhibition of CYP3A and/or P-glycoprotein). Clinical monitoring is recommended when coadministering PREZCOBIX® with these antifungals. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg.
isavuconazole posaconazole		Clinical monitoring is recommended when co administering PREZCOBIX® with posaconazole or isavuconazole.
voriconazole		Voriconazole should not be administered to patients receiving PREZCOBIX® unless an assessment of the benefit/risk ratio justifies the use of voriconazole.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Anti-gout: colchicine	↑ colchicine	Concomitant use of PREZCOBIX® with colchicine may increase concentrations of colchicine (inhibition of CYP3A). Refer to colchicine product information for dosing recommendations. **Patients with renal or hepatic impairment should not be given colchicine with PREZCOBIX®.**
Antimycobacterials: rifabutin	↓ darunavir ↓ cobicistat ↑ rifabutin	Co-administration of PREZCOBIX® with rifabutin may decrease darunavir and/or cobicistat concentrations (induction of CYP3A), which may result in loss of therapeutic effect and development of resistance. Rifabutin concentrations may be increased when co-administered with PREZCOBIX®. Co-administration of PREZCOBIX® with rifabutin is not recommended. A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e., rifabutin 150 mg every other day) is warranted if rifabutin is co-administered with PREZCOBIX®. Increased monitoring for rifabutin-related adverse events is warranted in patients receiving the combination.
Antiplatelets: clopidogrel	↓ clopidogrel active metabolite	Co-administration of PREZCOBIX® with clopidogrel is expected to decrease clopidogrel active metabolite plasma concentration, which may reduce the antiplatelet activity of clopidogrel. Co-administration of PREZCOBIX® with clopidogrel is not recommended.
β-Blockers: carvedilol metoprolol timolol	↑ β-blockers	Co-administration of PREZCOBIX® and beta-blockers may increase concentrations of the beta-blocker (inhibition of CYP2D6). Clinical monitoring is recommended when co- administering PREZCOBIX® with beta-blockers and a lower dose of the beta-blocker should be considered.
Calcium Channel Blockers: amlodipine diltiazem felodipine nifedipine verapamil	↑ calcium channel blockers	Plasma concentrations of calcium channel blockers (e.g., amlodipine, diltiazem, felodipine, nifedipine, verapamil) may increase when PREZCOBIX® are co-administered. Caution is warranted and clinical monitoring of patients is recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Corticosteroids: Systemic dexamethasone prednisone Primarily metabolized by CYP3A, including inhaled/nasal/topical betamethasone budesonide fluticasone mometasone triamcinolone	↓ darunavir ↓ cobicistat ↑ corticosteroid	Use with caution. Systemic dexamethasone induces CYP3A4 and can thereby decrease darunavir and/or cobicistat plasma concentrations. This may result in loss of therapeutic effect of darunavir and development of resistance. Corticosteroid concentrations may be increased when coadministered with PREZCOBIX®. Concomitant use may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Clinical monitoring is recommended when co-administering PREZCOBIX® with corticosteroids. Concomitant use of inhaled/topical corticosteroids and PREZCOBIX® may increase plasma concentrations of the corticosteroid. Alternatives should be considered, particularly for long-term use. For co-administration of cutaneously-administered corticosteroids sensitive to CYP3A inhibition, refer to the prescribing information of the corticosteroid for conditions or uses that augment its systemic absorption.
Endothelin Receptor Antagonists: bosentan	↓ darunavir ↓ cobicistat ↑ bosentan	Bosentan concentrations may be increased when co-administered with PREZCOBIX®. Clinical monitoring is recommended when co-administering PREZCOBIX® with bosentan and a dose adjustment of bosentan may be needed.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Estrogen-Based Contraceptives: drospirenone ethinyl estradiol norethindrone norgestimate	↑ drospirenone ↓ ethinyl estradiol ↑ norgestimate ↓ norethindrone	The results of an interaction trial between PREZCOBIX® and ethinyl estradiol and drospirenone demonstrated that single dose systemic exposures to ethinylestradiol and drospirenone are decreased by 30% and increased by 58%, respectively. When PREZCOBIX® is co-administered with a drospirenone-containing product, clinical monitoring is recommended due to the potential for hyperkalemia. No data are available to make recommendations on the use of PREZCOBIX® with other hormonal contraceptives. Therefore, additional or alternative (non-hormonal) methods of contraception are recommended. Drug interaction data with hormonal contraceptives are available from studies using one of the active products of PREZCOBIX® together with other products; it is not known which of the products is responsible for the observed effects. The results of an interaction trial between darunavir/rtv (600/100 mg b.i.d.) and ethinyl estradiol and norethindrone demonstrated that at steady-state, systemic exposures to ethinyl estradiol and norethindrone are decreased by 44% and 14%, respectively. A drug interaction study between elvitegravir/emtricitabine/tenofovir/cobicistat, which contains cobicistat, and a norgestimate/ethinyl estradiol containing hormonal oral contraceptive resulted in decreased plasma concentrations of ethinyl estradiol and an increase in norgestimate. The effects of increases in the concentration of the progestational component norgestimate are not fully known and can include increased risk of insulin resistance, dyslipedemia, acne and venous thrombosis. The potential unknown risks and benefits associated with co-administration of norgestimate/ethinyl estradiol with cobicistat should be considered, particularly in women who have risk factors for these events.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Eugeroics: modafinil	↓ darunavir ↓ cobicistat	Co-administration of PREZCOBIX® with modafinil may decrease darunavir and/or cobicistat concentrations (induction of CYP3A), which may result in loss of therapeutic effect and development of resistance. Co-administration of PREZCOBIX® and modafinil is not recommended.
HMG-CoA Reductase Inhibitors: atorvastatin rosuvastatin pravastatin	↑HMG-CoA reductase inhibitors	Concomitant use of a HMG-CoA reductase inhibitor and PREZCOBIX® may increase plasma concentrations of the lipid-lowering agent (inhibition of CYP3A and/or transport), which may lead to adverse events such as myopathy. Clinical monitoring is recommended when co-administering PREZCOBIX® with HMG-CoA reductase inhibitors and a lower dose of the lipid-lowering agent should be considered. The results of an interaction trial with PREZCOBIX® and atorvastatin (10 mg q.d.) showed a 3.9-fold increase in exposure to atorvastatin. When administration of atorvastatin and PREZCOBIX® is desired, it is recommended to start with an atorvastatin dose of 10 mg q.d. A gradual dose increase of atorvastatin may be tailored to the clinical response. The results of an interaction trial with PREZCOBIX® and rosuvastatin (10 mg q.d.) showed a 1.9-fold increase in exposure to rosuvastatin. When administration of rosuvastatin and PREZCOBIX® is desired, it is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety.
H2-Receptor Antagonists and Proton Pump Inhibitors: cimetidine famotidine nizatidine ranitidine esomeprazole lansoprazole omeprazole pantoprazole rabeprazole	↔ darunavir ↔ cobicistat	Based on mechanistic considerations (i.e. decreased gastric acidity) no interaction is expected when PREZCOBIX® is co-administered with H2-receptor antagonists. PREZCOBIX® can be co-administered with H2-receptor antagonists and proton pump inhibitors without dose adjustments.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Immunosuppressants: cyclosporine everolimus tacrolimus sirolimus	↑ immunosuppressants	Plasma concentrations of cyclosporine, everolimus, tacrolimus or sirolimus may be increased when co-administered with PREZCOBIX®. Therapeutic concentration monitoring of the immunosuppressive agent is recommended for immunosuppressant agents when co-administered with PREZCOBIX®. Concomitant use of everolimus and PREZCOBIX® is not recommended.
Narcotic Analgesics: methadone buprenorphine/naloxone	↓ methadone ↔ buprenorphine ↔naloxone ↑ norbuprenorphine	No dose adjustment of buprenorphine or methadone is required when co-administering with PREZCOBIX®. However, careful clinical monitoring is recommended as the dose of buprenorphine or methadone may need to be adjusted in some patients.
meperidine	↓ meperidine	PREZCOBIX® is expected to decrease meperidine concentrations and increase normeperidine metabolite concentrations. Dosage increase, and long-term use of meperidine and PREZCOBIX® are not recommended due to the increased concentrations of the metabolite normeperidine, which has both analgesic and CNS stimulant activity (e.g., seizures).
fentanyl oxycodone tramadol	↑ fentanyl ↑ oxycodone ↑ tramadol	Co-administration of PREZCOBIX® with these analgesics may increase concentrations of the analgesic (inhibition of CYP2D6 and/or CYP3A). Clinical monitoring is recommended when co- administering PREZCOBIX® with these analgesics.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Neuroleptics: perphenazine risperidone	↑ neuroleptics	Co-administration of PREZCOBIX® and these neuroleptics may increase concentrations of the neuroleptic (inhibition of CYP3A or CYP2D6). Clinical monitoring is recommended when co-administering PREZCOBIX® with these neuroleptics and a lower dose of the neuroleptic should be considered.
quetiapine	↑ quetiapine	PREZCOBIX® should not be used in combination with quetiapine. Due to CYP3A inhibition by PREZCOBIX®, concentrations of quetiapine are expected to increase, which can result in serious and/or life-threatening adverse reactions. The quetiapine dose should be substantially reduced when co-administered with PREZCOBIX®. For details, refer to the quetiapine prescribing information.
Protease Inhibitors [Hepatitis C Virus (HCV) direct-acting antivirals]**:** glecaprevir/pibrentasvir	↑ glecaprevir ↑ pibrentasvir	Concomitant use of glecaprevir/pibrentasvir and PREZCOBIX® may increase the exposure to glecaprevir and pibrentasvir (inhibition of P-gp, BCRP and/or OATP1B1/3). Co-administration of PREZCOBIX® with glecaprevir/pibrentasvir is not recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
PDE-5 Inhibitors: sildenafil tadalafil vardenafil	↑ PDE-5 inhibitors	Co-administration with PREZCOBIX® may result in an increase in PDE-5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances and priapism. <u>Use of PDE-5 inhibitors for erectile dysfunction:</u> Concomitant use of PDE-5 inhibitors, when used for the treatment of erectile dysfunction, should be done with caution. Co-administration of darunavir with sildenafil or tadalafil is expected to substantially increase the PDE-5 concentration and may result in an increase in PDE-5 inhibitor-associated adverse events including hypotension, visual changes, syncope, and priapism. If concomitant use of PREZCOBIX® with sildenafil or tadalafil is required, sildenafil at a single dose not exceeding 25 mg in 48 hours or tadalafil at a single dose not exceeding 10 mg in 72 hours is recommended. Vardenafil should not be used with PREZCOBIX®. <u>Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH):</u> Use of sildenafil is contraindicated (see Table 4). Based on theoretical considerations, co-administration of PREZCOBIX® with tadalafil may increase concentrations of tadalafil (CYP3A inhibition). Co-administration of PREZCOBIX® with tadalafil is not recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir and/or Cobicistat or Concomitant Drug	Clinical Comment
Sedatives/Hypnotics: buspirone clorazepate diazepam flurazepam zolpidem parenterally administered midazolam	↑ sedatives/hypnotics	Co-administration of PREZCOBIX® with these sedatives/hypnotics may increase concentrations of the sedative/hypnotic (inhibition of CYP3A). Clinical monitoring is recommended when co-administering PREZCOBIX® with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. 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 solifenacin	↑ Urinary antispasmodics	Use with caution. Monitor for fesoterodine or solifenacin adverse reactions, dose reduction of fesoterodine or solifenacin may be necessary.
Antidepressants: amitriptyline desipramine imipramine nortriptyline sertraline paroxetine trazodone	↑ antidepressant	Concomitant use of PREZCOBIX® and these antidepressants may increase concentrations of the antidepressant (inhibition of CYP2D6 and/or CYP3A). Clinical monitoring is recommended when co-administering PREZCOBIX® with these antidepressants and a dose adjustment of the antidepressant may be needed.

Other NRTIs

Based on the different elimination pathways of the other NRTIs (zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir) that are primarily renally excreted, no drug interactions are expected for these drugs and PREZCOBIX®.

9.5 Drug-Food Interactions

PREZCOBIX®, when given as a tablet should be taken with food. The type of food does not affect the exposure to darunavir from PREZCOBIX®.

Effects of Food on Oral Absorption

When administered with food, the rate and extent of darunavir exposure were 2.27 and 1.7-fold higher as compared to intake without food. Therefore, PREZCOBIX® tablets should be taken with food. The type of food does not affect exposure to darunavir from PREZCOBIX®.

9.6 Drug-Herb Interactions

Concomitant use of PREZCOBIX® and St. John's wort (*Hypericum perforatum*) or products containing St. John's wort is contraindicated. Co-administration of protease inhibitors (PIs), including PREZCOBIX®, with St. John's wort is expected to substantially decrease PI concentrations and may result in suboptimal concentrations of darunavir and lead to loss of virologic response and possible resistance to PREZCOBIX® or to the class of PIs (see **9.4 Drug-Drug Interactions**, Table 4).

Interactions with other herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Darunavir is an inhibitor of the dimerization and of the catalytic activity of the HIV-1 protease. It selectively inhibits the cleavage of HIV-encoded Gag-Pol polyproteins in virus-infected cells, thereby preventing the formation of mature infectious virus particles.

Darunavir tightly binds to the HIV-1 protease with a K_D of 4.5 x 10^{-12} M.

Darunavir is not an inhibitor of any of 13 tested human cellular proteases.

Cobicistat is a selective, mechanism-based inhibitor of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as darunavir, where bioavailability is limited, and half-life is shortened due to CYP3A-dependent metabolism.

10.2 Pharmacodynamics

Electrocardiogram (Effect on QT Interval)

In an open-label, randomized, placebo- and active-controlled, four-way crossover trial, 40 healthy subjects were administered supratherapeutic doses of darunavir/ritonavir 1,600/100 mg once daily and 800/100 mg twice daily for seven days.

At the mean maximum darunavir concentration of 6,599 ng/mL observed in this study, the mean increase in QTcF was 2.2 ms with a 90% two-sided confidence interval (CI) of –2.0 to 6.3 ms. When evaluating the two-sided 90% CI on the time-matched mean changes in QTcF versus placebo control, the upper bounds of both darunavir/ritonavir groups never exceeded the 10 ms boundary. In the setting of this trial, darunavir/ritonavir did not appear to prolong the QTc interval.

The electrocardiographic effects of cobicistat were determined in a study of 48 healthy subjects. Cobicistat did not prolong the QTcF interval at doses of 250 mg and 400 mg, providing exposures 2- and 4-fold above the recommended therapeutic dose, respectively. A modest increase in PR interval (+9.6 msec) occurred around C_{max}, 3 to 5 hours after dosing of cobicistat 250 mg. This finding was not considered to be clinically significant.

In a human clinical study of 35 healthy subjects, echocardiograms performed at baseline and after receiving 150 mg cobicistat once daily for at least 15 days indicated no clinically significant change in left ventricular function.

Effects on Serum Creatinine

The effect of cobicistat on serum creatinine was investigated in a Phase I study 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 change of 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).

These decreases in $eGFR_{CG}$ were reversible 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 cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in $eGFR_{CG}$, without affecting the actual glomerular filtration rate.

10.3 Pharmacokinetics

General

Darunavir exposure was shown to be comparable in a bioavailability study between PREZCOBIX® and darunavir/ritonavir 800/100 mg q.d. at steady-state and fed conditions in healthy subjects.

The bioequivalence between PREZCOBIX® and darunavir/cobicistat 800/150 mg co-administered as single agents was established under fed and fasted conditions in healthy subjects (see **14.3 Comparative Bioavailability Studies**).

Absorption

Absorption and Bioavailability

Darunavir was rapidly absorbed following oral administration of PREZCOBIX® in healthy volunteers. The maximum plasma concentration of darunavir in the presence of cobicistat is generally achieved within 3.0 to 4.5 hours. Following oral administration of PREZCOBIX® in healthy volunteers, maximum plasma concentrations of cobicistat were observed 2 to 5 hours post-dose for cobicistat.

The absolute oral bioavailability of a single 600 mg dose of darunavir alone was approximately 37%.

Table 6 displays the mean plasma concentrations over time of darunavir and cobicistat at steady state for darunavir/cobicistat 800/150 mg q.d.

Table 6: Mean Steady-State Plasma Concentration-Time Profiles of Darunavir and Cobicistat at 800/150 mg q.d. at Weeks 2-8 (Study GS-US-216-0130 PK substudy, n=60)

Scheduled Time	Darunavir		Cobicistat	
	Mean ± SD (ng/mL)	CV (%)	Mean ± SD (ng/mL)	CV (%)
0 h	1560 ± 1328	85.1	76.2 ± 186.2	244.3
1 h	3534 ± 2132	60.3	390.2 ± 375.1	96.1
2 h	5646 ± 2048	36.3	663.5 ± 371.5	56.0
3 h	6762 ± 1855	27.4	822.2 ± 374.6	45.6
3.5 h	6777 ± 1771	26.1	826.8 ± 338.5	40.9
4 h	6813 ± 1876	27.5	821.4 ± 342.5	41.7
4.5 h	6755 ± 2053	30.4	834.6 ± 341.2	40.9
5 h	6328 ± 1959	31.0	787.7 ± 322.2	40.9
6 h	5568 ± 1875	33.7	681.9 ± 283.6	41.6
8 h	4321 ± 1681	38.9	485.6 ± 233.8	48.2
10 h	3558 ± 1498	42.1	343.8 ± 204.9	59.6
12 h	3226 ± 1331	41.3	244.1 ± 165.3	67.7
24 h	1311 ± 969.5	74.0	32.8 ± 99.9	289.4

The relative mean minimum concentration (C_{min}) of darunavir at steady state when boosted with cobicistat was shown to be lower than the C_{min} of darunavir when boosted with ritonavir in comparative bioavailability studies.

When administered with food, the rate and extent of darunavir exposure were 2.27 and 1.7-fold higher as compared to intake without food. Therefore, PREZCOBIX® tablets should be taken with food. The type of food does not affect exposure to darunavir from PREZCOBIX® (see **4 DOSAGE AND ADMINISTRATION** and **9.5 Drug-Food Interactions**).

Distribution:

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

Cobicistat is 97 to 98% bound to human plasma proteins and the mean plasma to blood-drug concentration ratio was approximately 2.

Metabolism:

In vitro experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by the hepatic CYP system, and almost exclusively by isozyme CYP3A4. A ^{14}C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir/ritonavir dose was due to the parent drug. At least three oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 10-fold less than the activity of darunavir against wild-type HIV.

Cobicistat is metabolized via CYP3A (major) and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. Following oral administration of ^{14}C-cobicistat, 99% of circulating radioactivity in plasma was unchanged cobicistat. Low levels of metabolites are observed in urine and feces and do not contribute to the CYP3A inhibitory activity of cobicistat.

Elimination

Following oral administration of ^{14}C-cobicistat, 86% and 8.2% of the dose were recovered in feces and urine, respectively. The median terminal elimination half-life of cobicistat is approximately 3-4 hours.

After a 400/100 mg ^{14}C-darunavir/ritonavir dose, approximately 79.5% and 13.9% of the administered dose of ^{14}C-darunavir could be retrieved in feces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively. The terminal elimination half-life of darunavir was approximately 11 hours when combined with cobicistat. The intravenous clearance of darunavir alone (150 mg) and in the presence of low-dose ritonavir was 32.8 L/h and 5.9 L/h, respectively.

Special Populations and Conditions

- **Pediatrics** The pharmacokinetics of PREZCOBIX® in pediatric patients have not been investigated. PREZCOBIX® is not indicated for pediatric patients <18 years of age.
- **Geriatrics** Population pharmacokinetic analysis in HIV-infected patients showed that darunavir (co-administered with low dose ritonavir) pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV-infected patients (n=12, age ≥65) (see **7.1 Special Populations**, **7.1.4 Geriatrics**).

  Pharmacokinetics of PREZCOBIX® have not been fully evaluated in the elderly (65 years of age and older).
- **Sex** Population pharmacokinetic analysis showed a slightly higher darunavir (co-administered with low dose ritonavir) exposure (16.8%) in HIV-infected females (n=68) compared to males. This difference is not considered clinically relevant.

  No clinically relevant pharmacokinetic differences due to gender have been identified for cobicistat.
- **Pregnancy and Breast-feeding** 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. 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.

  The exposure to total 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. The decrease in unbound (i.e., active) darunavir pharmacokinetic parameters (C_{max} and AUC_{24h}) during pregnancy compared to postpartum was less pronounced than for total darunavir.

  In women receiving PREZCOBIX® during the 2nd trimester of pregnancy, mean intra-individual values for total darunavir C_{max}, AUC_{24h} and C_{min} were 49%, 56% and 92% lower, respectively, as compared with postpartum; during the 3rd trimester of pregnancy, total

darunavir C_{max}, AUC_{24h} and C_{min} values were 37%, 50% and 89% lower, respectively, as compared with postpartum.

- **Ethnic Origin** Population pharmacokinetic analysis of darunavir (co-administered with low dose ritonavir) in HIV-infected patients indicated that race had no apparent effect on the exposure to darunavir.

  No clinically relevant pharmacokinetic differences due to ethnicity have been identified for cobicistat.

- **Hepatic Insufficiency** PREZCOBIX® has not been investigated in patients with hepatic impairment.

  In a multiple dose study with darunavir co-administered with ritonavir (600/100 mg) twice daily, it was demonstrated that the steady-state pharmacokinetic parameters of darunavir in patients with mild (Child-Pugh Class A, n=8) and moderate (Child-Pugh Class B, n=8) hepatic impairment were comparable with those in healthy patients. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see **2 CONTRAINDICATIONS**, **4 DOSAGE AND ADMINISTRATION** and **7 WARNINGS AND PRECAUTIONS**).

  Cobicistat is primarily metabolized and eliminated by the liver. A study of the pharmacokinetics of cobicistat was performed in non-HIV-1 infected subjects with moderate hepatic impairment (Child-Pugh Class B). No clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with moderate impairment and healthy subjects. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of cobicistat has not been studied.

  Hepatitis B or Hepatitis C Virus Co-infection
  There were insufficient pharmacokinetic data in the clinical trials to determine the effect of hepatitis B and/or C virus infection on the pharmacokinetics of PREZCOBIX®

- **Renal Insufficiency** PREZCOBIX® has not been investigated in patients with renal impairment.

  Results from a mass balance study with ^{14}C-darunavir/ritonavir showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine as unchanged drug. As darunavir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis. Although darunavir has not been studied in patients with renal impairment, population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-infected patients with moderate renal impairment (CrCL between 30–60 mL/min, n=20) (see **4.2 Recommended Dose and Dosage Adjustment, Renal Impairment** and **7 WARNINGS AND PRECAUTIONS**).

  A study of the pharmacokinetics of cobicistat was performed in non-HIV-1 infected subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min). No meaningful differences in cobicistat pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects, consistent with low renal clearance of cobicistat.

Population Pharmacokinetics

Darunavir/Cobicistat

The population pharmacokinetics derived mean (SD) C_{0h} and AUC_{24h} for darunavir in HIV-1-infected patients after oral administration of darunavir/cobicistat 800/150 mg once daily co-administered as single agents with a background regimen (based on sparse sampling in 298 patients in Study GS-US-216-0130) is 2043 (±1257) ng/mL and 100152 (±32042) ng.h/mL, respectively; which is comparable to the darunavir pharmacokinetics in HIV-1-infected patients receiving 800/100 mg once daily darunavir/ritonavir (see Table 7) to HIV-1-infected patients.

Table 7: Population Pharmacokinetic Estimates of Darunavir Following Multiple-Dose Administration of Darunavir/Cobicistat 800/150 mg Once Daily Co-Administered as Single Agents + Background Regimen in HIV-1 Infected Subjects (Study GS-US-216-0130, 24 Week Analysis)

Parameter	darunavir/cobicistat 800/150 mg once daily + background regimen N=298
AUC_{24h} (ng·h/mL)	
Mean ± Standard Deviation	100152 ± 32042
Median (Range)	96900 (34500-224000)
C_{0h} (ng/mL)	
Mean ± Standard Deviation	2043 ± 1257
Median (Range)	1875 (70-6890)

N=number of patients with data.

Darunavir/Ritonavir

Population pharmacokinetic analysis in HIV-infected patients showed that darunavir pharmacokinetics is not considerably different in the age range (18 to 75 years) evaluated in HIV-infected patients. Population pharmacokinetic analysis showed a slightly higher darunavir exposure in HIV-infected females compared to males. This difference is not considered clinically relevant.

Population pharmacokinetic analysis of darunavir in HIV-infected patients indicated that race had no apparent effect on the exposure to darunavir. The steady-state pharmacokinetic parameters of darunavir in patients with mild and moderate hepatic impairment were comparable with those in healthy patients, therefore, no dose adjustment is required in patients with mild or moderate hepatic impairment. PREZCOBIX® has not been studied in patients with severe hepatic impairment.

Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-infected patients with moderate renal impairment. There are no pharmacokinetic data available in HIV-1-infected patients with severe renal impairment or end-stage renal disease. However, since the renal clearance of darunavir and cobicistat is limited, a decrease in total body clearance is not expected in patients with renal impairment.

The pharmacokinetics of darunavir, co-administered with low dose ritonavir (100 mg), has been evaluated in healthy adult volunteers and in HIV-1-infected patients. Table 8 displays the population pharmacokinetic estimates of darunavir after oral administration of darunavir/ritonavir 800/100 mg once daily (based on sparse sampling in 335 patients in Study TMC114-C211 and 280 patients in Study TMC114-C229) to HIV-1-infected patients.

Table 8: Population Pharmacokinetic Estimates of darunavir/ritonavir 800/100 mg Once Daily (Study TMC114-C211, 48 Week Analysis and Study TMC114-C229, 48 Week Analysis)

Parameter	Study TMC114-C211 darunavir/ritonavir 800/100 mg once daily N=335	Study TMC114-C229 darunavir/ritonavir 800/100 mg once daily N=280
AUC_{24h} (ng·h/mL)[1]		
Mean ± Standard Deviation	93026 ± 27050	93334 ± 28626
Median (Range)	87854 (45000-219240)	87788 (45456-236920)
C_{0h} (ng/mL)		
Mean ± Standard Deviation	2282 ± 1168	2160 ± 1201
Median (Range)	2041 (368-7242)	1896 (184-7881)

N=number of patients with data. [1]AUC_{24h} is calculated as AUC_{12h}*2

11 STORAGE, STABILITY AND DISPOSAL

Store PREZCOBIX® tablets in the original container between 15 – 30°C.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

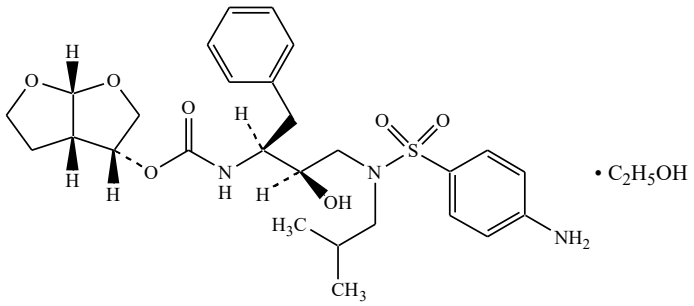
Proper name: Darunavir ethanolate

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 ethanolate.

Molecular formula: $C_{27}H_{37}N_3O_7S.C_2H_5OH$

Molecular mass: 593.73 g/mol

Structural formula:



Physicochemical properties:

Physical Description: Darunavir ethanolate is a white to off-white powder.

Solubility: The solubility of darunavir (or darunavir ethanolate) is approximately 0.015 mg/mL in water at 20°C.

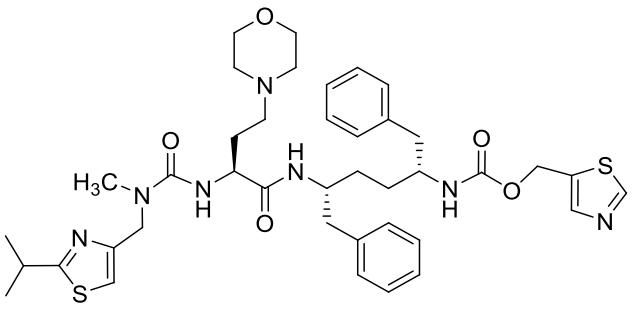
Proper name: Cobicistat

Chemical name: 1,3-Thiazol-5-ylmethyl[(*2R,5R*)-5-{[(*2S*)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl)carbamate.

Molecular formula: $C_{40}H_{53}N_7O_5S_2$

Molecular mass: 776.0 g/mol

Structural formula:



Physicochemical properties:

Physical Description: Cobicistat is a white to yellow solid. Cobicistat is adsorbed onto silicon dioxide.

Solubility: The solubility of cobicistat is approximately 0.1 mg/mL in water at 20°C.

14 CLINICAL TRIALS

General

The antiretroviral effect of PREZCOBIX® is due to the darunavir component. The activity of cobicistat as a pharmacokinetic enhancer to darunavir has been demonstrated in pharmacokinetic studies. In these pharmacokinetic studies, the exposure of darunavir 800 mg boosted with cobicistat 150 mg was consistent with that observed when boosted with ritonavir 100 mg. Darunavir as a component of PREZCOBIX® is bioequivalent to darunavir 800 mg once daily in combination with cobicistat 150 mg once daily co-administered as single agents (see **14 CLINICAL TRIALS**, **Pivotal Comparative Bioavailability Study**).

The efficacy of PREZCOBIX® is supported by the analysis of 24-week data from study GS-US-216-0130 in treatment-naïve and treatment-experienced patients and two Phase 3 trials, ARTEMIS (TMC114-C211) and ODIN (TMC114-C229), conducted with darunavir/ritonavir 800/100 mg q.d. in treatment-naïve and treatment-experienced patients, respectively.

For safety and efficacy studies using PREZISTA®, or TYBOST in combination with other antiretroviral agents, also consult the Product Monographs for these products.

14.1 Clinical Trials By Indication

Antiretroviral Treatment-Naïve Adult Patients (TMC114-C211 (ARTEMIS))

The evidence of efficacy of darunavir/ritonavir 800/100 mg q.d.in anti-retroviral treatment-naïve patients is based on the analyses of 192-week data from the randomized, controlled, open-label Phase 3 trial TMC114-C211 comparing darunavir/ritonavir 800/100 mg q.d. with lopinavir/ritonavir 800/200 mg per day (given as a twice-daily or as a once-daily regimen). Both arms used a fixed background regimen consisting of tenofovir disoproxil fumarate 300 mg q.d. (TDF) and emtricitabine 200 mg q.d. (FTC). Demographics and baseline characteristics were balanced between the darunavir/ritonavir arm and the lopinavir/ritonavir arm.

Analyses of the data at 192 weeks of treatment in the ARTEMIS trial demonstrated sustained antiretroviral efficacy and immunological benefit of the darunavir/ritonavir arm. In the 192-weeks analysis, virologic response (HIV-1 RNA<50 copies/mL) in the ITT population was 68.8% (N=343) and 57.2% (N=346) for the darunavir/ritonavir and lopinavir/ritonavir arm, respectively (p<0.001, difference = 11.6%, 95% CI = [-4.4; 18.8]).

Antiretroviral Treatment-Experienced Adult Patients with no darunavir resistance-associated mutations (TMC114-C229 (ODIN))

The evidence of efficacy of darunavir/ritonavir 800/100 mg q.d. in anti-retroviral treatment-experienced patients with no darunavir resistance-associated mutations is based on the 48-week analysis of the randomized, open-label Phase 3 trial TMC114-C229 (ODIN) comparing darunavir/ritonavir 800/100 mg q.d. with darunavir/ritonavir 600/100 mg per b.i.d. Both arms used an optimized background regimen consisting of ≥2 NRTIs selected by the investigator. No imbalances between the two arms were noted.

In the 48-week primary analysis, the virologic response defined as a confirmed plasma HIV-1 RNA viral load <50 copies/mL (ITT, TLOVR), was 72.1% (N=294) for the darunavir/ritonavir q.d. arm and 70.9% (N=296) for the darunavir/ritonavir b.i.d. arm (p<0.001, difference = 1.2%, 95% CI = [-6.1; 8.5]).

GS-US-216-0130

Demographics and Trial Design

GS-US-216-0130 is a single-arm, open-label, Phase 3 trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir with cobicistat in 313 HIV-1 infected adult patients (295 treatment-naïve and 18 treatment-experienced). These patients received darunavir 800 mg once daily in combination with cobicistat 150 mg once daily with an investigator-selected background regimen consisting of 2 active NRTIs.

HIV-1 infected patients who were eligible for this trial had a screening genotype showing no darunavir RAMs and plasma HIV-1 RNA ≥1000 copies/mL. Virologic response was defined as confirmed plasma HIV-1 RNA viral load <50 copies/mL using the Snapshot analysis.

Table 9: Demographic and Baseline Characteristics of Patients in Open-Label GS-US-216-0130 Trial

	All Subjects darunavir/cobicistat 800/150 mg q.d. + OBR **N=313**
Median Age (years) (range, years)	35 (18-72)
Sex	
Male	89%
Female	11%
Race	
White	60%

	All Subjects darunavir/cobicistat 800/150 mg q.d. + OBR **N=313**
Black	35%
American Indian or Alaska Native	1%
Asian	1%
Native Hawaiian or Pacific Islander	1%
Other	3%
Mean Baseline Plasma HIV-1 RNA (log_{10} copies/mL)	4.8
Median Baseline CD4+ Cell Count, 10^6 (cells/L) (range, cells/L)	361.0 (5-1473)
Percentage of Patients with Baseline Viral Load ≥100,000 copies/mL	42%
Percentage of Patients with Baseline CD4+ Cell Count ≤200x10^6 cells/L	19%

N=total number of patients in the ITT population with data; OBR=optimized background regimen

The table below shows the efficacy data of the 24-week analyses from the GS-US-216-0130 trial.

Table 10: Virologic Outcome of Randomized Treatment of Trial GS-US-216-0130 at 24 Weeks

	All Subjects darunavir/cobicistat 800/150 mg q.d. + OBR **N=313**
Virologic success HIV-1 RNA <50 copies/mL	82.4%
Virologic failure[1]	11.5%
No virologic data at Week 24 window[2] Reasons	
Discontinued study due to adverse event or death[3]	4.5%
Discontinued study for other reasons[4]	1.0%
Missing data during window‡ but on study	0.6%

N=total number of subjects with data

[1] Includes patients who discontinued prior to Week 24 for lack or loss of efficacy and patients who are ≥50 copies/mL in the 24-week window and patients who had a change in their background regimen that was not permitted by the protocol

[2] Window 20-30 weeks

[3] Includes patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window

[4] Other includes: withdrew consent, loss to follow-up, etc., if the viral load at the time of discontinuation was <50 copies/mL

14.2 Comparative Bioavailability Studies

Pivotal Comparative Bioavailability Study

In a Phase 1, single-dose, open-label, randomized 3-panel, 2-way crossover trial the rate and extent of absorption of darunavir following administration of a 800 mg darunavir/150 mg cobicistat fixed-dose combination tablet and 2 x 400 mg darunavir tablets (in the presence of 150 mg cobicistat) under fasted and fed (low fat, low calorie and high fat, high calorie) conditions was assessed in 133 healthy male and female subjects.

In Panel 1, 74 male and female subjects randomly received under fasted conditions a single oral dose of 800 mg darunavir formulated as the 400 mg tablet (2 x 400 mg) and 150 mg cobicistat (Treatment A) and a single oral dose of a 800 mg darunavir/150 mg cobicistat fixed-dose combination tablet (Treatment B) with a washout period of at least 7 days in between treatments. The results indicate that the bioavailabilities of darunavir and cobicistat from the 800 mg darunavir/150 mg cobicistat fixed-dose combination tablet are comparable to the bioavailabilities of darunavir and cobicistat from the 2 x 400 mg dose of darunavir co-administered with 150 mg of cobicistat under fasted conditions.

In Panel 2, 40 male and female subjects randomly received under fed conditions (low fat, low calorie) a single oral dose of 800 mg darunavir formulated as the 400 mg tablet (2 x 400 mg) and 150 mg cobicistat (Treatment C), and a single oral dose of a 800 mg darunavir/150 mg cobicistat fixed-dose combination tablet (Treatment D) with a washout period of at least 7 days in between treatments. The results indicate that the bioavailabilities of darunavir and cobicistat from the 800 mg darunavir/150 mg cobicistat fixed-dose combination tablet are comparable to the bioavailabilities of darunavir and cobicistat from 2 x 400-mg dose of darunavir co-administered with 150 mg of cobicistat under low fat, low calorie fed conditions. The summary of results is presented in Table 11.

Table 11: Summary Table of the Comparative Bioavailability Data Under Fed and Fasting Conditions

Geometric Least Square Mean Arithmetic Mean (CV%)						
Darunavir	**Fasted Conditions**			**Fed (Standardized Breakfast)**		
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means (90% Confidence Interval)	Test[1]	Reference[2]	% Ratio of Geometric Means (90% Confidence Interval)
AUC_{last} (ng.h/mL)	42831 46329 (39.9)	44524 47326 (38.7)	96.20 (90.98 – 101.71)	74744 78942 (33.8)	76499 81483 (33.8)	97.71 (93.08 – 102.57)
AUC_{∞} (ng.h/mL)	43058 46291 (40.6)	44851 47668 (39.2)	96.00 (90.30 – 102.07)	74302 78811 (34.6)	75962 79836 (33.7)	97.81 (92.85 – 103.05)
C_{max} (ng/mL)	2950 3087 (30.0)	2992 3129 (29.8)	98.59 (93.72 – 103.73)	6650 6773 (19.8)	6873 6979 (17.2)	96.76 (93.06 – 100.60)
T_{max}[3] (h)	3.00 (1.00 – 12.00)	3.00 (1.00 – 12.00)		4.03 (1.50 – 9.05)	4.00 (1.00 – 9.00)	
$T_{½}$[4] (h)	7.6 (46.9)	7.2 (46.2)		6.7 (51.3)	5.5 (29.6)	
Cobicistat	**Fasted Conditions**			**Fed (Standardized Breakfast)**		
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means (90% Confidence Interval)	Test[1]	Reference[2]	% Ratio of Geometric Means (90% Confidence Interval)
AUC_{last} (ng.h/mL)	4226 5219 (58.5%)	4175 4962 (50.2%)	101.20 (91.77 – 111.61)	5751 6285 (43.5)	5879 6401 (42.9)	97.82 (94.65 – 101.10)
AUC_{∞} (ng.h/mL)	4580 5448 (55.2%)	4390 5106 (48.4%)	104.33 (94.85 – 114.77)	5842 6388 (43.5)	5975 6511 (42.8)	97.77 (94.60 – 101.05)
C_{max} (ng/mL)	591 697 (48.6%)	572 664 (45.4%)	103.40 (94.25 – 113.44)	789 819 (27.0)	808 823 (25.3)	97.65 (93.77 – 101.70)
T_{max}[3] (h)	2.00 (1.00 – 5.03)	2.50 (1.00 – 5.03)		4.00 (1.00 – 5.02)	3.99 (1.00 – 5.03)	

$T_{½}$[4] (h)	3.9 (21.0%)	4.0 (22.3%)		3.8 (22.2)	3.9 (21.8)	

[1] 800 mg/150 mg (darunavir/cobicistat) fixed-dose combination tablet (G006).

[2] 2 x 400 mg darunavir tablet (F030) + 150 mg cobicistat tablet.

[3] Expressed arithmetic median (range) only.

[4] Expressed as the arithmetic mean (CV%) only.

In Panel 3, the effect of food on the oral bioavailability of darunavir when administered as the darunavir/cobicistat fixed-dose combination tablet was assessed in 19 male and female subjects. Exposure to darunavir following single-dose administration of the 800 mg darunavir/150 mg cobicistat fixed-dose combination tablet was higher with a high-fat breakfast relative to fasted conditions; the C_{max}, AUC_{last}, and AUC_{∞} values for darunavir were 2.27-, 1.63-, and 1.70-fold higher, respectively. Exposure to cobicistat following single-dose administration of the 800 mg darunavir/150 mg cobicistat fixed-dose combination tablet was comparable when it was administered with a high-fat breakfast and under fasted conditions.

15 MICROBIOLOGY

Antiviral Activity *In Vitro*

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 vitro* 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 <0.1 to 4.3 nM.

These EC_{50} values are well below the 50% cellular toxicity concentration range of 87 µM to >100 µM. The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum.

Darunavir showed synergistic antiviral activity when studied in combination with the PIs ritonavir, nelfinavir, or amprenavir, and additive antiviral activity when studied in combination with the PIs indinavir, saquinavir, lopinavir, atazanavir, or tipranavir, the nucleoside (nucleotide) reverse transcriptase inhibitors (N(t)RTIs) zidovudine, lamivudine, zalcitabine, didanosine, stavudine, abacavir, emtricitabine, or tenofovir, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine, delavirdine, etravirine, or efavirenz, and the fusion inhibitor enfuvirtide. No antagonism was observed between darunavir and any of these antiretrovirals *in vitro*.

Cobicistat has no detectable antiviral activity against HIV-1, HBV, or HCV and does not antagonize the antiviral effect of darunavir.

Resistance *In Vitro*

In vitro selection of darunavir-resistant virus from wild-type HIV-1 was lengthy (more than 2 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 220 nM. Viruses selected in these conditions and showing decreased susceptibility to darunavir (range: 23- to 50-fold) harboured 2 to 4 amino acid substitutions in the protease gene. Identification of determinants of decreased susceptibility to darunavir in those viruses is under investigation.

In vitro selection of darunavir-resistant HIV-1 (range: 53- to 641-fold change in EC_{50} values) from 9 HIV-1 strains harbouring multiple PI resistance-associated mutations (RAMs) resulted in the overall emergence of 22 mutations in the protease, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were present in more than 50% of the 9 darunavir-resistant isolates. A minimum of 8 of these darunavir *in vitro* selected mutations, from which at least 2 were already present in the protease prior to selection, were required in the HIV-1 protease to render a virus resistant (fold change (FC) >10) to darunavir.

In 1113 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir, and in 886 baseline isolates from treatment-experienced patients only the subgroups with >10 PI resistance-associated mutations showed a median FC for darunavir >10.

Cross-Resistance *In Vitro*

Cross-resistance has been observed among PIs. Darunavir has a <10-fold decreased susceptibility against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to most PIs remain susceptible to darunavir.

Seven of the 9 darunavir-resistant viruses selected from PI-resistant viruses had phenotypic data for tipranavir. Six of those showed a FC in EC_{50} value <3 for tipranavir, indicative of limited cross-resistance between these 2 PIs.

Cross-resistance between darunavir and the nucleoside/nucleotide reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors, the entry inhibitors, or the integrase inhibitor is unlikely because the viral targets for those inhibitors are different.

***In Vivo* Selection of Viral Resistance**

The resistance profile of PREZCOBIX® is driven by darunavir. Cobicistat does not select any HIV resistance mutations, due to its lack of antiviral activity. The resistance profile of PREZCOBIX® is supported by the analysis of 24-week data from trial GS-US-216-0130 in treatment-naïve and treatment-experienced patients and two Phase 3 trials conducted with darunavir/ritonavir in treatment-naïve and treatment-experienced patients, respectively.

***In Vivo* Selection of Viral Resistance During PREZCOBIX® Therapy**

In the 24-week analysis of the GS-US-216-130 trial, no PI or NRTI RAMs developed in the treatment-naïve patients. One treatment-experienced patient developed a DRV RAM. This mutation was not associated with a decreased susceptibility to darunavir. One treatment-experienced patient developed an NRTI RAM, which was not associated with a decreased susceptibility to the NRTIs included in the background regimen.

***In Vivo* Selection of Viral Resistance During darunavir/ritonavir 800/100 mg q.d. Therapy**

In the 192-week analysis of the TMC114-C211 (ARTEMIS) trial, the number of virologic failures was lower in the group of patients receiving darunavir/ritonavir 800/100 mg q.d. than in patients receiving lopinavir/ritonavir 800/200 mg per day (16.0% vs. 20.5%, respectively). In the virologic failures of the darunavir/ritonavir arm with paired baseline/endpoint genotype data, four patients with developing PI RAMs were identified. In the virologic failures of the lopinavir/ritonavir arm with paired baseline/endpoint genotype data, nine patients with developing PI RAMs at endpoint were identified. This was not associated with a loss in susceptibility to lopinavir. None of the developing mutations in the darunavir/ritonavir group or in the lopinavir/ritonavir group were

primary (i.e., major) PI mutations. In four virologic failures in the darunavir/ritonavir arm and seven virologic failures in the lopinavir/ritonavir arm, a maximum of two developing NRTI RAMs were identified. The development of the NRTI RAM at position 184 (n=9) was identified, which was associated with a decreased susceptibility to emtricitabine (FTC) included in the fixed background regimen.

In the 48-week analysis of the TMC114-C229 (ODIN) trial, the number of virologic failures was comparable in the darunavir/ritonavir 800/100 mg q.d. group and the darunavir/ritonavir 600/100 mg b.i.d. group (22.1% vs. 18.2%, respectively). Of the virologic failures, the darunavir/ritonavir 800/100 mg q.d. group reported 7 (12%) patients with developing PI RAMs compared to 4 (10%) patients in the darunavir/ritonavir 600/100 mg b.i.d group. Only 1 subject, in the darunavir/ritonavir q.d. group, developed primary (major) PI mutations (V32I, M46I, L76V and I84V), which included 3 DRV RAMs (V32I, L76Vand I84V). The emergence of these DRV RAMs was associated with loss of darunavir susceptibility.

All virologic failures from the darunavir/ritonavir 600/100 mg b.i.d. group retained susceptibility to darunavir. Four (6.7%) and 3 (7.1%) virologic failures developed 1 or 2 NRTI RAMs in the darunavir/ritonavir 800/100 mg q.d. and the darunavir/ritonavir 600/100 mg b.i.d. groups, respectively. In 3 and 2 of these virologic failures in the darunavir/ritonavir 800/100 mg q.d. and the darunavir/ritonavir 600/100 mg b.i.d. groups, respectively, the development of these NRTI RAMs (V75I+M184V; M184V; T215Y in the q.d. group and M184V; M41L+T215Y in the b.i.d. group) was associated with a decreased susceptibility to a NRTI included in the background regimen.

***In Vivo* Cross-Resistance with Other Protease Inhibitors**

In the virologic failures of the GS-US-216-0130 trial no cross-resistance with other PIs was observed.

In the virologic failures of the ARTEMIS trial, no cross-resistance with other PIs was observed.

Of the viruses isolated from patients receiving darunavir/ritonavir 800/100 mg q.d. experiencing virologic failure in the ODIN trial, 98% remained susceptible to darunavir after treatment. In the same group of patients, 96% to 100% that were susceptible at baseline to amprenavir, atazanavir, indinavir, lopinavir, saquinavir or tipranivir remained susceptible to these protease inhibitors after treatment. In the virologic failures receiving darunavir/ritonavir 600/100 mg b.i.d. no cross-resistance with other PIs was observed.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Animal toxicology studies have been conducted with darunavir alone, in mice, rats and dogs and in combination with ritonavir in rats and dogs. Animal toxicology studies have been conducted with cobicistat alone, in mice, rats, rabbits and dogs. Animal studies have not been conducted with darunavir in combination with cobicistat. Animal toxicology for darunavir and cobicistat in combination is based on the studies conducted in the individual products.

In chronic toxicology studies in rats and dogs, there were only limited effects of treatment with darunavir. In the rat the key target organs identified were the hematopoietic system, the blood coagulation system, liver, and thyroid, observed at 100 mg/kg/day and above and at exposures below clinical levels. A variable but limited decrease in red blood cell-related parameters was

observed, together with increases in activated PTT. The observed liver and thyroid changes were considered to reflect an adaptive response to enzyme induction in the rat rather than an adverse effect. In combination toxicity studies with ritonavir, no additional target organs of toxicity were reported in rats. In the dog, no major toxicity findings or key target organs were identified at doses up to 120 mg/kg/day and exposures equivalent to clinical exposure at the recommended dose.

Carcinogenicity:

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 incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or 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 (based on AUC) to darunavir were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg once daily).

In a long-term carcinogenicity study of cobicistat in mice, no drug-related increases in tumour incidence were observed at doses up to 50 and 100 mg/kg/day (males and females, respectively). Cobicistat exposures at these doses were approximately 7 (males) 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.

Genotoxicity:

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

Cardiovascular

Ex vivo rabbit studies and *in vivo* dog studies suggest that cobicistat has a low potential for QT prolongation, and may slightly prolong the PR interval and decrease left ventricular function at mean concentrations at least 10-fold higher than the human exposure at the recommended 150 mg daily dose (see **10.2 Pharmacodynamics**, **Electrocardiogram (Effect on QT Intervals)**.

Reproductive and Developmental Toxicology:

Investigation of fertility and early embryonic development with darunavir was performed in rats, teratogenicity studies were conducted in mice, rats and rabbits, and the pre- and post-natal development study was conducted in rats.

In the fertility and early embryonic development study conducted with darunavir, a significant decrease in body weight gain with subsequent related reduction in the number of ovulations resulting in a reduction in the number of live fetuses was observed in female rats treated with 1000 mg/kg. Otherwise, there were no effects on mating or fertility with darunavir treatment up to 1000 mg/kg/day and exposure levels below (AUC 0.5-fold) that in humans at the clinically recommended dose. Up to the same dose levels, there was no teratogenicity with darunavir in rats and rabbits when treated alone nor in mice when treated in combination with ritonavir. The exposure levels were lower than those observed with the recommended clinical dose in humans. In a pre- and post-natal development assessment in rats, darunavir with and without ritonavir caused a transient reduction in body weight gain of the offspring during lactation. This was attributed to drug exposure via the milk. No post-weaning functions were affected with darunavir alone or in combination with ritonavir.

Reproductive studies with cobicistat were conducted in rats and rabbits. Animal studies do not indicate direct or indirect harmful effects of cobicistat with respect to pregnancy, fetal development, parturition, or postnatal development. There were no effects on mating and fertility parameters. Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with cobicistat during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal NOAELs in rats and rabbits were respectively 1.4 and 3.3 times higher than the exposure in humans at the recommended daily dose of 150 mg.

Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 3.3-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.

Juvenile Toxicity

In juvenile rats directly dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age, mortality was observed and, in some of the animals, convulsions. Within this age range exposures in plasma, liver and brain were dose and age dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the CYP450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. No treatment-related mortalities were noted in juvenile rats dosed at 1000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats. In humans, the activity of drug-metabolizing enzymes approaches adult values by 3 years of age.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrPREZCOBIX®

Darunavir (as darunavir ethanolate) /cobicistat

Film-coated Tablets

Read this carefully before you start taking **PREZCOBIX®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PREZCOBIX®**.

What is PREZCOBIX® used for?

- PREZCOBIX® is used for the treatment of HIV (Human Immunodeficiency Virus) infection in adults. PREZCOBIX is used in combination with other antiretroviral medications. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
- Ask your healthcare professional if you have any questions on how to prevent passing HIV to other people.

How does PREZCOBIX® work?

PREZCOBIX® contains two prescription medicines, darunavir and cobicistat. Darunavir is a type of anti-HIV medicine called a protease (PRO-tee-ase) inhibitor. It blocks HIV protease, an enzyme needed for HIV to multiply. Darunavir needs to be combined with another medicine, cobicistat. Cobicistat increases the amount of darunavir in your blood to control your HIV infection.

When used with other anti-HIV medicines, PREZCOBIX® can help to reduce the amount of HIV in your blood (called “viral load”) and increase your CD4+ (T) cell count. HIV infection destroys CD4+ (T) cells, which are important to the immune system. The immune system helps fight infection. Reducing the amount of HIV and increasing the CD4+ (T) cell count may improve your immune system (your body’s natural defences).

PREZCOBIX® is always taken in combination with other anti-HIV medicines. PREZCOBIX® should also be taken with food.

PREZCOBIX® does not cure HIV infection or AIDS. At present, there is no cure for HIV infection. People taking PREZCOBIX® may still develop infections or other conditions associated with HIV infection. Because of this, it is very important for you to remain under the care of a healthcare professional.

What are the ingredients in PREZCOBIX®?

Medicinal ingredients: darunavir ethanolate and cobicistat

Non-medicinal ingredients: The other ingredients are crospovidone, hypromellose, magnesium stearate, and silicified microcrystalline cellulose. The tablet film coating contains OPADRY® II Pink (polyethylene glycol, polyvinyl alcohol - partially hydrolyzed, talc, titanium dioxide, iron oxide red, iron oxide black).

PREZCOBIX® comes in the following dosage forms:

Film-coated tablets containing 800 mg darunavir (as darunavir ethanolate) and 150 mg cobicistat.

Do not use PREZCOBIX® if:

- you are allergic to PREZCOBIX or any of its ingredients, including non-medicinal ingredients or components of the container (see "**What are the ingredients in PREZCOBIX?**")
- you have severe liver disease
- you take any of the following types of medicines because you could experience serious side effects:

Type of Drug	**Examples of Generic Names (Brand Names)**
Alpha1-Adrenoreceptor Antagonists (to treat enlarged prostate)	alfuzosin
Anticoagulant	apixaban (ELIQUIS) dabigatran (PRADAXA) rivaroxaban (XARELTO)
Anti-convulsants (to prevent seizures)	carbamazepine (TEGRETOL) phenobarbital phenytoin (DILANTIN)
Antiarrhythmics/ **Antianginals** (to treat abnormal heart rhythms)	amiodarone (CORDARONE) dronedarone (MULTAQ) ivabradine (LANCORA) lidocaine (when given by injection)
Anti-gout (to treat gout and familial Mediterranean fever)	colchicine
Antimycobacterials (to treat tuberculosis)	rifampin (RIFADIN, RIFATER)
Antivirals (to treat hepatitis C infection)	elbasvir/grazoprevir (ZEPATIER)
Ergot Derivatives (to treat migraine and headaches)	dihydroergotamine (MIGRANAL) ergonovine ergotamine (CAFERGOT)
Herbal products (to improve mood)	St. John's Wort
HMG-CoA **Reductase Inhibitors** also known as statins (to lower cholesterol) **Other Lipid Modifying Agents** cholesterol lowering drug	lovastatin (MEVACOR) simvastatin (ZOCOR) lomitapide
Inhaled Beta-Agonists (to treat asthma and/or chronic obstructive pulmonary disease)	salmeterol (ADVAIR)
Neuroleptics (to treat psychiatric conditions)	lurasidone (LATUDA) pimozide (ORAP)
PDE-5 Inhibitor (to treat pulmonary arterial hypertension)	sildenafil (REVATIO)

Type of Drug	Examples of Generic Names (Brand Names)
Platelet Aggregation Inhibitor (to prevent blood clots)	ticagrelor (BRILINTA)
Sedatives/Hypnotics (to treat trouble with sleeping and/or anxiety)	triazolam (HALCION)
Opioid Antagonist (to treat opioid-induced constipation)	naloxegol (MOVANTIK)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PREZCOBIX®. Talk about any health conditions or problems you may have, including if you:

- have diabetes. In general, anti-HIV medicines, such as PREZCOBIX®, might increase sugar levels in the blood.
- have mild to moderate liver problems, including hepatitis B and/or C infection. It is also possible to develop hepatitis from taking PREZCOBIX.
- have hemophilia. Anti-HIV medicines, such as PREZCOBIX®, might increase the risk of bleeding.
- have Pancreatitis (inflamed pancreas).
- have increased cholesterol or triglycerides (a type of fat in your blood) levels. Your healthcare professional will do a blood test to check your lipid (fat) levels before starting treatment with PREZCOBIX. Your healthcare professional will also check your lipid levels periodically during your treatment with PREZCOBIX.
- have Renal impairment (kidney problems). Your healthcare professional will determine your creatinine levels (kidney function tests).
- are pregnant or planning to become pregnant. It is not known if PREZCOBIX® can harm your unborn baby. You should not take PREZCOBIX® during pregnancy. If you take PREZCOBIX® while you are pregnant, talk to your healthcare professional about how you can be included in the Antiretroviral Pregnancy Registry.
- are breast-feeding. Do not breast-feed if you are taking PREZCOBIX®. You should not breast-feed if you have HIV because of the chance of passing HIV to your baby. Talk with your healthcare professional about the best way to feed your baby.
- are allergic to sulfonamide medications.
- are less than 18 years of age.

Other warnings you should know about:

PREZCOBIX® is not a cure for HIV-1 infection or AIDS. If you are taking PREZCOBIX or any other antiretroviral medication, you may continue to develop infections and other complications of HIV-1 infection.

- PREZCOBIX® does not reduce the risk of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. Never use or share dirty needles.
- During the initial phase of treatment with PREZCOBIX, you may develop infections. You may also develop autoimmune disorders (such as Graves' disease, autoimmune hepatitis, polymyositis and Guillain-Barré syndrome) during treatment with PREZCOBIX.

- You may develop a skin reaction during treatment with PREZCOBIX. Signs and symptoms can include severe rash or rash accompanied with fever, general malaise (discomfort), fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis (pink eye), hepatitis and/or eosinophilia (increased white blood cells). If you experience any of these signs or symptoms, stop taking PREZCOBIX immediately and tell your healthcare professional.

Check-ups and Testing:

Liver problems that may occasionally be severe have been reported. Your healthcare professional should do blood tests prior to initiating PREZCOBIX®. If you have chronic hepatitis B or C infection, your healthcare professional should check your blood tests more often because you have an increased chance of developing liver problems. Talk to your healthcare professional about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea coloured) urine, pale coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on your right side below your ribs.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with PREZCOBIX®:

- PREZCOBIX® should not be combined with vardenafil, because you may be at increased risk of side effects of vardenafil such as low blood pressure, visual changes, and penile erection lasting more than 4 hours.
- Tell your healthcare professional if you are taking estrogen-based contraceptives. PREZCOBIX® might reduce the effectiveness of estrogen-based contraceptives (birth control). Therefore, additional, or alternative methods of (non-hormonal) contraception, such as a condom, are recommended.
- Tell your healthcare professional if you take other anti-HIV medicines (e.g., rilpivirine, tenofovir disoproxil fumarate). PREZCOBIX® can be combined with some other anti-HIV medicines while other combinations are not recommended.
- Tell your healthcare professional about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements, including St. John's wort (Hypericum perforatum). PREZCOBIX® and many other medicines can interact. Sometimes serious side effects will happen if PREZCOBIX® is taken with certain other medicines (see **"When it should not be used"**)

If you are taking PREZCOBIX® you should not take:

- medications that may affect your kidneys and have not been discussed with your healthcare professional
- other medicines that contain protease inhibitors: e.g., atazanavir (Reyataz), indinavir (Crixivan), saquinavir (Invirase), lopinavir (Kaletra), or darunavir (Prezista®)
- other medicines that contain cobicistat (Stribild)
- ritonavir (Kaletra, Norvir).

Tell your healthcare professional if you are taking any of the following medicines. Your healthcare professional might want to do some additional blood tests.

Type of Drug	Examples of Generic Names (Brand Names)
Antiarrhythmics/Antianginals (for the heart)	digoxin disopyramide flecainide mexiletine propafenone
Anticancer Agents (to treat cancer)	dasatinib (SPRYCEL) nilotinib (TASIGNA) vinblastine vincristine everolimus (AFINITOR) irinotecan
Anticoagulants (to prevent the clotting of red blood cells)	dabigatran (PRADAXA) edoxaban (LIXIANA) warfarin (COUMADIN)
Anticonvulsants (to treat epilepsy and prevent seizures)	clonazepam (CLONAPAM) ethosuximide (ZARONTIN) oxcarbazepine (TRILEPTAL)
Antidepressants (to treat depression, anxiety, or panic disorder)	amitriptyline desipramine imipramine nortriptyline paroxetine (PAXIL) sertraline (ZOLOFT) trazodone (OLEPTRO)
Anti-infectives (to treat bacterial infections)	clarithromycin (BIAXIN) erythromycin (ERYC)
Antifungals (to treat fungal infections)	fluconazole (DIFLUCAN) ketoconazole (NIZORAL) itraconazole (SPORANOX®) isavuconazole posaconazole (POSANOL) voriconazole (VFEND)
Anti-gout (to treat gout and familial Mediterranean fever)	colchicine
Antimycobacterials	rifabutin (MYCOBUTIN)

Type of Drug	Examples of Generic Names (Brand Names)
(to treat bacterial infections)	rifampin (RIFADIN, RIFATER)
Antiplatelets (to prevent the clotting of red blood cells)	clopidogrel (PLAVIX)
Antivirals (to treat hepatitis C infection)	glecaprevir/pibrentasvir (MAVIRET)
Beta-Blockers (to treat heart disease)	carvedilol metoprolol (BETALOC, LOPRESOR) timolol
Calcium Channel Blockers (to treat heart disease)	amlodipine (CADUET, TWYNSTA) diltiazem (CARDIZEM, TIAZAC) felodipine nifedipine (ADALAT) verapamil (ISOPTIN, VERELAN)
Corticosteroids (to treat inflammation or asthma)	betamethasone budesonide (PULMICORT, RHINOCORT, SYMBICORT) dexamethasone fluticasone propionate (ADVAIR DISKUS, CUTIVATE, FLONASE, FLOVENT DISKUS) mometasone prednisone (WINPRED) triamcinolone
Endothelin Receptor Antagonists (to treat pulmonary arterial hypertension)	bosentan (TRACLEER®)
Estrogen-Based Contraceptives	ethinyl estradiol norethindrone norgestimate drospirenone
Eugeroics	modafinil
HIV- CCR5 Antagonist (to treat HIV infection)	maraviroc (CELSENTRI)
HIV- Integrase strand transfer Inhibitors (to treat HIV infection)	elvitegravir (STRIBILD)
HIV- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (to treat HIV infection)	delavirdine (RESCRIPTOR) efavirenz (SUSTIVA) etravirine (INTELENCE®)

Type of Drug	Examples of Generic Names (Brand Names)
	nevirapine (VIRAMUNE)
HMG-CoA Reductase Inhibitors (to lower cholesterol levels)	atorvastatin (LIPITOR) pravastatin (PRAVACHOL) rosuvastatin (CRESTOR)
Immunosuppressants (to prevent organ transplant rejection)	cyclosporine (SANDIMMUNE, NEORAL) tacrolimus (PROGRAF) sirolimus (RAPAMUNE) everolimus (AFINITOR)
Narcotic Analgesics (to treat opioid dependence)	buprenorphine/naloxone (SUBOXONE) fentanyl (ABSTRAL, DURAGESIC®) methadone meperidine oxycodone tramadol (DURELA, RALIVIA, TRAMACET®, TRIDURAL, ULTRAM®, ZYTRAM XL)
Neuroleptics (to treat psychotic disorders)	perphenazine risperidone (RISPERDAL®, RISPERDAL CONSTA®) quetiapine (SEROQUEL)
PDE-5 Inhibitors (to treat erectile dysfunction)	sildenafil (VIAGRA) vardenafil (LEVITRA) tadalafil (CIALIS)
Sedatives/Hypnotics (to treat trouble with sleeping and/or anxiety)	buspirone clorazepate diazepam (DIAZEMULS, VALIUM) midazolam (taken by injection) flurazepam (DALMANE, SOM-PAM) zolpidem
Antiemetics (to manage symtoms of upper gastrointestinal motility disorders)	domperidone
Urinary antispasmodics (to treat overactive bladder)	fesoterodine solifenacin

Tell your healthcare professional if you are taking any medicines that you obtained without a prescription.

This is **not** a complete list of medicines that you should tell your healthcare professional that you are taking. Know and keep track of all the medicines you take and have a list of them with you. Show this list to all your healthcare professionals any time you get a new medicine. Your healthcare professional can tell you if you can take these other medicines with PREZCOBIX®. Do not start any new medicines while you are taking PREZCOBIX® without first talking with your healthcare professional You can ask your healthcare professional for a list of medicines that can interact with PREZCOBIX®.

How to take PREZCOBIX®:

- Always use PREZCOBIX® exactly as your healthcare professional has told you. You must check with your healthcare professional if you are not sure.
- PREZCOBIX® tablets must be swallowed whole without breaking or crushing. Swallow with water if needed.
- If you have questions about when to take PREZCOBIX® your healthcare professional can help you decide which schedule works for you.
- **You should always take PREZCOBIX® with food.** The type of food is not important.
- Continue taking PREZCOBIX® unless your healthcare professional tells you to stop. Take the exact amount of PREZCOBIX® that your healthcare professional tells you to take, right from the very start. To help make sure you will benefit from PREZCOBIX®, you must not skip doses or interrupt therapy. If you don't take PREZCOBIX® as prescribed, the beneficial effects of PREZCOBIX® may be reduced or even lost.
- If you have also been prescribed enteric-coated didanosine as well as PREZCOBIX®, take didanosine at least 1 hour before or 2 hours after PREZCOBIX®

Usual dose:

Usual adult dose:

Take PREZCOBIX® tablets every day exactly as prescribed by your healthcare professional.

The dose of PREZCOBIX® is 1 tablet once a day (1 tablet containing 800 mg darunavir and 150 mg cobicistat).

Overdose:

If you think you, or a person you are caring for, have taken too much PREZCOBIX®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of PREZCOBIX® by more than 12 hours, wait and then take the next dose of PREZCOBIX® at the regularly scheduled time. If you miss a dose by less than 12 hours, take your missed dose of PREZCOBIX® immediately. Then take your next dose of PREZCOBIX® at the regularly scheduled time.

If a dose of PREZCOBIX® is skipped, do not double the next dose. Do not take more or less than your prescribed dose of PREZCOBIX® at any one time.

Do not stop using PREZCOBIX® without talking to your healthcare professional first.

What are possible side effects from using PREZCOBIX®?

These are not all the possible side effects you may have when taking PREZCOBIX®. If you experience any side effects not listed here, tell your healthcare professional.

Rash has been reported in 15.7% of patients receiving PREZCOBIX®. In patients taking PREZCOBIX® and raltegravir, rashes (generally mild or moderate) may occur more frequently than in patients taking either drug separately. Contact your healthcare professional immediately if you develop a rash. Your healthcare professional will advise you whether your symptoms can be managed on therapy or whether PREZCOBIX® should be stopped.

In some patients, severe or life-threatening rash has been reported. **If you develop a severe rash (e.g., blisters, peeling skin) which may be accompanied with symptoms such as fever, fatigue, swelling of the face or lymph glands, muscle aches and pain, and liver problems, immediately discontinue PREZCOBIX® and contact your healthcare professional.**

Other relevant severe side effects reported at an uncommon or rare frequency were inflammation of the liver or pancreas, increased blood fat levels, diabetes, and changes in body fat. Darunavir crystals may form in the kidney. These can cause kidney disease.

The most common side effects include diarrhea, nausea, headache, abdominal pain and vomiting.

Some side effects are typical for anti-HIV medicines in the same family as PREZCOBIX®. These are:

- high blood sugar (hyperglycemia) and diabetes. This can happen in patients taking PREZCOBIX® or other protease inhibitor medicines. Some patients have diabetes before starting treatment with PREZCOBIX®, which gets worse. Some patients get diabetes during treatment with PREZCOBIX®. Some patients will need changes in their diabetes medicine. Some patients may need new diabetes medicine.
- increased bleeding in patients with hemophilia (a disorder in which the blood cannot clot properly). This may happen in patients taking PREZCOBIX® as it has been reported with other protease inhibitor medicines.
- changes in body fat. These changes can happen in patients taking anti-HIV medicines. The changes may include an increased amount of fat in the upper back and neck, breast, and around the back, chest, and stomach area. 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
- increases in triglycerides and cholesterol (forms of fat that are found in your blood). Your healthcare professional may order blood testing for you.
- development of pancreatitis (inflammation of the pancreas) with symptoms such as abdominal pain, nausea, and vomiting. If you suffer these symptoms while taking PREZCOBIX®, contact your healthcare professional.
- changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and

begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body. These can include Grave's disease (which affects the thyroid gland), autoimmune hepatitis, Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles). It may develop at any time, sometimes months later after the start of HIV therapy. Sometimes symptoms can be severe. If you develop any of the following symptoms, tell your healthcare professional right away:

- high temperature (fever)
- joint or muscle pain
- redness, rash, swelling
- abdominal pain
- yellowing of the skin and eyes
- fatigue
- any new symptoms

Tell your healthcare professional promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM			
	Talk with your healthcare professional		Stop taking drug and get immediate medical help
Symptom / effect	Only if severe	In all cases	
Uncommon			
Severe and sometimes life-threatening rash: blisters and peeling skin which may be accompanied by fever, fatigue, swelling of the face or lymph glands, muscle aches and pain, and liver problems.			✓
Liver problems, disease or failure: yellowing of the skin or whites of the eyes, dark (tea coloured) urine, pale coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on right side below ribs.		✓	
Diabetes (high blood sugar)**:** excessive thirst, excessive urination, excessive eating, unexplained weight loss, poor wound healing, infections.		✓	
Pancreatitis (Inflammation of the pancreas)**:** abdominal pain, nausea, and vomiting.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of reach and sight of children.

Store PREZCOBIX® tablets in the original container, at room temperature between 15 to 30°C. Ask your healthcare professional if you have any questions about storing your tablets.

This medication is prescribed for your particular condition. Do not use it for any other condition or give it to anybody else. Keep PREZCOBIX® and all of your medicines out of the reach of children. If you suspect that more than the prescribed dose of this medicine has been taken, contact your local poison control centre or emergency room immediately.

This leaflet provides a summary of information about PREZCOBIX®. If you have any questions or concerns about either PREZCOBIX® or HIV, talk to your healthcare professional.

If you want more information about PREZCOBIX®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.janssen.com/canada, or by contacting the manufacturer at: 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by Janssen Inc., Toronto, Ontario, M3C 1L9.

Last Revised: March 3, 2023

Marketing Status in United States

Drug Databases (https://www.fda.gov/Drugs/InformationOnDrugs/)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Product Details for NDA 205395

PREZCOBIX (COBICISTAT; DARUNAVIR)
150MG;800MG
Marketing Status: Prescription

Active Ingredient: COBICISTAT; DARUNAVIR
Proprietary Name: PREZCOBIX
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 150MG;800MG
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N205395
Product Number: 001
Approval Date: Jan 29, 2015
Applicant Holder Full Name: JANSSEN PRODUCTS LP
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=205395&Appl_type=N)