เอกสารกำกับยาภาษาอังกฤษสำหรับแพทย์

FULL PRESCRIBING INFORMATION

1. Name of the Medicinal Product

1.1 Product Name

PREZCOBIX®

1.2 Strength

Darunavir 800 mg and cobicistat 150 mg

1.3 Pharmaceutical Dosage Form

Film-coated tablets.

2. Qualitative and Quantitative Composition

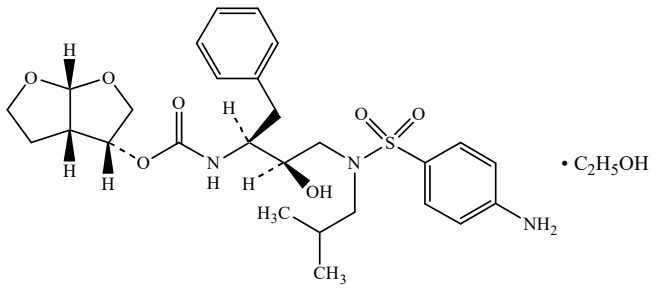
2.1 Qualitative Declaration

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.

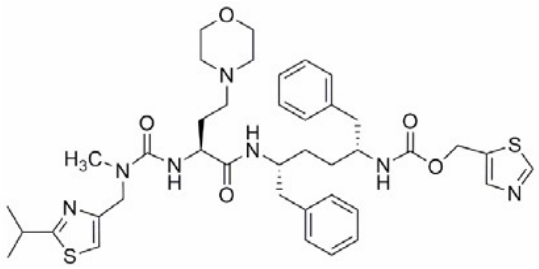
2.2 Quantitative Declaration

PREZCOBIX tablets are for oral administration. Each tablet contains darunavir ethanolate equivalent to 800 mg of darunavir and 150 mg of cobicistat.

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:



3. Pharmaceutical Form

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. Clinical Particulars

4.1 Therapeutic indication

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).

4.2 Posology and method of administration

4.2.1 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.

4.2.2 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 Special Warnings and Precautions for use (4.4.3)]*. When co-administering PREZCOBIX with tenofovir disoproxil fumarate (tenofovir DF) assess estimated creatinine clearance, urine glucose, and urine protein at baseline *[see Special Warnings and Precautions for use (4.4.4)]*.

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 Special Warnings and Precautions for use (4.4.4) and Undesirable effects (4.8.1)]*.

4.2.4 Not Recommended in Severe Hepatic Impairment

PREZCOBIX is not recommended for use in patients with severe hepatic impairment *[see Posology and method of administration (4.2.8) and Pharmacokinetic Properties (5.2)]*.

4.2.5 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 Pregnancy 4.6.1 and Pharmacokinetic Properties (5.2)]*.

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

4.2.6 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 Undesirable effects (4.8.1), Pharmacokinetic Properties (5.2) and Clinical Studies (5.3.2.2)]*.

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.

4.2.7 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 Pharmacokinetic Properties (5.2)]*.

4.2.8 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 Pharmacokinetic Properties (5.2)]*.

4.2.9 Renal Impairment

A renal impairment trial was not conducted for darunavir co-administered with cobicistat *[see Pharmacokinetic Properties (5.2)].* 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 Special Warnings and Precautions for use (4.4.3) and Pharmacodynamic Properties (5.1))]*.

4.3 Contraindication

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 Interaction with other medicinal products and other forms of interactions (4.5) and Pharmacokinetic Properties (5.2)] 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
- GI motility agent: cisapride
- 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

4.4 Special warning and precautions for use

4.4.1 Hepatotoxicity

During the darunavir clinical development program (N=3063), where darunavir was co-administered with ritonavir 100 mg once or twice daily, drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) was reported in 0.5% of subjects. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse reactions.

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

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

Evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on PREZCOBIX should prompt consideration of interruption or discontinuation of treatment.

4.4.2 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

4.4.3 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 Posology and Method of Administration (4.2.2)]*. Dosage recommendations are not available for drugs that require dosage adjustments in PREZCOBIX-treated patients with renal impairment *[see Interaction with other medicinal products and other forms of interactions (4.5.3) and Pharmacodynamic Properties (5.1)]*. 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.

4.4.4 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 Posology and Method of Administration (4.2.3)]*.

- Document urine glucose and urine protein at baseline *[see Posology and Method of Administration (4.2.2)]* 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.

4.4.5 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 (4.3) and Interaction with other medicinal products and other forms of interactions (4.5)]*.

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 Interaction with other medicinal products and other forms of interactions (4.5) and Pharmacokinetic Properties (5.2)]*.

4.4.6 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 Interaction with other medicinal products and other forms of interactions (4.5)]*.

4.4.7 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.

4.4.8 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.

4.4.9 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.

4.4.10 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.

4.4.11 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.

4.5 Interaction with other medicinal products and other forms of interactions

4.5.1 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).

4.5.2 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).

4.5.3 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 (4.3)]*.

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.

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	
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.
	↔ posaconazole	
voriconazole	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.
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.
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. <u>Initiation of PREZCOBIX in patients on bosentan</u>: 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. <u>Switching from darunavir co-administered with ritonavir to PREZCOBIX in patients on bosentan</u>: Maintain bosentan dose.
Ergot derivatives: e.g. dihydroergotamine, ergotamine, methylergonovine	↑ ergot derivatives	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agent: cisapride	↑ cisapride	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Hepatitis C virus (HCV): <u>Direct-Acting Antivirals:</u> 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: drospirenone/ethinylestradiol	↑ drospirenone ↓ ethinylestradiol	Additional or alternative (non-hormonal) forms of contraception should be considered when estrogen-containing contraceptives are co-administered with PREZCOBIX *[see Females and Males Reproductive Potential (4.6.3)]*. For co-administration with drospirenone, clinical monitoring is

Other progestin/estrogen contraceptives	progestin: effects unknown estrogen: effects unknown	recommended due to the potential for hyperkalemia. No data are available to make recommendations on co-administration with other hormonal contraceptives.
Immunosuppressants: cyclosporine, sirolimus, tacrolimus	↑ immunosuppressants	These immunosuppressant agents are metabolized by CYP3A. Therapeutic drug monitoring is recommended with concomitant use
Immunosuppressant /neoplastic: everolimus irinotecan	↑ immunosuppressants	Co-administration of everolimus and PREZCOBIX is not recommended. Discontinue PREZCOBIX at least 1 week prior to starting irinotecan therapy. Do not administer PREZCOBIX with irinotecan unless there are no therapeutic alternatives.
Inhaled beta agonist: salmeterol	↑ salmeterol	Co-administration with salmeterol is not recommended and may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Lipid Modifying Agents **HMG-CoA reductase inhibitors:** lovastatin, simvastatin atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin	↑ lovastatin ↑ simvastatin ↑ atorvastatin ↑ fluvastatin ↑ pravastatin ↑ rosuvastatin pitavastatin: effect unknown	Co-administration is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis. For atorvastatin, fluvastatin, pitavastatin, pravastatin, and rosuvastatin, start with the lowest recommended dose and titrate while monitoring for safety (e.g. myopathy). Dosage recommendations with atorvastatin or rosuvastatin are as follows: • atorvastatin dosage should not exceed 20 mg/day • rosuvastatin dosage should not exceed 20 mg/day

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.
Phosphodiesterase PDE-5 inhibitors: e.g. avanafil, sildenafil, tadalafil, vardenafil	↑ PDE-5 inhibitors	Co-administration with avanafil is not recommended because a safe and effective avanafil dosage regimen has not been established. Co-administration with PDE-5 inhibitors may result in an increase in PDE-5 inhibitor-associated adverse reactions including hypotension, syncope, visual disturbances and priapism. Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH): Co-administration with sildenafil used for PAH is contraindicated due to potential for sildenafil

		associated adverse reactions (which include visual disturbances, hypotension, prolonged erection, and syncope). The following dose adjustments are recommended for use of tadalafil with PREZCOBIX: • *Initiation of tadalafil in patients taking PREZCOBIX*: In patients receiving PREZCOBIX for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. • *Initiation of PREZCOBIX in patients taking tadalafil*: Avoid use of tadalafil during the initiation of PREZCOBIX. Stop tadalafil at least 24 hours prior to starting PREZCOBIX. After at least one week following the initiation of PREZCOBIX, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. • *Patients switching from darunavir co-administered with ritonavir to PREZCOBIX*: Maintain tadalafil dose. Use of PDE-5 inhibitors for erectile dysfunction: Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE-5 inhibitor-associated adverse reactions.
Platelet aggregation inhibitor:		Co-administration of PREZCOBIX and ticagrelor is not recommended.
ticagrelor	↑ ticagrelor	
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.
<u>metabolized by CYP3A:</u> 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

4.5.4 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).

4.6 Pregnancy and lactation

4.6.1 Pregnancy

<u>Pregnancy Exposure Registry</u>

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to PREZCOBIX during pregnancy.

Risk Summary

PREZCOBIX is not recommended during pregnancy because of substantially lower exposures of darunavir and cobicistat during the second and third trimesters [*see Posology and method of administration (4.2.5)*]. 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 Pharmacokinetic properties(5.2)*].

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 Pharmacokinetic Properties (5.2)]*.

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 Pharmacokinetic Properties (5.2)]*.

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.

4.6.2 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.

4.6.3 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 Interaction with other medicinal products and other forms of interactions (4.5)].*

4.7 Effect on ability to drive and use machine

No trials on the effects of PREZCOBIX, darunavir, or cobicistat on the ability to drive or use machines have been performed. However, dizziness has been reported in some patients during treatment with regimens containing darunavir and should be borne in mind when considering a patient's ability to drive or operate machinery.

4.8 Undesirable effects

The following adverse reactions are discussed in other sections of the labeling:

- Hepatotoxicity *[see Special warning and precautions for use (4.4.1)]*
- Severe skin reactions *[see Special warning and precautions for use (4.4.2)]*
- Effects on serum creatinine *[see Special warning and precautions for use (4.4.3)]*
- New onset or worsening renal impairment when used with tenofovir DF *[see Special warning and precautions for use (4.4.4)]*
- Immune Reconstitution Syndrome *[see Special warning and precautions for use (4.4.10)]*

4.8.1 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 (5.3.2.2)]*.

4.8.2 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 Special Warnings and Precautions for use (4.4.2)]*.

4.9 Overdose

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

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Mechanism of Action

PREZCOBIX is a fixed-dose combination of an HIV-1 antiviral drug, darunavir and a CYP3A inhibitor, cobicistat *[see Microbiology (5.3)].*

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.

5.2 Pharmacokinetic Properties

The pharmacokinetics of darunavir co-administered with cobicistat (150 mg) have been evaluated in healthy adult subjects and in HIV-1 infected subjects.

Darunavir is primarily metabolized by CYP3A. Cobicistat inhibits CYP3A, thereby increasing the plasma concentrations of darunavir.

Under fed (535 total kcal, 171 kcal from fat, 268 kcal from carbohydrates, 96 kcal from protein) and fasted conditions in healthy subjects, the 90% confidence intervals when comparing darunavir exposure between PREZCOBIX and darunavir 800 mg co-administered with cobicistat 150 mg as single entities were within 80-125%.

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

Table 2: Population Pharmacokinetic Estimates of Darunavir as Darunavir 800 mg Co-administered with Ritonavir 100 mg Once Daily (Trial TMC114-C211, 48 Week Analysis and Trial TMC114-C229, 48 Week Analysis) and Darunavir 800 mg Co-administered with Cobicistat 150 mg Once Daily (Trial GS-US-216-130, 24 Week Analysis)

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

N=number of subjects with data

Absorption and Bioavailability

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

Effects of Food on Oral Absorption

When compared to fasted conditions, administration of PREZCOBIX to healthy adult subjects with a high-fat meal (965 total kcal: 129 kcal from protein, 236 kcal from carbohydrates and 600 kcal from fat) resulted in a 70% increase in $AUC_{(0\text{-}inf)}$ and a 127% increase in C_{max} for darunavir. Cobicistat exposures were not affected by food. PREZCOBIX should be taken with food.

Distribution

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

Cobicistat: Cobicistat is 97-98% bound to human plasma proteins and the mean blood–to-plasma ratio was approximately 0.5.

Metabolism

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

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

Elimination

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

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

Cobicistat: When single doses of the darunavir and cobicistat fixed-dose combination tablet were administered, the terminal elimination half-life of cobicistat was approximately 4 hours under fed conditions. With single dose administration of ^{14}C-cobicistat after multiple dosing of cobicistat for six days, the mean percent of the administered dose excreted in feces and urine was 86.2% and 8.2%, respectively.

Specific Populations

Hepatic Impairment

Darunavir: Darunavir is primarily metabolized by the liver. The steady-state pharmacokinetic parameters of darunavir were similar after multiple dose co-administration of darunavir 600 mg co-administered with ritonavir 100 mg twice daily to subjects with normal hepatic function (n=16), mild hepatic impairment (Child-Pugh Class A, n=8), and moderate hepatic impairment (Child-Pugh Class B, n=8). The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been evaluated *[see Posology and Method of Administration (4.2.8)].*

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 Posology and Method of Administration (4.2.8)].*

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 Posology and Method of Administration (4.2.9)].*

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 Posology and Method of Administration (4.2.9)].*

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 *Posology and Method of Administration (4.2.7)].*

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

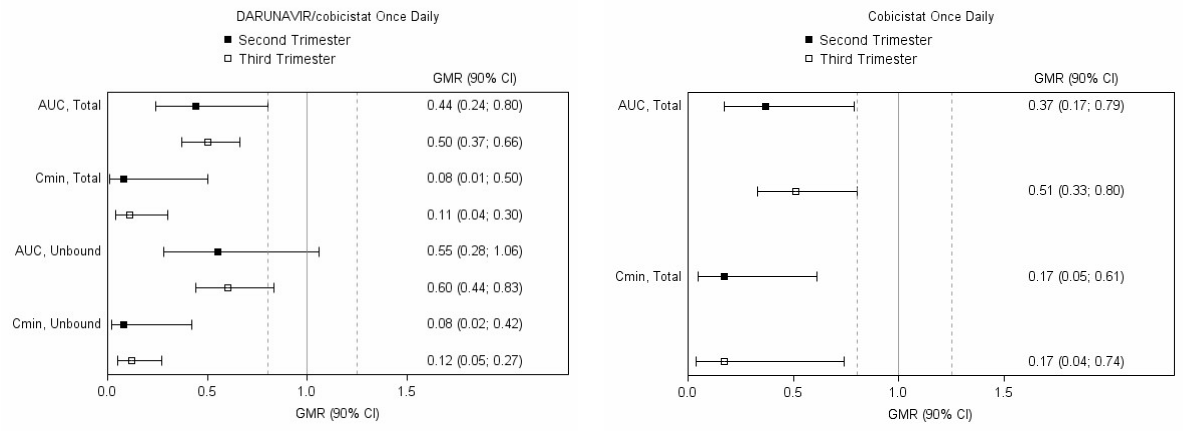
The exposure to total and unbound darunavir boosted with cobicistat after intake of PREZCOBIX as part of an antiretroviral regimen was substantially lower during the second and third trimesters of pregnancy compared with 6-12 weeks postpartum (see Table 4 and Figure 1).

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 Interaction with other medicinal products and other forms of interactions (4.5)]*.

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

Co-administered drug	Dose/Schedule		N	PK	LS Mean ratio (90% CI) of co-administered drug pharmacokinetic parameters with/without darunavir no effect =1.00		
	Co-administered drug	Darunavir/ cobicistat			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.

5.3 Preclinical Safety Data

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

5.3.1 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.

5.3.2 CLINICAL STUDIES

5.3.2.1 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].*

5.3.2.2 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/mm³ (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.

6. Pharmaceutical Particulars

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.

6.1 List of excipients

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.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

See expiry date on the outer pack.

6.4 Special precautions for storage

Do not store above 30°c.

Keep PREZCOBIX and all medicines out of reach of children.

6.5 Nature and contents of container

PREZCOBIX is packaged in bottles of 30 tablets.

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 Posology and Method of Administration (4.2.2)].*

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 Special Warnings and Precautions for use (4.4.1)]*.

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 Special Warnings and Precautions for use (4.4.2)]*.

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 Special Warnings and Precautions for use (4.4.4)]*.

Pregnancy

Advise patients that PREZCOBIX is not recommended during pregnancy and to alert their healthcare provider if they get pregnant while taking PREZCOBIX *[see Pregnancy (4.6.1)]*. Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant individuals exposed to PREZCOBIX *[see Pregnancy (4.6.1)].*

Lactation

Instruct individuals with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk *[see Lactation (4.6.2)]*.

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 Special Warnings and Precautions for use (4.4.10)]*.

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 Special Warnings and Precautions for use (4.4.9)]*.

7. Marketing Authorization Holder

Imported by

Janssen-Cilag Ltd., Bangkok, Thailand

To report Suspected Adverse Reactions, please contact us at aepqcjacth@its.jnj.com
For any product information, please contact us at medinfosea@its.jnj.com

8. Marketing Authorization Numbers and Date of Authorization

MANUFACTURED BY	MARKETING AUTHORIZATION NUMBER	DATE OF AUTHORIZATION
Janssen Ortho LLC Gurabo, Puerto Rico Packaged and released by Janssen Cilag S.p.A. Latina, Italy	2C 15119/64 (NC)	14-Dec-2021

9. Date of revision of the text

USPI version Mar-2023 and Effects on Ability to Drive and Use Machines CCDS version 04 Jul 2022

Please see full prescribing information at https://ndi.fda.moph.go.th