AUSTRALIAN PRODUCT INFORMATION

PREZCOBIX®

DARUNAVIR/COBICISTAT

FILM-COATED TABLETS

1. NAME OF THE MEDICINE

Darunavir/cobicistat

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PREZCOBIX 800/150 mg tablets contain 800 mg of darunavir (as 867.28 mg darunavir ethanolate) and 150 mg of cobicistat.

For a full list of excipients, see **section 6.1** List of excipients.

3. PHARMACEUTICAL FORM

PREZCOBIX 800/150 mg film-coated tablet: Pink oval-shaped tablet, debossed with “800” on one side and “TG” on the opposite side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PREZCOBIX, a fixed dose combination of darunavir and cobicistat, is indicated in combination with other antiretroviral agents for the treatment of adult patients with human immunodeficiency virus-1 (HIV-1) infection in:

- Antiretroviral treatment-naive patients
- Antiretroviral treatment-experienced patients with no darunavir resistance associated mutations and who have plasma HIV-1 RNA <100,000 copies/mL
- Antiretroviral treatment-experienced but HIV protease inhibitor-naive patients for whom HIV-1 genotype testing is unavailable (see **section 4.2** Dose and method of administration)

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose in adults

The recommended dose regimen is PREZCOBIX one tablet taken once daily with food. The type of food does not affect the exposure to PREZCOBIX.

For antiretroviral treatment-experienced patients* HIV-1 genotype testing is recommended.

*Darunavir resistance associated mutations: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V.

When HIV genotypic testing is not feasible:

- PREZISTA(darunavir) should be used for protease inhibitor-experienced patients. Refer to PREZISTA Product Information for dosing recommendations.
- PREZCOBIX can be used in protease inhibitor naïve patients

Dose in paediatric patients (17 years of age and younger)

The safety and efficacy of PREZCOBIX have not been established in paediatric patients.

Dose in elderly (65 years of age and older)

Limited information is available on the use of PREZCOBIX in patients 65 and older. Therefore PREZCOBIX should be used with caution in this age group (see **section 5.2** Pharmacokinetic properties).

Method of administration

PREZCOBIX consists of the HIV protease inhibitor darunavir and the pharmacokinetic enhancer cobicistat. PREZCOBIX should be swallowed whole without breaking or crushing to ensure administration of the entire dose.

After therapy with PREZCOBIX has been initiated, patients should not alter the dosage or discontinue therapy without instruction of their physician. 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. Please refer to the respective Product Information for proper use of the products.

PREZCOBIX must be taken with food. The type of food does not affect the exposure to PREZCOBIX (see **section 5.2** Pharmacokinetic properties).

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.

Dosage adjustment

Hepatic insufficiency

There are no pharmacokinetic data obtained with PREZCOBIX in patients with hepatic impairment. However, there are pharmacokinetic data for the single agents of PREZCOBIX, darunavir and cobicistat.

Darunavir and cobicistat are metabolised by the liver. Studies with darunavir/ritonavir and with cobicistat single agent suggest no dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

There are no data regarding the use of darunavir and/or cobicistat with severe hepatic impairment, therefore, specific dosage recommendations cannot be made. PREZCOBIX should be used with caution in patients with severe hepatic impairment (**section 4.4** Special warnings and precautions for use and **section 5.2** Pharmacokinetic properties).

Renal insufficiency

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 **section 4.4** Special warnings and precautions for use, **section 4.8** Adverse effects (Undesirable effects), **section 5.1** Pharmacodynamic properties, Pharmacodynamic effects and **section 5.2** Pharmacokinetic properties).

Pregnancy and postpartum

Treatment with PREZCOBIX during pregnancy results in low darunavir exposure (see **section 5.2** Pharmacokinetic properties). Therefore, 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 (**section 4.4** Special warnings and precautions for use). Darunavir/ritonavir may be considered as an alternative.

4.3 CONTRAINDICATIONS

Hypersensitivity to darunavir, cobicistat or to any of the excipients.

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). Examples include alfuzosin, astemizole, apixaban, cisapride, colchicine (in patients with renal and/or hepatic impairment), dapoxetine, dronedarone, elbasvir/grazoprevir, ivabradine, lomitapide, lovastatin, lurasidone, oral midazolam, naloxegol, pimozide, ranolazine, ergot alkaloids (e.g., dihydroergotamine, ergotamine, ergonovine and methylergonovine), sildenafil (when used for treatment of pulmonary arterial hypertension), simvastatin, terfenadine, and triazolam and antiarrhythmic drugs (e.g. amiodarone, bepridil, flecainide, systemic lidocaine, quinidine) (see **section 4.5** Interactions with other medicines and other forms of interactions).

Darunavir and cobicistat are both substances 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. Patients taking PREZCOBIX should not use products containing potent CYP3A inducers such as carbamazepine, phenobarbital, phenytoin, rifampin or St. John's wort (see **section 4.5** Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients should be advised that current antiretroviral therapy does not cure HIV. Reduction in the risk of sexual transmission is dependant on effective viral suppression. Appropriate precautions to prevent sexual and bloodborne transmission of HIV should continue to be employed.

Severe skin reactions

During the darunavir clinical development program (N=3063), where darunavir was co-administered with low-dose ritonavir, severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported in 0.4% of patients. Stevens Johnson Syndrome has been rarely (< 0.1%) reported; and during post-marketing experience toxic epidermal necrolysis, Drug reaction 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 severity grades, regardless of causality) occurred in 10.3% of patients treated with darunavir/ritonavir (see **section 4.8** Adverse effects (Undesirable effects)). 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 subjects 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.

Darunavir contains a sulfonamide moiety. PREZCOBIX should be used with caution in patients with a known sulfonamide allergy. In clinical studies with darunavir/ritonavir, the incidence and severity of rash was similar in patients with or without a history of sulfonamide allergy.

Immune reconstitution inflammatory syndrome

In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders such as Graves' disease 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 treatment (see **section 4.8** Adverse effects (Undesirable effects)).

Metabolic disorders

Diabetes mellitus/hyperglycaemia

New onset diabetes mellitus, hyperglycemia, or exacerbation of existing diabetes mellitus has been reported in patients receiving antiretroviral therapy, including HIV PIs. In some of these patients the hyperglycemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycemia.

Consideration should be given to measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see **section 4.8** Adverse effects (Undesirable effects)).

Interactions with medicinal products

See section 4.3 Contraindications and section 4.5 Interactions with other medicines and other forms of interactions.

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 section 4.5 Interactions with other medicines and other forms of interactions).

PREZCOBIX should not be used in combination with another antiretroviral that requires pharmacokinetic boosting. PREZCOBIX should not be used concurrently with products or regimens containing darunavir, ritonavir or cobicistat.

Patients with co-existing conditions

Haemophiliac patients

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis in patients with haemophilia type A and B treated with HIV protease inhibitors (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 has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Patients with hepatic impairment

There are no pharmacokinetic data obtained with PREZCOBIX in patients with hepatic impairment. However, there are pharmacokinetic data for the single agents of PREZCOBIX, darunavir and cobicistat. PREZCOBIX should be used with caution in patients with severe hepatic impairment.

Data demonstrated that the steady state pharmacokinetic parameters of darunavir co-administered with low-dose ritonavir in subjects with mild and moderate hepatic impairment were comparable with those in healthy subjects. No clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with moderate hepatic impairment (Child-Pugh Class B) and healthy subjects. No dose adjustment for PREZCOBIX is required in patients with mild or moderate hepatic impairment (see **section 5.2** Pharmacokinetic properties and **section 4.2** Dose and method of administration).

Hepatotoxicity

Drug induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with darunavir/ritonavir. During the darunavir clinical development program (N=3063), hepatitis was reported in 0.5% of patients receiving combination therapy with darunavir/ritonavir. 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 events.

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.

Patients with renal impairment

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 haemodialysis or peritoneal dialysis. (see **section 5.2** Pharmacokinetic properties and **section 4.2** Dose and method of administration).

Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function (see also **section 5.1** Pharmacodynamic effects on serum creatinine, and Product Information for cobicistat). 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 PREZCOBIX is co-administered with a drug that has dosing adjustment recommendations guided by estimated creatinine clearance.

Use in the elderly

As limited information is available on the use of PREZCOBIX in patients aged 65 and over, caution should be exercised in the administration of PREZCOBIX in elderly patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy (see **section 5.2** Pharmacokinetic properties).

Paediatric use

The safety and efficacy of PREZCOBIX in paediatric patients have not been established.

Effects on laboratory tests

None known.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

PREZCOBIX contains darunavir and cobicistat, and interactions that have been identified either with darunavir (in combination with cobicistat or low-dose ritonavir) or with cobicistat determine the interactions that may occur with PREZCOBIX.

Darunavir and cobicistat are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to lower plasma concentrations of darunavir and cobicistat, which could potentially lead to loss of efficacy of darunavir and possible development of resistance (see **section 4.3** Contraindications). Co-administration of PREZCOBIX and other drugs 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. PREZCOBIX should not be used concurrently with products or regimens containing darunavir, ritonavir or cobicistat.

Darunavir is an inhibitor of CYP3A, a weak inhibitor of CYP2D6, and an inhibitor of P-gp. Cobicistat is an inhibitor of CYP3A and CYP2D6. Cobicistat inhibits the transporters p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. 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). Co-administration of PREZCOBIX and medicinal products primarily metabolized by CYP3A and/or CYP2D6 may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect and can be associated with serious and/or life threatening adverse events (see **section 4.3** Contraindications). 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.

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.

For additional drug-drug interactions with darunavir or cobicistat, consult their respective Product Information when using PREZCOBIX.

The below list of examples of drug-drug interactions is not comprehensive and therefore the Product Information 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.

Table 1: Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

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	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.
emtricitabine/tenofovir alafenamide	↔ darunavir ↔ tenofovir alafenamide ↑ tenofovir	Tenofovir exposure is increased when PREZCOBIX is used in combination with emtricitabine/tenofovir alafenamide. The recommended dose of emtricitabine/tenofovir alafenamide when used in combination with PREZCOBIX is 200/10 mg daily.
Other NRTIs: abacavir, emtricitabine, lamivudine, stavudine, zalcitabine, zidovudine	↔ darunavir	Based on the different elimination pathways of the other NRTIs, which are primarily renally excreted, no drug interactions are expected for these medicinal products and PREZCOBIX

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, cobicistat or Concomitant Drug	Clinical Comment
HIV-1-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 doses of PREZCOBIX and delavirdine have not been established. The combination of PREZCOBIX and delavirdine is not recommended.
efavirenz, etravirine, nevirapine	↓ darunavir ↓ cobicistat ↑ nevirapine	Co-administration of PREZCOBIX with these NNRTIs 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 these NNRTIs is not recommended. The recommendation is different from ritonavir-boosted darunavir. Consult the local Product Information for darunavir 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-1-Antiviral Agents: CCR5 co-receptor antagonists		
maraviroc	↑ maraviroc ↔ darunavir	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.
HIV-1-Antiviral Agents: Integrase strand transfer Inhibitors		

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, cobicistat or Concomitant Drug	Clinical Comment
dolutegravir	↔ darunavir ↔ cobicistat	Ritonavir-boosted darunavir did not impact dolutegravir pharmacokinetics 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 co-administered with dolutegravir can be used without dose adjustment.
raltegravir	↓ darunavir	Some clinical studies suggest raltegravir may cause a modest decrease in darunavir concentrations (mechanism unknown). At present the effect of raltegravir on darunavir concentrations does not appear to be clinically relevant. PREZCOBIX and raltegravir can be used without dose adjustments.
Other Agents		
Alpha 1- adrenoreceptor antagonist alfuzosin	↑ alfuzosin	Alfuzosin is primarily metabolized by CYP3A. Co-administration with PREZCOBIX may result in increased plasma concentrations of alfuzosin, which is associated with the potential for serious and/or life-threatening reactions. Co-administration of PREZCOBIX and alfuzosin is contraindicated.
Antacids: aluminium/magnesium hydroxide, calcium carbonate	↔ darunavir ↔ cobicistat	PREZCOBIX and antacids can be used concomitantly without dose adjustment.
Antiarrhythmics/ anti-anginals: amiodarone, bepridil, disopyramide dronedarone, flecainide, ivabradine, lidocaine (systemic), mexiletine, propafenone, quinidine ranolazine	↑ antiarrhythmics/anti-anginals	Co-administration of PREZCOBIX with these antiarrhythmics may increase concentrations of the antiarrhythmic (inhibition of CYP3A and/or CYP2D6). Concomitant use of these antiarrhythmics/anti-anginals and PREZCOBIX is contraindicated.

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, cobicistat or Concomitant Drug	Clinical Comment
digoxin	↑ digoxin	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.
Antibacterials (ketolide or macrolide antibiotics) clarithromycin, erythromycin, telithromycin	↔ darunavir ↑ cobicistat ↑ antibacterial	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 Product Information for clarithromycin for the recommended dosage.
Anticancer agents: dasatinib, nilotinib, vinblastine, vincristine	↑ 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 co-administering PREZCOBIX with these anticancer agents.
everolimus, irinotecan		Concomitant use of everolimus or irinotecan and PREZCOBIX is not recommended.

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, cobicistat or Concomitant Drug	Clinical Comment
Anticoagulants: Direct Oral Anticoagulants (DOACs):	↑ DOACs	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.
apixaban, rivaroxaban		Co-administration of a DOAC affected by both P-gp and CYP3A4, including rivaroxaban, is not recommended with PREZCOBIX. Co-administration of apixaban with PREZCOBIX is contraindicated.
dabigatran etexilate, edoxaban	↑ dabigatran	The results of a drug-drug interaction study between darunavir/cobicistat 800/150 mg and dabigatran etexilate 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 Cmax after single dosing of darunavir/cobicistat and a 2.0-fold increase in dabigatran plasma Cmax after repeated dosing of darunavir/cobicistat. Clinical monitoring is required when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate and edoxaban, is co-administered with PREZCOBIX. A dose reduction of the DOAC may be needed.
warfarin	effect on warfarin unknown	Co-administration of PREZCOBIX with warfarin may affect warfarin concentrations. When PREZCOBIX is co-administered with warfarin, the international normalized ratio (INR) should be monitored and used for titration of warfarin dose to obtain the desired clinical effect.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ darunavir ↓ cobicistat	Carbamazepine, a potent CYP3A inducer, decreases cobicistat plasma concentrations and that of darunavir, which may result in loss of therapeutic effect and development of resistance. Co-administration of PREZCOBIX with carbamazepine, phenobarbital, or phenytoin is contraindicated.

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, cobicistat or Concomitant Drug	Clinical Comment
oxcarbazepine		Co-administration of PREZCOBIX with oxcarbazepine may decrease darunavir and/or cobicistat concentrations (induction of CYP3A), which may result in loss of therapeutic effect and development of resistance. Co-administration PREZCOBIX with oxcarbazepine is not recommended. Alternative anticonvulsants should be considered.
clonazepam,	↑ clonazepam	Co-administration of PREZCOBIX with this anticonvulsant may increase concentrations of the anticonvulsant (inhibition of CYP3A). Clinical monitoring is recommended when co-administering PREZCOBIX with this anticonvulsant.
Antidepressants: desipramine, paroxetine, sertraline, trazodone, amitriptyline, imipramine, nortriptyline	↔ darunavir ↓ sertraline ↓ paroxetine ↑ amitriptyline ↑ desipramine ↑ imipramine ↑ nortriptyline ↑ trazodone	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.
Antiemetics: domperidone	↑ domperidone	Use with caution: monitor for domperidone adverse reactions.
Antifungals: clotrimazole, fluconazole, isavuconazole, itraconazole, ketoconazole,	↑ 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 co-administering PREZCOBIX with these antifungals. When used in combination with PREZCOBIX, the dose of itraconazole or ketoconazole should not exceed 200 mg per day.
posaconazole		Clinical monitoring is recommended when co-administering PREZCOBIX with posaconazole.
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 Examples	Effect on Concentration of Darunavir, cobicistat or Concomitant Drug	Clinical Comment
Anti-gout: colchicine	↑ colchicine	Concomitant use of colchicine and PREZCOBIX may increase the exposure to colchicine. The following dose adjustments are recommended for colchicine. For the treatment of gout-flares in patients on PREZCOBIX, the recommended dose of colchicine is 0.6 mg, followed by 0.3 mg 1 hour later. Treatment course to be repeated no earlier than 3 days. For the prophylaxis of gout-flares in patients on PREZCOBIX, the recommended dose of colchicine is 0.3 mg q.d. or q.o.d. For the treatment of familial Mediterranean fever in patients on PREZCOBIX, the maximum dose of colchicine is 0.6 mg q.d. (may be given as 0.3 mg b.i.d.). Patients should be monitored for clinical symptoms of colchicine toxicity. Co-administration of PREZCOBIX with colchicine in patients with renal or hepatic impairment is contraindicated.
Antihistamines: astemizole, terfenadine	↑ astemizole ↑ terfenadine	Exposure to these antihistamines may be increased when co-administered with PREZCOBIX. Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimalarial: artemether/lumefantrine	↔ darunavir ↑ artemether ↑ lumefantrine	Co-administration of PREZCOBIX with artemether/lumefantrine may increase concentrations of artemether and lumefantrine (inhibition of CYP3A). The combination of PREZCOBIX and artemether/lumefantrine can be used without dose adjustments; however, due to the expected increase in lumefantrine exposure, the combination should be used with caution.

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, cobicistat or Concomitant Drug	Clinical Comment
Antimycobacterial: rifabutin, rifampin, rifapentine	↓ darunavir ↓ cobicistat ↑ rifabutin	Co-administration of PREZCOBIX with rifabutin, rifampin, or rifapentine 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 rifampin is contraindicated. Rifabutin concentrations may be increased when co-administered with PREZCOBIX. Co-administration of PREZCOBIX with rifabutin and rifapentine is not recommended. If combination of rifabutin and PREZCOBIX is required, the recommended dose of rifabutin is 150 mg every other day. Clinical monitoring is recommended when co-administering PREZCOBIX with rifabutin. This recommendation is different from ritonavir-boosted darunavir. Consult the darunavir Product Information for further details.
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. Coadministration of PREZCOBIX with clopidogrel is not recommended.
prasugrel	↔prasugrel active metabolite	PREZCOBIX is not expected to have a clinically relevant effect on plasma concentrations of the active metabolite of prasugrel.
β-blockers: carvedilol, metoprolol, timolol	↑ beta-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.

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, cobicistat or Concomitant Drug	Clinical Comment
Calcium channel blockers: amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil	↑ calcium channel blockers	Co-administration of PREZCOBIX with calcium channel blockers may increase concentrations of the calcium channel blocker (inhibition of CYP3A). Clinical monitoring is recommended when co-administering PREZCOBIX with calcium channel blockers.
Contraceptives:		
drospirenone/ethinyl oestradiol	↑ drospirenone ↓ ethinyl oestradiol	When PREZCOBIX is co-administered with a drospirenone-containing product, clinical monitoring is recommended due to the potential for hyperkalemia.
norgestimate/ethinyl estradiol	↓ or ↑ ethinyl oestradiol	No data are available to make recommendations on the use of PREZCOBIX with other hormonal contraceptives. Therefore, additional or alternative methods of contraception are recommended.
norethindrone/ethinyl oestradiol	↓ norethindrone (based on theoretical considerations)	
Corticosteroid: dexamethasone (systemic),	↓ darunavir ↓ cobicistat	Co-administration of PREZCOBIX with systemic dexamethasone may decrease darunavir and/or cobicistat concentrations (induction of CYP3A) which may result in loss of therapeutic effect of and development of resistance. Co-administration of PREZCOBIX with (systemic) dexamethasone is not recommended.
Corticosteroids primarily metabolized by CYP3A4: betamethasone, budesonide, mometasone, fluticasone, prednisone, triamcinolone	↑ corticosteroid	Corticosteroid concentrations may be increased when co-administered 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. 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.

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, cobicistat or Concomitant Drug	Clinical Comment
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. Co-administration of bosentan with PREZCOBIX may lead to decreased cobicistat plasma concentrations and consequently that if atazanavir or darunavir, which may result in loss of therapeutic effect and development of resistance. Co-administration is not recommended.
Ergot alkaloids: dihydroergotamine, ergonovine, ergotamine, methylergonovine	↑ ergot derivatives	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. Exposure to the ergot alkaloids may be increased when co-administered with PREZCOBIX Concomitant use of PREZCOBIX with ergot alkaloids is contraindicated.
Eugeroics armodafinil, modafinil	↓ darunavir ↓ cobicistat	Co-administration of PREZCOBIX with armodafanil or 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 armodafanil or modafinil is not recommended.
GI motility agents: cisapride	↑ cisapride	Cisapride is primarily metabolized by CYP3A. Co-administration with PREZCOBIX may result in increased plasma concentrations of cisapride, which is associated with the potential for serious and/or life-threatening reactions. Co-administration of PREZCOBIX and cisapride is contraindicated.
H_2-receptor antagonists: cimetidine, famotidine, nizatidine, ranitidine	↔ 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 without dose adjustment.

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, cobicistat or Concomitant Drug	Clinical Comment
Herbal products: St. John's wort (*Hypericum perforatum*)	↓ darunavir ↓ cobicistat	Co-administration of St John's wort a potent CYP3A inducer, may significantly decrease cobicistat plasma concentrations and consequently that of darunavir, which may result in loss of therapeutic effect and development of resistance. Co-administration of PREZCOBIX with products containing St John's wort (Hypericum perforatum) is contraindicated.
Hepatitis C Virus (HCV) direct-acting agents: **NS3-4A protease inhibitors:** boceprevir, telaprevir,	↓ darunavir ↓ boceprevir ↓ telaprevir	Concomitant administration of PREZCOBIX with boceprevir or telaprevir may decrease darunavir, boceprevir and/or telaprevir concentrations (mechanism unknown). Co-administration of PREZCOBIX with boceprevir or telaprevir is not recommended.
elbasvir/grazoprevir,	↑ grazoprevir	Concomitant use of elbasvir/grazoprevir and PREZCOBIX may increase the exposure to grazoprevir (inhibition of OATPB1 and CYP3A). Concomitant use of PREZCOBIX with elbasvir/grazoprevir is contraindicated.
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.
HMG-CoA reductase inhibitors: atorvastatin, pitavastatin, pravastatin, rosuvastatin, lovastatin, simvastatin	↑ 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. Co-administration of PREZCOBIX with lovastatin or simvastatin is contraindicated. 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. 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.

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, cobicistat or Concomitant Drug	Clinical Comment
Other lipid modifying agents: lomitapide	↑ lomitapide	PREZCOBIX is expected to increase the exposure of lomitapide when co-administered. Co-administration is contraindicated.
Immunosuppressants: cyclosporine, everolimus, rapamycin, sirolimus, tacrolimus	↑ immunosuppressants	Co-administration of PREZCOBIX and these immunosuppressants may increase concentrations of the immunosuppressants (inhibition of CYP3A). Caution is warranted and therapeutic concentration monitoring is recommended for the immunosuppressant when co-administered with PREZCOBIX. Concomitant use of everolimus and PREZCOBIX is not recommended.
Inhaled beta agonist: salmeterol	↑ salmeterol	Co-administration of PREZCOBIX with salmeterol may increase concentrations of salmeterol (inhibition of CYP3A). The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Co-administration of PREZCOBIX with salmeterol is not recommended.
Narcotic analgesics: fentanyl, oxycodone, tramadol	↑ analgesic	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.
Narcotic analgesic/ treatment of opioid dependence: buprenorphine, buprenorphine/naloxone, naloxone, methadone	↔ buprenorphine ↑ norbuprenorphine ↔ naloxone ↓ methadone	No a priori 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.
Antipsychotics/ neuroleptics: lurasidone, perphenazine, pimozide, risperidone, thioridazine, quetiapine	↑ neuroleptics	Co-administration of PREZCOBIX and these neuroleptics may increase concentrations of the neuroleptic (inhibition of CYP3A or CYP2D6). Concomitant use of PREZCOBIX with lurasidone and pimozide is contraindicated due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, cobicistat or Concomitant Drug	Clinical Comment
		Concomitant use of quetiapine and PREZCOBIX may increase the exposure to quetiapine (inhibition of CYP3A). The quetiapine dose should be substantially reduced when co-administered with PREZCOBIX. For details, refer to the quetiapine Product Information. Clinical monitoring is recommended when co-administering PREZCOBIX with these neuroleptics and a lower dose of the neuroleptic should be considered.
Opioid antagonist: naloxegol	↑ naloxegol	Co-administration of PREZCOBIX and naloxegol is contraindicated.
Phosphodiesterase PDE-5 inhibitors: avanafil, sildenafil, tadalafil, vardenafil	↑ PDE-5 inhibitors	Co-administration of PREZCOBIX and PDE-5 inhibitors may increase concentrations of the PDE-5 inhibitor (inhibition of CYP3A), which may lead to adverse events such as hypotension, syncope, visual disturbances and priapism. *Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH):* • Co-administration of PREZCOBIX with sildenafil is contraindicated [see **section 4.3** Contraindications]. • The following dose adjustments are recommended for use of tadalafil with PREZCOBIX: • *Co-administration of tadalafil in patients on 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. Co-administration of PREZCOBIX in patients on 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. *Use of PDE-5 inhibitors for erectile dysfunction:*

Concomitant Drug Class: Drug Name Examples	Effect on Concentration of Darunavir, cobicistat or Concomitant Drug	Clinical Comment
		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 events. Co-administration of PREZCOBIX and avanafil is not recommended
Platelet aggregation inhibitors: ticagrelor	↑ ticagrelor	Co-administration of PREZCOBIX with ticagrelor may increase concentrations of ticagrelor (inhibition of CYP3A and/or P-glycoprotein). Co-administration of PREZCOBIX and ticagrelor is not recommended.
Proton pump inhibitors: esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	↔ darunavir ↔ cobicistat	PREZCOBIX and proton pump inhibitors can be co-administered without dose adjustment.
Sedatives/hypnotics: buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem	↑ sedatives/hypnotics	Co-administration of PREZCOBIX with these sedatives/hypnotics may increase concentrations of the benzodiazepine (inhibition of CYP3A). Co-administration of PREZCOBIX with oral midazolam or triazolam is contraindicated. 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. Clinical monitoring is recommended when co-administering PREZCOBIX with the other sedatives/hypnotics listed and a lower dose of the sedatives/hypnotics should be considered.
Treatment of premature ejaculation: dapoxetine	↑ dapoxetine	Co-administration of PREZCOBIX with dapoxetine is contraindicated.
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.

Other HIV protease inhibitors:

The concomitant administration of darunavir/ritonavir and HIV PIs other than lopinavir/ritonavir, saquinavir, atazanavir, and indinavir has not been studied. Therefore, such concomitant administration is not recommended.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no effect on mating or fertility with darunavir or cobicistat treatment in rats. No effect on mating or fertility is expected with PREZCOBIX.

Darunavir: In a study conducted in rats, there were no effects on mating with darunavir treatment up to 1000 mg/kg/day, but exposure levels were below (AUC -0.5 fold) that in humans at the clinically recommended dose. The number of corporea lutea and hence the number of live young was lower for females at 1000 mg/kg/day darunavir, and correlated with lower maternal body weight; the NOEL for effects on fertility was 200 mg/kg/day darunavir (corresponding to an exposure level 0.3 – fold that in humans at the recommended clinical dose).

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.

Use in pregnancy

Category B2

There are no adequate and well-controlled studies of PREZCOBIX, darunavir, or cobicistat in pregnant women.

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 and cobicistat was substantially lower during pregnancy compared with postpartum (see **section 5.2** Pharmacokinetic properties). Virologic response was sustained throughout the study period in 5 out of 6 women who completed the study; the subject with virologic failure was not compliant with study medication.

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 **section 4.2** Dosage and method of administration). Darunavir/ritonavir may be considered as an alternative.

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.

Use in lactation

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 breastfeed if they are receiving PREZCOBIX.

In a pre and postnatal development assessment in rats, darunavir with and without ritonavir, caused a transient reduction in body weight 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.

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. Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, darunavir /ritonavir should not be used in paediatric patients below 3 years of age.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

A causal relationship with darunavir/cobicistat cannot be reliably established in individual cases. Further, 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.

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.

Adverse Drug Reactions (ADRs) to darunavir/ritonavir or to cobicistat are considered ADRs to PREZCOBIX unless otherwise specified.

Adverse 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 median exposure in 313 patients treated with darunavir/cobicistat was 64.3 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 2-4) 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 2-4 severity reported in GS-US-216-0130, considered ADRs to PREZCOBIX are presented in Table 2 below*:

Table 2: Adverse Drug Reactions at least Grade 2 Severity in GS-US-216-0130 - Week 48 Analyses

System Organ Class **Adverse Drug Reaction**	**GS-US-216-0130** **darunavir/cobicistat** **800 mg/150 mg q.d. + OBR** **N=313**
Gastrointestinal Disorders	
Abdominal Pain	1.3%
Diarrhea	5.4%
Dyspepsia	0.3%
Flatulence	1.0%
Nausea	3.5%
Vomiting	1.9%

Table 2: Adverse Drug Reactions at least Grade 2 Severity in GS-US-216-0130 - Week 48 Analyses	
System Organ Class **Adverse Drug Reaction**	**GS-US-216-0130** **darunavir/cobicistat** **800 mg/150 mg q.d. + OBR** **N=313**
General Disorders and Administration Site Conditions	
Fatigue	0.6%
Immune System Disorders	
(Drug) Hypersensitivity	1.9%
Immune Reconstitution Inflammatory Syndrome	0.3%
Metabolism and Nutrition Disorders	
Diabetes Mellitus	0.6%
Musculoskeletal and Connective Tissue Disorders	
Myalgia	0.6%
Nervous System Disorders	
Headache	2.9%
Psychiatric Disorders	
Abnormal Dreams	0.3%
Skin and Subcutaneous Tissue Disorders	
Rash	5.4%
Pruritus	0.6%

N=total number of subjects with data

Laboratory abnormalities, Grade 2-4, reported in GS-US-216-0130 and considered ADRs are shown in the table below*:

Table 3: Laboratory abnormalities, Grade 2-4, considered ADRs in GS-US-216-0130 Week 48 Analysis		
Laboratory parameter n (%)*	**Limit**	**GS-US-216-0130** **darunavir/cobicistat** **800 mg/150 mg q.d. + OBR** **N=313**
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	6.19 to 7.77 mmol/L	10.6%
Grade 3	> 7.77 mmol/L	1.0%
Glucose		
Grade 2	13.89 to < 27.75 mmol/L	6.5%
LDL Cholesterol		
Grade 2	4.12 to < 4.90 mmol/L	10.9%
Grade 3	≥ 4.90 mmol/L	4.8%
Triglycerides		
Grade 2	5.64 to 8.47 mmol/L	1.4%
Grade 3	> 8.47 to 13.55 mmol/L	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%

Alkaline Phosphatase		
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
*The number of subjects with data can vary per laboratory parameter, but the % reflects the true percentage of observed abnormalities.

In the Phase 3 single-arm trial (GS-US-216-0130), a decrease in the estimated glomerular filtration rate, as estimated by the Cockcroft-Gault formula (eGFRCG), was noted at Week 2, which remained stable through Week 48. The mean eGFRCG change from baseline was –9.6 mL/min at Week 2, and –11.5 mL/min at Week 24, and -9.6 mL/min at Week 48.

In addition to trial GS-US-216-0130, the safety of darunavir in combination with cobicistat has been evaluated in the control arm (darunavir/cobicistat fixed-dose combination + emtricitabine [FTC]/tenofovir disoproxil fumarate [TDF]) of the Phase 3 trial TMC114FD2HTX3001 (AMBER) in treatment-naïve subjects over 48 weeks. The safety results of the AMBER trial were generally similar to the results in trial GS-US-216-0130.

Adverse drug reactions in trials with darunavir/ritonavir 800/100 mg q.d.

Adverse drug reactions Grade 2-4 reported in the ARTEMIS trial (192 weeks) using darunavir/ritonavir 800/100 mg q.d. and considered ADRs to PREZCOBIX are presented in Table 4 below*:

Table 4: Adverse Drug Reactions at Least Grade 2 reported in ARTEMIS (192 weeks)		
System Organ Class Adverse Drug Reaction	**darunavir/ritonavir 800/100 mg q.d. + TDF/FTC#** N=343	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC#** N=346
Nervous system disorders		
Headache	6.7%	5.5%
Gastrointestinal disorders		
Abdominal pain	5.8%	6.1%
Acute pancreatitis	0.6%	0.6%
Diarrhoea	8.7%	15.9%
Dyspepsia	0.3%	0.3%
Flatulence	0.9%	0.9%
Nausea	4.1%	3.8%
Vomiting	2.0%	3.5%
Skin and subcutaneous tissue disorders		
Angioedema+	0.6%	0%
Pruritus	1.2%	0.9%
Rash	2.9%	4.6%
Stevens-Johnson Syndrome	0.3%	0%
Urticaria+	1.2%	0.6%
Musculoskeletal and connective tissue disorders		
Myalgia	0.6%	1.4%
Osteonecrosis+	0.3%	0%
Metabolism and nutrition disorders		
Anorexia	1.5%	0.9%
Diabetes mellitus	0.6%	0.9%

Table 4: Adverse Drug Reactions at Least Grade 2 reported in ARTEMIS (192 weeks)		
System Organ Class Adverse Drug Reaction	**darunavir/ritonavir 800/100 mg q.d. + TDF/FTC#** N=343	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC#** N=346
General disorders and administration site conditions		
Asthenia	0.9%	0%
Fatigue	0.9%	2.9%
Immune system disorders		
(Drug) Hypersensitivity+	0.6%	1.4%
Immune reconstitution syndrome	0.3%	0.3%
Hepatobiliary disorders		
Acute hepatitis	0.3%	0.9%
Psychiatric disorders		
Abnormal dreams	0.3%	0.3%

* Excluding laboratory abnormalities reported as ADRs
# Tenofovir disoproxil fumarate/emtricitabine
+ Adverse drug reactions identified from post-marketing experience

Laboratory abnormalities, Grade 2-4, in the ARTEMIS trial (192 weeks) using darunavir/ritonavir 800mg/100 q.d. and considered ADRs to PREZCOBIX are shown in the table below*:

Table 5: Laboratory abnormalities, Grade 2-4, considered ADRs in ARTEMIS 192 week analysis			
Laboratory parameter	**Limit**	**darunavir/ritonavir 800/100 mg q.d. + TDF/FTC#** N=343	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC#** N=346
ALT			
Grade 2	> 2.5 to ≤ 5.0 x ULN	8.8%	9.4%
Grade 3	> 5.0 to ≤ 10.0 x ULN	2.9%	3.5%
Grade 4	> 10.0 x ULN	0.9%	2.9%
AST			
Grade 2	> 2.5 to ≤ 5.0 x ULN	7.3%	9.9%
Grade 3	> 5.0 to ≤ 10.0 x ULN	4.4%	2.3%
Grade 4	> 10.0 x ULN	1.2%	2.6%
ALP			
Grade 2	> 2.5 to ≤ 5.0 x ULN	1.5%	1.5%
Grade 3	> 5.0 to ≤ 10.0 x ULN	0%	0.6%
Grade 4	> 10.0 x ULN	0%	0%
Triglycerides			
Grade 2	5.64 to 8.47 mmol/L	2.6%	9.9%
Grade 3	> 8.47 to 13.55 mmol/L	1.8%	5.0%
Grade 4	> 13.55 mmol/L	1.5%	1.2%
Total cholesterol*			
Grade 2	6.19 to 7.77 mmol/L	22.9%	27.1%
Grade 3	> 7.77 mmol/L	1.5%	5.5%
LDL cholesterol*			
Grade 2	4.12 to 4.90 mmol/L	14.1%	12.3%
Grade 3	> 4.90 mmol/L	8.8%	6.1%

Elevated glucose levels Grade 2 Grade 3 Grade 4	 6.95 to < 13.89 mmol/L 13.89 to < 27.75 mmol/L ≥ 27.75 mmol/L	 10.8% 1.2% 0%	 9.6% 0.3% 0%
Pancreatic lipase Grade 2 Grade 3 Grade 4	 > 1.5 to ≤ 3.0 x ULN > 3.0 to ≤ 5.0 x ULN > 5.0 x ULN	 2.6% 0.6% 0%	 1.7% 1.2% 0.9%
Pancreatic amylase Grade 2 Grade 3 Grade 4	 > 1.5 to ≤ 2.0 x ULN > 2.0 to ≤ 5.0 x ULN > 5.0 x ULN	 4.7% 4.7% 0%	 2.3% 4.1% 0.9%
* Grade 4 data not applicable in Division of AIDS grading scale # Tenofovir disoproxil fumarate/emtricitabine			

Additional ADRs of at least moderate intensity, reported in clinical trials with darunavir/ritonavir were gynecomastia and abdominal distension.

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience. The frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports

In Table 6, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 6: Post-marketing ADRs to darunavir/ritonavir presented by frequency category based on spontaneous reporting rates

System Organ Class	Adverse Drug Reaction	Incidence
Skin and subcutaneous tissue disorders	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Very rare
	Toxic epidermal necrolysis	Very rare
	Acute generalized exanthematous pustulosis	Very rare
Renal and urinary disorders	Crystal nephropathy	Very rare

Effects of combination antiretroviral therapy

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (immune reconstitution inflammatory syndrome). Autoimmune disorders such as Graves' disease and autoimmune hepatitis have also been reported in the context of immune reconstitution inflammatory syndrome (see **section 4.4** Special warnings and precautions for use).

There have been reports of increased spontaneous bleeding in haemophilia patients receiving PIs.

Increased CPK, myalgia, myositis and rarely, rhabdomyolysis have been reported with the use of HIV protease inhibitors, particularly in combination with NRTIs.

Special populations

Patients co-infected with hepatitis B and/or hepatitis C virus

Limited information is available on the use of PREZCOBIX in patients co-infected with hepatitis B and/or C virus. In patients co-infected with hepatitis B or C virus receiving darunavir/ritonavir, the incidence of adverse events and clinical chemistry abnormalities was not higher than in patients receiving darunavir/ritonavir who were not co-infected, except for increased hepatic enzymes. The pharmacokinetic exposure with darunavir/ritonavir in co-infected patients was comparable to that in patients without co infection.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Human experience of acute overdose with PREZCOBIX is limited. Single doses up to 3200 mg of the oral solution of darunavir alone and up to 1600 mg of the tablet formulation of darunavir in combination 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.

Management of overdosage

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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antivirals for systemic use, Antivirals for treatment of HIV infection, Combinations - ATC code: J05AR22.

Mechanism of action

Darunavir: 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 shows resilience to the effects of HIV protease inhibitors Resistance-Associated Mutations (RAMs).

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

Cobicistat: Cobicistat is a 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 by CYP3A-dependent metabolism.

Pharmacodynamic effects

Microbiology

Antiviral activity *in vitro*

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 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 *in vitro*.

Darunavir showed synergistic antiviral activity when studied in combination with the HIV protease inhibitors amprenavir, nelfinavir, or ritonavir and additive antiviral activity when studied in combination with the protease inhibitors atazanavir, indinavir, lopinavir, 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. No antagonism was observed between darunavir and any of those antiretrovirals.

Cobicistat: Cobicistat has no detectable antiviral activity in cell culture against HIV-1 and does not antagonize the antiviral activity of darunavir.

Resistance *in vitro*

Darunavir: In vitro selection of darunavir-resistant virus from wildtype HIV-1 was lengthy (> 3 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 400 nM. Viruses selected in these conditions and showing decreased susceptibility to darunavir (range: 23-50-fold) harboured 2 to 4 amino acid substitutions in the protease gene.

The decreased susceptibility to darunavir of the emerging viruses in the selection experiment could not be explained by the emergence of these protease mutations.

In vitro selection of darunavir-resistant HIV-1 (range: 53-641-fold change [FC] in EC_{50} values) from 9 HIV-1 strains harbouring multiple PI 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 (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 RAMs showed a median FC for darunavir > 10.

Cross-resistance *in vitro*

Cross-resistance has been observed among HIV protease inhibitors. 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 < 3 for tipranavir, indicative of limited cross-resistance between these 2 protease inhibitors.

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

Selection of viral resistance *in vivo*

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.

Selection of viral resistance during PREZCOBIX therapy *in vivo*

In the 24 week analysis of the GS-US-216-0130 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.

Selection of viral resistance during darunavir/ritonavir 800/100 mg q.d. therapy *in vivo*

In the 192 week analysis of the ARTEMIS trial, the proportion 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 group, 4 patients with developing PI RAMs were identified. In the virologic failures of the lopinavir/rtv group, 9 patients with developing PI RAMs were identified. None of the developing mutations in the darunavir/ritonavir group or in the lopinavir/rtv group were primary (i.e. major) PI mutations. In 4 virologic failures of the darunavir/ritonavir group and 7 virologic failures of the lopinavir/rtv group, a maximum of 2 developing NRTI RAMs were identified identified The development of the NRTI RAM at position 184 (n=9) was associated with a decreased susceptibility to FTC included in the background regimen.

In the 48 week analysis of the ODIN trial the proportion 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). In the virologic failures in the darunavir/ritonavir 800/100 mg q.d. group 7 subjects (12%) with developing PI RAMs were identified, compared to 4 subjects (10%) in the darunavir/ritonavir 600/100 mg b.i.d. group. One virologic failure subject in the darunavir/ritonavir 800/100 mg q.d. group developed primary (i.e. major) PI mutations, which included 3 DRV RAMs, resulting in decreased susceptibility to darunavir. All the 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 was associated with a decreased susceptibility to a NRTI included in the treatment regimen.

Cross-resistance with other HIV protease inhibitors *in vivo*

In the virologic failures of the GS-US-216-130 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 subjects 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 subjects, 96% to 100% that were susceptible at baseline to amprenavir, atazanavir, indinavir, lopinavir, saquinavir or tipranavir remained susceptible to these protease inhibitors after treatment. In the virologic failures receiving darunavir/rtv 600/100 mg b.i.d. no cross-resistance with other PIs was observed.

Effects on electrocardiogram

Darunavir: In a four-way crossover trial, 40 healthy subjects were administered supratherapeutic doses of darunavir 1600 mg and ritonavir 100 mg once daily and darunavir 800 mg and ritonavir 100 mg twice daily (approximately 2 times the recommended darunavir dose) for seven days. When evaluating the 2-sided 90% CI on the time-matched mean changes in QTcF versus placebo, the upper bounds of both darunavir co-administered with ritonavir groups never exceeded the 10 ms boundary.

Cobicistat: The electrocardiographic effects of cobicistat were determined in a study of 48 healthy adult 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.

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.

Clinical trials

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 **section 5.2** Pharmacokinetic properties).

The evidence of efficacy of PREZCOBIX once daily is based on 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 and ODIN conducted with darunavir/ritonavir 800/100 mg q.d. in treatment-naïve and treatment-experienced patients, respectively.

Description of clinical study of darunavir/cobicistat 800/150 mg q.d. in adults

Efficacy of darunavir 800 mg once daily co-administered with 150 mg cobicistat once daily in treatment-naïve and treatment-experienced patients

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 TLOVR analysis.

The 313 patients in total had a median age of 35 years (range 18-72), 89.1% were male, 59.7% white, 34.5% black, 21.7% hispanic, and 1.3% asian. The mean baseline plasma HIV-1 RNA and the median baseline CD4+ cell count were 4.8 $\log_{10}$ copies/mL, 370 x 10^6 cells/L (range 6 - 1473 x 10^6 cells/L) and 4.8 $\log_{10}$ copies/mL, 107 x 10^6 cells/L (range 5 – 643 x 10^6 cells/L) for the treatment-naïve and treatment-experienced patients respectively.

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

Table 7: Virologic Outcome of Randomized Treatment of Trial GS–US–216–0130 at 24 Weeks

	GS-US-216-0130		
Outcomes at Week 24[a]	**Treatment-Naïve darunavir/cobicistat 800/150 mg q.d. + OBR N=295**	**Treatment-Experienced darunavir/cobicistat 800/150 mg q.d. + OBR N=18**	**All subjects darunavir/cobicistat 800/150 mg q.d. + OBR N=313**
HIV-1 RNA < 50 copies/mL	232 (78.6%)	8 (44.4%)	240 (76.7%)
mean HIV-1 RNA log change from baseline ($\log_{10}$ copies/mL)[e]	-3.00	-2.56	-2.98
CD4+ cell count mean change from baseline	145	99	142

[a] Imputations according to TLOVR analysis

Efficacy of darunavir/cobicistat fixed-dose combination 800/150 mg once daily in treatment-naïve patients

TMC114FD2HTX3001 (AMBER) is a randomized, active-controlled, double blind, Phase 3 trial to evaluate the efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide versus darunavir/cobicistat fixed-dose combination + emtricitabine/tenofovir disoproxil fumarate.

HIV-1 infected patients who were eligible for this trial had a plasma HIV-1 RNA ≥ 1,000 copies/mL. The table below shows the 48-week efficacy data of the AMBER trial:

Table 8: Efficacy data from AMBER trial at 48 weeks

	AMBER	
Outcomes at week 48	**Treatment-naïve darunavir/cobicistat/emtricitabine/ tenofovir alafenamide once daily N=362**	**Treatment-naïve darunavir/cobicistat 800/150 mg once daily + emtricitabine/tenofovir disoproxil fumarate N = 363**
HIV-1 RNA < 50 copies/mL[a]	331 (91.4%)	321 (88.4%)
Virologic failure[a]	16 (4.4%)	12 (3.3%)
No virologic data in 48-week window[a]	15 (4.1%)	30 (8.3%)

CD4+ cell count mean change from baseline[b]	+188.7	+173.8

[a] Imputations according to the Snapshot algorithm.
[b] Non completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0

The virological response (< 50 copies/mL) at 48 weeks by baseline viral load and baseline CD4+ cell count is presented in Table 9 below:

Table 9: Virologic Outcome of Randomized Treatment of the AMBER trial at 48 weeks

	Treatment-naïve darunavir/cobicistat/ emtricitabine/ tenofovir alafenamide once daily N=362		**Treatment-naïve darunavir/cobicistat 800/150 mg once daily + emtricitabine/tenofovir disoproxil fumarate N = 363**		**Treatment difference**
	N	number of responders at Week 48 n (%)	N	number of responders at Week 48 n (%)	Difference in % response (95% CI of difference in % response)[a]
Baseline plasma viral load (copies/mL)					
≤ 100000	303	278 (91.7%)	293	265 (90.4%)	1.3 (-3.4, 6.1)
> 100000	59	53 (89.8%)	70	56 (80.0%)	9.8 (-3.3, 22.5)
Baseline CD4+ cell count cells/mm^3					
< 200	22	16 (72.7%)	29	25 (86.2%)	-13.5 (-37.8, 9.6)
≥ 200	340	315 (92.6%)	334	296 (88.6%)	4 (-0.4, 8.6)

[a] Exact (unconditional) CI with confidence coefficient of at least 95%.

Description of clinical studies of darunavir/ritonavir 800/100 mg q.d. in adults

Efficacy of darunavir/ritonavir 800/100 mg q.d in treatment-naïve adult patients

The evidence of efficacy of darunavir/ritonavir 800/100 mg q.d. is based on the analyses of 192 week data from the randomized, controlled, open label Phase 3 trial ARTEMIS in antiretroviral treatment-naïve HIV-1 infected patients 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).

HIV-1 infected patients who were eligible for this trial had plasma HIV-1 RNA > 5000 copies/mL. Randomizations was stratified by screening plasma viral load and screening CD4+ cell count. Virologic response was defined as a confirmed plasma HIV-1 RNA viral load < 50 copies/mL.

Demographics and baseline characteristics were balanced between the darunavir/ritonavir arm and the lopinavir/ritonavir arm. The 343 patients on darunavir/ritonavir 800/100 mg q.d. had a median age of 34 years (range 18-70), 70% were male, 40% white, 23% black, 23% hispanic, and 13% asian. The mean baseline plasma HIV-1 RNA was 4.86 $\log_{10}$ copies/mL and the median baseline CD4+ cell count was 228 x 10^6 cells/L (range 4 – 750 x 10^6 cells/L).

Table 10 below shows the efficacy data of the 48 week and 192 week analyses from the ARTEMIS trial:

Table 10: Efficacy data from the ARTEMIS trial (48 week and 192 week analyses)						
	ARTEMIS					
	At Week 48[a]			At Week 192[b]		
Outcomes	darunavir/ ritonavir 800/100 mg q.d. N=343	lopinavir/ ritonavir 800/200 mg per day N=346	Treatment difference (95% CI of difference)	darunavir/ ritonavir 800/100 mg q.d. N=343	lopinavir/ ritonavir 800/200 mg per day N=346	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/mL[c]	287 (83.7%)	271 (78.3%)	5.3 (-0.5; 11.2)[d]	236 (68.8%)	198 (57.2%)	11.6 (4.4; 18.8)[d]
HIV-1 RNA < 400 copies/mL [c]	301 (87.8%)	295 (85.3%)	2.5 (-2.6; 7.6)[b]	258 (75.2%)	225 (65.0%)	10.2 (3.4; 17.0)
mean HIV-1 RNA log change from baseline (log_{10} copies/mL) [e]	-2.77	-2.65	-0.11[f] (-0.30; 0.07)[d]	-2.35	-2.03	-0.32[f] (-0.55; -0.09)
median CD4+ cell count change from baseline (x 10^6/L)[e]	137	141		258	263	

[a] Data based on analyses at Week 48
[b] Data based on analyses at Week 192
[c] Imputations according to the TLOVR algorithm
[d] Based on normal approximation to the difference in % response
[e] Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0
[f] Difference in means

In the 48 week analysis, the virologic response (HIV-1 RNA < 50 copies/mL) for the darunavir/ritonavir arm was 83.7% and for the lopinavir/rtv arm 78.3%. Statistical comparisons between the treatment arms at Week 48 confirmed non-inferiority of darunavir/ritonavir versus lopinavir/rtv (p-value < 0.001) for both ITT (Intent-To-Treat) & OP (On Protocol) population.

Analyses of 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 week analysis, virologic response (HIV-1 RNA < 50 copies/mL) was 68.8% and 57.2% for the darunavir/ritonavir and lopinavir/ritonavir arm, respectively. Non-inferiority in virologic response was demonstrated (p < 0.001) for both ITT and OP population. Furthermore, statistical superiority of the darunavir/ritonavir arm over the lopinavir/ ritonavir arm was demonstrated (p=0.002) for both ITT and OP population.

The virological response (< 50 copies/mL) at 192 weeks by baseline viral load and baseline CD4+ cell count is presented in Table 11 below:

Table 11: Virologic Response of Randomized Treatment trial ARTEMIS Week 192					
	darunavir/ritonavir 800/100 mg q.d. N=343		**lopinavir/ritonavir 800/200 mg per day N=346**		**Treatment difference**
	N	number of responders at Week 192 n (%)	N	number of responders at Week 192 n (%)	Difference in % response (95% CI of difference in % response)[a]
Baseline plasma viral load (copies/mL)					
< 100000	226	157 (69.5%)	226	136 (60.2%)	9.3 (0.5; 18.1)
≥ 100000	117	79 (67.5%)	120	62 (51.7%)	15.9 (3.5; 28.3)
Baseline CD4+ cell count (x 10^6/L)					
< 200	141	92 (65.2%)	148	80 (54.1%)	11.2 (-0.1; 22.5)
≥ 200	202	144 (71.3%)	198	118 (59.6%)	11.7 (2.4; 21.0)

[a] Based on a normal approximation to the difference in % response

Efficacy of darunavir/ritonavir 800/100 mg q.d. in treatment-experienced adult patients

The evidence of comparable efficacy of darunavir/ritonavir 800/100 mg q.d. and darunavir/ritonavir 600/100 mg b.i.d. in treatment-experienced patients with no darunavir RAMs is based on the 48 week analysis of the Phase 3 trial ODIN.

ODIN is a randomized, open-label trial 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 testing showing no darunavir RAMs (i.e. V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) and a viral load of > 1000 HIV-1 RNA copies/mL. Both arms used an optimized background regimen consisting of ≥ 2 NRTIs selected by the investigator.

Demographics and baseline characteristics were balanced between the darunavir/ritonavir q.d. arm and the darunavir/ritonavir b.i.d. arm. The 590 patients in total had a median age of 40 years (range 18-77), 64% were male, 36% white, 26% black, 18% hispanic, and 15% asian. The mean baseline plasma HIV-1 RNA was 4.16 $\log_{10}$ copies/mL and the median baseline CD4+ cell count was 228 x 10^6 cells/L (range 24 – 1306 x 10^6 cells/L).

The table below shows the efficacy data of the 48 week analysis from the ODIN trial:

Table 12: Virologic Outcome of ODIN Trial at Week 48			
	ODIN		
Outcomes	darunavir/ritonavir 800/100 mg q.d. + OBR N=294	darunavir/ritonavir 600/100 mg b.i.d. + OBR N=296	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/mL[a]	212 (72.1%)	210 (70.9%)	1.2% (-6.1; 8.5)[b]
mean HIV-1 RNA log change from baseline (log_{10} copies/mL)[e]	-1.84	-1.80	-0.04[d] (-0.24; 0.16)
mean CD4+ cell count change from baseline (x 10^6/L)[c]	108	112	-5[d] (-25; 16)

OBR=optimized background regimen

[a] Imputations according to the TLOVR algorithm

[b] Based on a normal approximation of the difference in % response

[c] Last Observation Carried Forward imputation

[d] Difference in means

[e] NC=F

In the 48 week analysis, the virologic response defined as a confirmed plasma HIV-1 RNA viral load < 50 copies/mL, was 72.1% for the darunavir/ritonavir q.d. arm and 70.9% for the darunavir/ritonavir b.i.d. arm. Statistical comparisons between the treatment arms at Week 48 confirmed non-inferiority of darunavir/ritonavir q.d. versus darunavir/rtv b.i.d. for both the ITT and OP population (p-value < 0.001).

5.2 PHARMACOKINETIC PROPERTIES

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

Bioequivalence between PREZCOBIX and darunavir/cobicistat 800/150 mg co-administered as single agents was established under fed and fasted conditions in healthy subjects (TMC114IFD1001).

Absorption

The absolute oral bioavailability of darunavir alone is approximately 37%.

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 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.

When administered with food, the relative exposure of darunavir is 1.7-fold higher as compared to intake without food. Therefore, PREZCOBIX should be taken with food. The type of food does not affect exposure to PREZCOBIX.

Distribution

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

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

Metabolism

Darunavir: In vitro experiments with human liver microsomes indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by the hepatic CYP system and almost exclusively by isozyme CYP3A. 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 3 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 wildtype HIV.

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

Excretion

Darunavir: 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 faeces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in faeces and urine, respectively. 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.

The terminal elimination half-life of darunavir was approximately 11 hours when combined with cobicistat.

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

Special populations

Paediatrics

The pharmacokinetics of PREZCOBIX in paediatric patients have not been investigated.

Elderly

Darunavir: Population pharmacokinetic analysis in HIV infected patients showed that darunavir pharmacokinetics are not different in the age range (18 to 75 years) evaluated in HIV infected patients (see **section 4.4** Special warnings and precautions for use).

Cobicistat: Pharmacokinetics of cobicistat have not been fully evaluated in the elderly (65 years of age and older).

Renal impairment

PREZCOBIX has not been investigated in patients with renal impairment.

Darunavir: 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. 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 **section 4.4** Special warnings and precautions for use).

Cobicistat: 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.

Hepatic impairment

PREZCOBIX has not been investigated in patients with hepatic impairment.

Darunavir: Darunavir is primarily metabolised and eliminated by the liver. 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 subjects with mild (Child-Pugh Class A, n=8) and moderate (Child-Pugh Class B, n=8) hepatic impairment were comparable with those in healthy subjects. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see **section 4.2** Dose and method of administration and **section 4.4** Special warnings and precautions for use).

Cobicistat: 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. No dosage adjustment of cobicistat is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of cobicistat has not been studied.

Hepatitis B and/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.

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

Pregnancy and postpartum

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 (see Table 13). 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.

Table 13: Pharmacokinetic Results of Total Darunavir after Administration of Darunavir/Cobicistat 800/150 mg q.d. 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 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

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

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. Dose-related increases 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).

Toxicology

Darunavir: Animal toxicology studies have been conducted with darunavir alone, in mice, rats and dogs and in combination with ritonavir in rats and dogs.

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 haematopoietic 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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Hypromellose
Silicon dioxide
Microcrystalline cellulose
Crospovidone
Magnesium stearate
OPADRY® II complete film coating system 85F140053 Pink (ARTG PI No.109886) as the tablet film coating

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Keep out of the sight and reach of children. Store in the original packaging to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

PREZCOBIX 800/150 mg film-coated tablets are provided in high density polyethylene (HDPE) plastic bottles containing 30 tablets, fitted with polypropylene (PP) child resistant closures.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

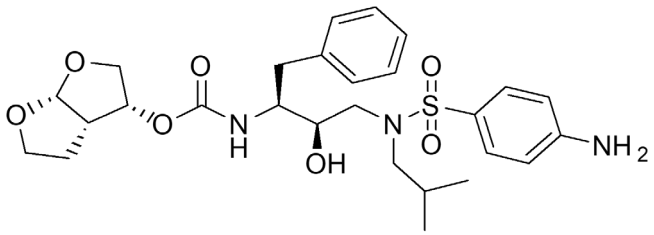
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Darunavir

The chemical name for darunavir is [(1S,2R)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester.

Darunavir has the following structural formula:



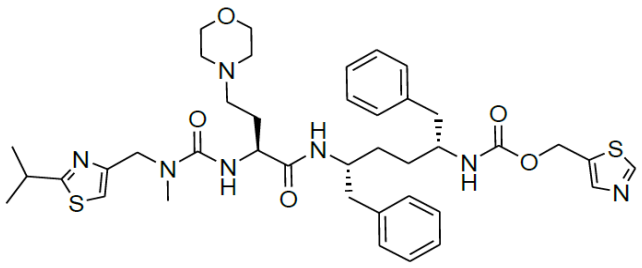
It has an empirical formula of $C_{27}H_{37}N_3O_7S$ and a molecular weight of 547.66.

Darunavir is isolated as darunavir ethanolate, a pseudo-polymorphic form of darunavir. Darunavir ethanolate is a white to off-white powder that is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol, and freely soluble in acetone and dichloromethane.

Cobicistat

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-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate.

Cobicistat has the following structural formula:



It has an empirical formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.0.

Cobicistat is a white to pale yellow solid with a solubility of 0.1 mg/mL in water at 20 °C. The partition coefficient (*log p*) for cobicistat is 4.3 and the pKa is 6.4.

CAS numbers

Darunavir: 206361-99-1
Cobicistat: 1004316-88-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine

8. SPONSOR

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Telephone: 1800 226 334

NZ Office: Auckland New Zealand

9. DATE OF FIRST APPROVAL

24 September 2015

10. DATE OF REVISION

23 May 2025

Summary table of changes

Section changed	Summary of new information
4.4	Amendment of the statement related to HIV transmission