The content of this leaflet was updated according to the guidelines of the Ministry of Health

1. NAME OF THE MEDICINAL PRODUCT

REZOLSTA 800 mg/150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 800 mg of darunavir (as ethanolate) and 150 mg of cobicistat.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).
Pink oval shaped tablet of 23 mm x 11.5 mm, debossed with “800” on one side and “TG” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REZOLSTA is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV 1) infection in treatment-naïve and treatment-experienced adults with no darunavir resistance-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V).

4.2 Posology and method of administration

Therapy should be initiated by a healthcare provider experienced in the management of HIV infection.

Posology
After therapy with REZOLSTA has been initiated, patients should not alter the dosage or discontinue therapy without the instruction of their healthcare provider.

ART-naïve patients
The recommended dose regimen is one film-coated tablet of REZOLSTA once daily taken with food.

ART-experienced patients
One film-coated tablet of REZOLSTA once daily taken with food may be used in patients with prior exposure to antiretroviral medicinal products but without darunavir resistance associated mutations (DRV-RAMs)* and who have plasma HIV-1 RNA < 100,000 copies/mL and CD4+ cell count ≥ 100 cells x 10^6/l (see section 4.1).
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V.

In all other ART-experienced patients or if HIV-1 genotype testing is not available, the use of REZOLSTA is not appropriate and another antiretroviral regimen should be used. Refer to the Summary of Product Characteristics of other antiretroviral medicinal products for dosing information.

Advice on missed doses
If REZOLSTA is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of REZOLSTA with food as soon as possible. If this is noticed later than

12 hours of the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.
If a patient vomits within 4 hours of taking the medicine, another dose of REZOLSTA should be taken with food as soon as possible. If a patient vomits more than 4 hours after taking the medicine, the patient does not need to take another dose of REZOLSTA until the next regularly scheduled time.

Special populations

Elderly
Limited information is available in this population, and therefore, REZOLSTA should be used with caution in patients above 65 years of age (see sections 4.4 and 5.2).

Hepatic impairment
There are no pharmacokinetic data regarding the use of REZOLSTA in patients with hepatic impairment.

Darunavir and cobicistat are metabolised by the hepatic system. Separate trials of darunavir/ritonavir and cobicistat suggest no dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, REZOLSTA should be used with caution in these patients.

There are no data regarding the use of darunavir or cobicistat in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir and/or cobicistat exposure and a worsening of its safety profile. Therefore, REZOLSTA must not be used in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.3, 4.4 and 5.2).

Renal impairment
Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine. REZOLSTA should not be initiated in patients with creatinine clearance less than 70 mL/min if any co-administered medicinal product (e.g. emtricitabine, lamivudine, tenofovir disoproxil (as
fumarate, phosphate or succinate), or adefovir dipivoxil) requires dose adjustment based on creatinine clearance (see sections 4.4, 4.8 and 5.2).

Based on the very limited renal elimination of cobicistat and darunavir, no special precautions or dose adjustments of REZOLSTA are required for patients with renal impairment. Darunavir, cobicistat, or the combination of both have not been studied in patients receiving dialysis, and therefore no recommendation can be made for these patients (see section 5.2).

For more information consult the cobicistat Summary of Product Characteristics.

Paediatric population

The safety and efficacy of REZOLSTA in paediatric patients aged 3 to 17 years. have not been established (see sections 4.4 and 5.3). No data are available. REZOLSTA should not be used in paediatric patients below 3 years of age because of safety concerns (see sections 4.4 and 5.3).

Pregnancy and postpartum
Treatment with REZOLSTA during pregnancy results in low darunavir exposure (see sections 4.4 and 5.2). Therefore, therapy with REZOLSTA should not be initiated during pregnancy, and women who become pregnant during therapy with REZOLSTA should be switched to an alternative regimen (see sections 4.4 and 4.6). Darunavir/ritonavir may be considered as an alternative.

Method of administration
Oral use
To ensure administration of the entire dose of both darunavir and cobicistat, the tablet should be swallowed whole.

For patients unable to swallow the whole tablet, REZOLSTA may be split into two pieces using a tablet-cutter, and the entire dose should be consumed immediately after splitting.
Patients should be instructed to take REZOLSTA within 30 minutes after completion of a meal (see sections 4.4, 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Patients with severe (Child-Pugh Class C) hepatic impairment.

Co-administration with the following medicinal products due to the potential for loss of therapeutic effect (see section 4.5):
- carbamazepine, phenobarbital, phenytoin
- rifampicin
- lopinavir/ritonavir
- St John's wort, (*Hypericum perforatum*).

Co-administration with the following medicinal products due to the potential for serious and/or life-threatening adverse reactions (see section 4.5):
- alfuzosin
- amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine
- astemizole, terfenadine
- colchicine, when used in patients with renal and/or hepatic impairment (see section 4.5)
- rifampicin
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- cisapride
- dapoxetine
- domperidone
- naloxegol
- lurasidone, pimozide, quetiapine, sertindole (see section 4.5)
- elbasvir/grazoprevir
- triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5)
- sildenafil - when used for the treatment of pulmonary arterial hypertension, avanafil
- simvastatin, lovastatin and lomitapide (see section 4.5)
- dabigatran, ticagrelor.

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Regular assessment of virological response is advised. In the setting of lack or loss of virological response, resistance testing should be performed.

Darunavir binds predominantly to α_1-acid glycoprotein. This protein binding is concentration dependent indicative for saturation of binding. Therefore, protein displacement of medicinal products highly bound to α_1-acid glycoprotein cannot be ruled out (see section 4.5).

ART-experienced patients
REZOLSTA should not be used in treatment-experienced patients with one or more DRV-RAMs or HIV-1 RNA ≥ 100,000 copies/mL or CD4+ cell count < 100 cells x 10^6/l (see section 4.2).

Combinations with optimised background regimens (OBRs) other than ≥ 2 NRTIs have not been studied in this population. Limited data is available in patients with HIV-1 clades other than B (see section 5.1).

Pregnancy
Treatment with darunavir/cobicistat 800/150 mg during the second and third trimester has been shown to result in low darunavir exposure, with a reduction of around 90% in C_{min} levels (see section 5.2). Cobicistat levels decrease and may not provide sufficient boosting. The substantial reduction in darunavir exposure may result in virological failure and an increased risk of mother to child transmission of HIV infection. Therefore, therapy with REZOLSTA should not be initiated during pregnancy, and women who become pregnant during therapy with REZOLSTA should be switched to an alternative regimen (see sections 4.2 and 4.6). Darunavir given with low dose ritonavir may be considered as an alternative.

Elderly
As limited information is available on the use of REZOLSTA in patients aged 65 and over, caution should be exercised, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy (see sections 4.2 and 5.2).

Severe skin reactions
During the darunavir/ritonavir clinical development program (N = 3,063), severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported in 0.4% of patients. DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and Stevens-Johnson syndrome has been rarely (< 0.1%) reported, and during post-marketing experience toxic epidermal necrolysis and acute generalised exanthematous pustulosis have been reported. REZOLSTA should be discontinued 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 occurred more commonly in treatment-experienced patients receiving regimens containing darunavir/ritonavir + raltegravir compared to patients receiving darunavir/ritonavir without raltegravir or raltegravir without darunavir/ritonavir (see section 4.8).

Sulphonamide allergy
Darunavir contains a sulphonamide moiety. REZOLSTA should be used with caution in patients with a known sulphonamide allergy.

Hepatotoxicity
Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with darunavir/ritonavir. During the clinical development program (N = 3,063), hepatitis was reported in 0.5% of patients receiving combination antiretroviral 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 and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

Appropriate laboratory testing should be conducted prior to initiating therapy with REZOLSTA 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 REZOLSTA treatment.

If there is 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 using REZOLSTA, interruption or discontinuation of treatment should be considered promptly.

Patients with coexisting conditions

Hepatic impairment
The safety and efficacy of REZOLSTA, darunavir, or cobicistat have not been established in patients with severe underlying liver disorders. REZOLSTA is, therefore, contraindicated in patients with severe hepatic impairment. Due to an increase in the unbound darunavir plasma concentrations, REZOLSTA should be used with caution in patients with mild or moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal impairment
Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine. This effect on serum creatinine, leading to a decrease in the estimated creatinine clearance, should be taken into consideration when REZOLSTA is administered to patients, in whom the estimated creatinine clearance is used to guide aspects of their clinical management, including adjusting doses of co-administered medicinal products. For more information consult the cobicistat Summary of Product Characteristics.

REZOLSTA should not be initiated in patients with creatinine clearance less than 70 mL/min when co-administered with one or more agent requiring dose adjustment based on creatinine clearance (e.g. emtricitabine, lamivudine, tenofovir disoproxil (as fumarate, phosphate or succinate) or adefovir dipivoxil) (see sections 4.2, 4.8 and 5.2).

No special precautions or dose adjustments are required 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 sections 4.2 and 5.2).

There are currently inadequate data to determine whether co-administration of tenofovir disoproxil and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil without cobicistat.

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 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.

Weight and metabolic parameters
An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Osteonecrosis
Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Immune reconstitution inflammatory syndrome (IRIS)
In HIV infected patients with severe immune deficiency at the time of initiation 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, generalised and/or focal mycobacterial infections and pneumonia caused by *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. In addition, reactivation of herpes simplex and herpes zoster has been observed in clinical trials with darunavir co-administered with low dose ritonavir.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.8).

Interactions with medicinal products
Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A and P-glycoprotein (see section 4.5).

REZOLSTA should not be used in combination with another antiretroviral that requires pharmacoenhancement since dosing recommendations for such combination have not been established. REZOLSTA should not be used concurrently with products containing ritonavir or regimens containing ritonavir or cobicistat.

Unlike ritonavir, cobicistat is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGT1A1. If switching from ritonavir as a pharmacoenhancer to cobicistat, caution is required during the first two weeks of treatment with REZOLSTA, particularly if doses of any concomitantly administered medicinal products have been titrated or adjusted during use of ritonavir as a pharmacoenhancer.

Paediatric population
REZOLSTA is not recommended for use in paediatric patients (3 to 17 years of age). REZOLSTA should not be used in paediatric patients below 3 years of age (see sections 4.2 and 5.3).

REZOLSTA contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

Medicinal products that may be affected by darunavir/cobicistat
Darunavir is an inhibitor of CYP3A, a weak inhibitor of CYP2D6 and an inhibitor of P-gp. Cobicistat is a mechanism based inhibitor of CYP3A, and a weak CYP2D6 inhibitor. Cobicistat inhibits the transporters p-glycoprotein (P-gp), BCRP, MATE1, OATP1B1 and OATP1B3. Co-administration of cobicistat with medicinal products that are substrates of these transporters can result in increased plasma concentrations of the co-administered medicinal products. Cobicistat is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19. Cobicistat is not expected to induce CYP1A2, CYP3A4, CYP2C9, CYP2C19, UGT1A1, or P-gp (MDR1). Co-administration of darunavir/cobicistat and medicinal products primarily metabolised by CYP3A may result in increased systemic exposure to such medicinal products, which could increase or prolong their therapeutic effect and adverse reactions.

REZOLSTA must therefore not be combined with medicinal products that are highly dependent on CYP3A for clearance and for which increased systemic exposure is associated with serious and/or life-threatening events (narrow therapeutic index) (see section 4.3).

Co-administration of REZOLSTA with medicinal products 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. These interactions are described in the interaction table below.

Medicinal products that affect darunavir/cobicistat exposure
Darunavir and cobicistat are metabolised by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and cobicistat, resulting in lowered plasma concentrations of darunavir and cobicistat (e.g. efavirenz, carbamazepine, phenytoin, phenobarbital, rifampicin, rifapentine, rifabutin, St John's wort) (see section 4.3 and interaction table below).

Co-administration of REZOLSTA and other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and cobicistat and may result in increased plasma concentrations of darunavir and cobicistat (e.g. azole antifungals such as clotrimazole). These interactions are described in the interaction table below.

REZOLSTA should not be used concurrently with products or regimens containing ritonavir or cobicistat. REZOLSTA should not be used in combination with the individual components of REZOLSTA (darunavir or cobicistat). REZOLSTA should not be used in combination with another antiretroviral that requires pharmacoenhancement since dosing recommendations for such combination have not been established.

Interaction table
Expected interactions between REZOLSTA and antiretroviral and non-antiretroviral medicinal products are listed in the table below and are based on the identified interactions with darunavir/ritonavir, darunavir/cobicistat and with cobicistat.

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

The below list of examples of drug drug interactions is not comprehensive and therefore the label of each drug that is co-administered with REZOLSTA 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.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
HIV ANTIRETROVIRALS		
Integrase strand transfer inhibitors		
Dolutegravir	Based on theoretical considerations dolutegravir is not expected to affect the pharmacokinetics of REZOLSTA.	REZOLSTA and dolutegravir can be used without dose adjustments.
Raltegravir	Some clinical trials suggest raltegravir may cause a modest decrease in darunavir plasma concentrations.	At present the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically relevant; REZOLSTA and raltegravir can be used without dose adjustments.

HIV Nucleo(s/t)ide reverse transcriptase inhibitors (NRTIs)		
Didanosine 400 mg once daily	No mechanistic interaction expected based on theoretical consideration.	REZOLSTA and didanosine can be used without dose adjustments. When didanosine is co-administered with REZOLSTA, didanosine should be administered on an empty stomach 1 hour before or 2 hours after REZOLSTA (which is administered with food).
Tenofovir disoproxil * *study was done with tenofovir disoproxil fumarate	Based on theoretical considerations REZOLSTA is expected to increase tenofovir plasma concentrations. (P-glycoprotein inhibition)	REZOLSTA and tenofovir disoproxil can be used without dose adjustments. Monitoring of renal function may be indicated when REZOLSTA is given in combination with tenofovir disoproxil, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.
Emtricitabine/tenofovir alafenamide	Tenofovir alafenamide ↔ Tenofovir ↑	The recommended dose of emtricitabine/tenofovir alafenamide is 200/10 mg once daily when used with REZOLSTA.
Abacavir Emtricitabine Lamivudine Stavudine Zidovudine	Based on the different elimination pathways of the other NRTIs (i.e. emtricitabine, lamivudine, stavudine and zidovudine) that are primarily renally excreted, and abacavir for which metabolism is not mediated by CYP, no interactions are expected for these medicinal compounds and REZOLSTA.	REZOLSTA can be used with these NRTIs without dose adjustment.
HIV Non-nucleo(s/t)ide reverse transcriptase inhibitors (NNRTIs)		
Efavirenz	Based on theoretical considerations efavirenz is expected to decrease darunavir and/or cobicistat plasma concentrations. (CYP3A induction)	Co-administration of REZOLSTA and efavirenz is not recommended. This recommendation is different from ritonavir-boosted darunavir. Consult the Summary of Product Characteristics for darunavir for further details.
Etravirine	Based on theoretical considerations etravirine is expected to decrease darunavir and/or cobicistat plasma concentrations. (CYP3A induction)	Co-administration of REZOLSTA and etravirine is not recommended. This recommendation is different from ritonavir-boosted darunavir. Consult the Summary of Product Characteristics for darunavir for further details.

Nevirapine	Based on theoretical considerations nevirapine is expected to decrease darunavir and/or cobicistat plasma concentrations, (CYP3A induction). REZOLSTA is expected to increase nevirapine plasma concentrations. (CYP3A inhibition)	Co-administration of REZOLSTA and nevirapine is not recommended. This recommendation is different from ritonavir-boosted darunavir. Consult the Summary of Product Characteristics for darunavir for further details.
Rilpivirine	Based on theoretical considerations REZOLSTA is expected to increase rilpivirine plasma concentrations. (CYP3A inhibition)	Co-administration of REZOLSTA and rilpivirine can be used without dose adjustments, as the expected increase in rilpivirine concentrations is not considered clinically relevant.
CCR5 ANTAGONIST		
Maraviroc 150 mg twice daily	Based on theoretical considerations REZOLSTA is expected to increase maraviroc plasma concentrations. (CYP3A inhibition)	The recommended dose of maraviroc is 150 mg twice daily when co-administered with REZOLSTA. For further details, consult the maraviroc Summary of Product Characteristics.
α1-ADRENORECEPTOR ANTAGONIST		
Alfuzosin	Based on theoretical considerations REZOLSTA is expected to increase alfuzosin plasma concentrations. (CYP3A inhibition)	Co-administration of REZOLSTA with alfuzosin is contraindicated (see section 4.3).
ANAESTHETIC		
Alfentanil	Based on theoretical considerations REZOLSTA is expected to increase alfentanil plasma concentrations.	The concomitant use with REZOLSTA may require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression.
ANTACIDS		
Aluminium/magnesium hydroxide Calcium carbonate	No mechanistic interaction expected based on theoretical consideration.	REZOLSTA and antacids can be used concomitantly without dose adjustment.
ANTIANGINA/ANTIARRHYTHMIC		
Disopyramide Flecainide Lidocaine (systemic) Mexiletine Propafenone Amiodarone Bepridil Dronedarone Ivabradine Quinidine Ranolazine	Based on theoretical considerations REZOLSTA is expected to increase these antiarrhythmic plasma concentrations. (CYP3A and/or CYP2D6 inhibition)	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for these antiarrhythmics when co-administered with REZOLSTA. Co-administration of amiodarone, bepridil, dronedarone, ivabradine, quinidine, or ranolazine and REZOLSTA is contraindicated (see section 4.3).

Digoxin	Based on theoretical considerations REZOLSTA is expected to increase digoxin plasma concentrations. (P-glycoprotein inhibition)	It is recommended that the lowest possible dose of digoxin should initially be given to patients on REZOLSTA. The digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state of the subject.
ANTIBIOTIC		
Clarithromycin	Based on theoretical considerations clarithromycin is expected to increase darunavir and/or cobicistat plasma concentrations. (CYP3A inhibition) Concentrations of clarithromycin may be increased upon co-administration with REZOLSTA. (CYP3A inhibition)	Caution should be exercised when clarithromycin is combined with REZOLSTA. For patients with renal impairment the Summary of Product Characteristics for clarithromycin should be consulted for the recommended dose.
ANTICOAGULANT/PLATELET AGGREGATION INHIBITOR		
Apixaban Edoxaban Rivaroxaban	Based on theoretical considerations co-administration of REZOLSTA with these anticoagulants may increase concentrations of the anticoagulant. which may lead to an increased bleeding risk. (CYP3A and/or P-glycoprotein inhibition)	Co-administration of REZOLSTA and these anticoagulants is not recommended.
Dabigatran Ticagrelor	Based on theoretical considerations co-administration of REZOLSTA with dabigatran or ticagrelor may increase concentrations of the anticoagulant. (CYP3A and/or P-glycoprotein inhibition).	Concomitant administration of REZOLSTA with dabigatran or ticagrelor is contraindicated.
Clopidogrel	Based on theoretical considerations co-administration of REZOLSTA with clopidogrel is expected to decrease clopidogrel active metabolite plasma concentration, which may reduce the antiplatelet activity of clopidogrel.	Co-administration of REZOLSTA with clopidogrel is not recommended. Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended (see section 4.3).
Warfarin	Based on theoretical considerations REZOLSTA may alter warfarin plasma concentrations.	It is recommended that the international normalised ratio (INR) be monitored when warfarin is co-administered with REZOLSTA.

ANTICONVULSANTS		
Carbamazepine Phenobarbital Phenytoin	Based on theoretical considerations these anticonvulsants are expected to decrease darunavir and/or cobicistat plasma concentrations. (CYP3A induction).	Co-administration of REZOLSTA and these anticonvulsants is contraindicated (see section 4.3).
Clonazepam	Based on theoretical considerations REZOLSTA is expected to increase concentrations of clonazepam. (inhibition of CYP3A)	Clinical monitoring is recommended when co-administering REZOLSTA with clonazepam.
ANTI-DEPRESSANTS		
Herbal supplements St John's wort	Based on theoretical considerations St John's wort is expected to decrease darunavir and/or cobicistat plasma concentrations. (CYP3A induction)	Co-administration of St John's wort and REZOLSTA is contraindicated (see section 4.3).
Paroxetine Sertraline	Based on theoretical considerations REZOLSTA is expected to increase these anti-depressant plasma concentrations. (CYP2D6 and/or CYP3A inhibition) Prior data with ritonavir-boosted darunavir however showed a decrease in these anti-depressant plasma concentrations (unknown mechanism); the latter may be specific to ritonavir.	If these anti-depressants are to be used with REZOLSTA clinical monitoring is recommended and a dose adjustment of the anti-depressant may be needed.
Amitriptyline Desipramine Imipramine Nortriptyline Trazodone	Based on theoretical considerations REZOLSTA is expected to increase these anti-depressant plasma concentrations. (CYP2D6 and/or CYP3A inhibition)	
ANTI-DIABETICS		
Metformin	Based on theoretical considerations REZOLSTA is expected to increase metformin plasma concentrations. (MATE1 inhibition)	Careful patient monitoring and dose adjustment of metformin is recommended in patients who are taking REZOLSTA.
ANTIEMETICS		
Domperidone	Not studied.	Co-administration of domperidone with REZOLSTA is contraindicated.

ANTIFUNGALS		
Clotrimazole Fluconazole Itraconazole Isavuconazole Posaconazole	Based on theoretical considerations REZOLSTA is expected to increase these antifungal plasma concentrations, and darunavir and/or cobicistat plasma concentrations may be increased by the antifungals. (CYP3A inhibition and/or P-gp inhibition)	Caution is warranted and clinical monitoring is recommended. When co-administration is required, the daily dose of itraconazole should not exceed 200 mg.
Voriconazole	Concentrations of voriconazole may increase or decrease when co-administered with REZOLSTA.	Voriconazole should not be combined with REZOLSTA unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
ANTIGOUT MEDICINES		
Colchicine	Based on theoretical considerations REZOLSTA is expected to increase colchicine plasma concentrations. (CYP3A and/or P-glycoprotein inhibition)	A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with REZOLSTA is required. The combination of colchicine and REZOLSTA is contraindicated in patients with renal or hepatic impairment (see section 4.3).
ANTIMALARIALS		
Artemether/Lumefantrine	Based on theoretical considerations REZOLSTA is expected to increase lumefantrine plasma concentrations. (CYP3A inhibition)	REZOLSTA and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.
ANTIMYCOBACTERIALS		
Rifampicin	Based on theoretical considerations rifampin is expected to decrease darunavir and/or cobicistat plasma concentrations. (CYP3A induction)	The combination of rifampicin and REZOLSTA is contraindicated (see section 4.3).

Rifabutin Rifapentine	Based on theoretical considerations these antimycobacterials are expected to decrease darunavir and/or cobicistat plasma concentrations. (CYP3A induction)	Co-administration of REZOLSTA with rifabutin and rifapentine is not recommended. If the combination is needed, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin. Further dosage reduction of rifabutin has not been studied. It should be kept in mind that the twice weekly dosage of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients. This recommendation is different from ritonavir-boosted darunavir. Consult the Summary of Product Characteristics for darunavir for further details.
ANTI-NEOPLASTICS		
Dasatinib Nilotinib Vinblastine Vincristine	Based on theoretical considerations REZOLSTA is expected to increase these anti-neoplastic plasma concentrations. (CYP3A inhibition)	Concentrations of these medicinal products may be increased when co-administered with REZOLSTA resulting in the potential for increased adverse events usually associated with these medicinal products. Caution should be exercised when combining one of these anti-neoplastic agents with REZOLSTA.
Everolimus Irinotecan		Concomitant use of everolimus or irinotecan and REZOLSTA is not recommended.

ANTIPSYCHOTICS/NEUROLEPTICS		
Perphenazine Risperidone Thioridazine	Based on theoretical considerations REZOLSTA is expected to increase these neuroleptic plasma concentrations. (CYP3A, CYP2D6 and/or P-gp inhibition)	Clinical monitoring is recommended when co-administering REZOLSTA perphenazine, risperidone or thioridazine. For these neuroleptics, consider reducing the dose of the neuroleptic upon co-administration with REZOLSTA.
Lurasidone Pimozide Sertindole Quetiapine		The combination of lurasidone, pimozide, quetiapine or sertindole and REZOLSTA is contraindicated (see section 4.3).
β-BLOCKERS		
Carvedilol Metoprolol Timolol	Based on theoretical considerations REZOLSTA is expected to increase these beta blocker plasma concentrations. (CYP3A inhibition)	Clinical monitoring is recommended when co-administering REZOLSTA with beta-blockers and a lower dose of the beta-blocker should be considered.
CALCIUM CHANNEL BLOCKERS		
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Based on theoretical considerations REZOLSTA is expected to increase these calcium channel blocker plasma concentrations. (CYP3A and/or CYP2D6 inhibition)	Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are co-administered with REZOLSTA.
CORTICOSTEROIDS		
Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone).	Based on theoretical considerations REZOLSTA is expected to increase these corticosteroid plasma concentrations. (CYP3A inhibition)	Concomitant use of REZOLSTA and corticosteroids (all routes of administration) that are metabolised by CYP3A may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone should be considered, particularly for long term use.
Dexamethasone (systemic)	Based on theoretical considerations (systemic) dexamethasone is expected to decrease darunavir and/or cobicistat plasma concentrations. (CYP3A induction)	Systemic dexamethasone should be used with caution when combined with REZOLSTA.

ENDOTHELIN RECEPTOR ANTAGONISTS		
Bosentan	Based on theoretical considerations bosentan is expected to decrease darunavir and/or cobicistat plasma concentrations. (CYP3A induction) REZOLSTA is expected to increase bosentan plasma concentrations. (CYP3A inhibition)	Co-administration of REZOLSTA and bosentan is not recommended.
HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS		
NS3-4A inhibitors		
Elbasvir/grazoprevir	Based on theoretical considerations REZOLSTA may increase the exposure to grazoprevir. (OATP1B and CYP3A inhibition)	Concomitant use of REZOLSTA with elbasvir/grazoprevir is contraindicated (see section 4.3).
Glecaprevir/pibrentasvir	Based on theoretical considerations REZOLSTA may increase the exposure to glecaprevir and pibrentasvir. (P-gp, BCRP and/or OATP1B1/3 inhibition)	It is not recommended to co-administer REZOLSTA with glecaprevir/pibrentasvir.
HMG CO-A REDUCTASE INHIBITORS		
Atorvastatin Fluvastatin Pitavastatin Pravastatin Rosuvastatin	Atorvastatin (10 mg once daily): atorvastatin AUC ↑ 290% atorvastatin Cmax ↑ 319% atorvastatin Cmin ND Rosuvastatin (10 mg once daily): rosuvastatin AUC ↑ 93% rosuvastatin Cmax ↑ 277% rosuvastatin Cmin ND Based on theoretical considerations REZOLSTA is expected to increase the plasma concentrations of fluvastatin, pitavastatin, pravastatin, lovastatin and simvastatin. (CYP3A inhibition and/or transport)	Concomitant use of a HMG CoA reductase inhibitor and REZOLSTA may increase plasma concentrations of the lipid lowering agent, which may lead to adverse events such as myopathy. When administration of HMG CoA reductase inhibitors and REZOLSTA is desired, it is recommended to start with the lowest dose and titrate up to the desired clinical effect while monitoring for safety. Concomitant use of REZOLSTA with lovastatin and simvastatin is contraindicated (see section 4.3).
Lovastatin Simvastatin		
OTHER LIPID MODIFYING AGENTS		
Lomitapide	Based on theoretical considerations, REZOLSTA is expected to increase the exposure of lomitapide when co-administered. (CYP3A inhibition)	Co-administration is contraindicated (see section 4.3)
H_2-RECEPTOR ANTAGONISTS		
Cimetidine Famotidine Nizatidine Ranitidine	Based on theoretical considerations, no mechanistic interaction is expected.	REZOLSTA can be co-administered with H_2-receptor antagonists without dose adjustments.

IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus Everolimus	Based on theoretical considerations REZOLSTA is expected to increase these immunosuppressant plasma concentrations. (CYP3A inhibition)	Therapeutic drug monitoring of the immunosuppressive agent must be done when co-administration occurs. Concomitant use of everolimus and REZOLSTA is not recommended.
INHALED BETA AGONISTS		
Salmeterol	Based on theoretical considerations REZOLSTA is expected to increase salmeterol plasma concentrations. (CYP3A inhibition)	Concomitant use of salmeterol and REZOLSTA is not recommended. The combination may result in increased risk of cardiovascular adverse event with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESICS/TREATMENT OF OPIOID DEPENDENCE		
Buprenorphine/naloxone	Based on theoretical considerations REZOLSTA may increase buprenorphine and/or norbuprenorphine plasma concentrations.	Dose adjustment for buprenorphine may not be necessary when co-administered with REZOLSTA but a careful clinical monitoring for signs of opiate toxicity is recommended.
Methadone	Based on theoretical considerations REZOLSTA may increase methadone plasma concentrations. With ritonavir-boosted darunavir, a small decrease in methadone plasma concentrations was observed. Consult the Summary of Product Characteristics for darunavir for further details.	No adjustment of methadone dosage is expected when initiating co-administration with REZOLSTA. Clinical monitoring is recommended, as maintenance therapy may need to be adjusted in some patients.
Fentanyl Oxycodone Tramadol	Based on theoretical considerations REZOLSTA may increase plasma concentrations of these analgesics. (CYP2D6 and/or CYP3A inhibition)	Clinical monitoring is recommended when co-administering REZOLSTA with these analgesics.

OESTROGEN-BASED CONTRACEPTIVES		
Drospirenone (3 mg once daily) Ethinylestradiol (0.02 mg once daily) Norethindrone	drospirenone AUC ↑ 58% drospirenone C_{max} ↑ 15% drospirenone C_{min} ND ethinylestradiol AUC ↓ 30% ethinylestradiol C_{max} ↓ 14% ethinylestradiol C_{min} ND Based on theoretical considerations REZOLSTA may alter norethindrone plasma concentrations. (CYP3A inhibition, UGT/SULT induction)	Alternative or additional contraceptive measures are recommended when oestrogen based contraceptives are co administered with REZOLSTA. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency. When REZOLSTA is co-administered with a drospirenone-containing product, clinical monitoring is recommended due to the potential for hyperkalaemia.
OPIOID ANTAGONIST		
Naloxegol	Not studied.	Co-administration of REZOLSTA and naloxegol is contraindicated.
PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS		
For the treatment of erectile dysfunction Sildenafil Tadalafil Vardenafil	Based on theoretical considerations REZOLSTA is expected to increase these PDE-5 inhibitor plasma concentrations. (CYP3A inhibition)	Concomitant use of PDE-5 inhibitors for the treatment of erectile dysfunction with REZOLSTA should be done with caution. If concomitant use of REZOLSTA with sildenafil, vardenafil or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 72 hours or tadalafil at a single dose not exceeding 10 mg in 72 hours is recommended.
Avanafil		The combination of avanafil and REZOLSTA is contraindicated (see section 4.3).

For the treatment of pulmonary arterial hypertension Sildenafil Tadalafil	Based on theoretical considerations REZOLSTA is expected to increase these PDE-5 inhibitor plasma concentrations. (CYP3A inhibition)	A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension co-administered with REZOLSTA has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope). Therefore, co-administration of REZOLSTA and sildenafil when used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3). Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with REZOLSTA is not recommended.
PROTON PUMP INHIBITORS		
Dexlansoprazole Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole	Based on theoretical considerations, no mechanistic interaction is expected.	REZOLSTA can be co-administered with proton pump inhibitors without dose adjustments.

SEDATIVES/HYPNOTICS		
Buspirone Clorazepate Diazepam Estazolam Flurazepam Midazolam (parenteral) Zolpidem	Based on theoretical considerations REZOLSTA is expected to increase these sedative/hypnotic plasma concentrations. (CYP3A inhibition)	Clinical monitoring is recommended when co-administering REZOLSTA with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. Caution should be used with co-administration of REZOLSTA and parenteral midazolam. If REZOLSTA is co-administered with parenteral midazolam, it should be done in an intensive care unit or similar setting, which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
Midazolam (oral) Triazolam		Co-administration of oral midazolam or triazolam and REZOLSTA is contraindicated (see section 4.3).
TREATMENT FOR PREMATURE EJACULATION		
Dapoxetine	Not studied.	Co-administration of REZOLSTA with dapoxetine is contraindicated.
UROLOGICAL DRUGS		
Fesoterodine Solifenacin	Not studied.	Use with caution. Monitor for fesoterodine or solifenacin adverse reactions, dose reduction of fesoterodine or solifenacin may be necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well controlled trials with darunavir, or cobicistat, in pregnant women. Studies in animals do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Treatment with darunavir/cobicistat 800/150 mg during pregnancy results in low darunavir exposure (see section 5.2), which may be associated with an increased risk of treatment failure and an increased risk of HIV transmission to the child. Therapy with REZOLSTA should not be initiated during pregnancy, and women who become pregnant during therapy with REZOLSTA should be switched to an alternative regimen (see sections 4.2 and 4.4).

Breast-feeding

It is not known whether darunavir or cobicistat are excreted in human milk. Studies in rats have demonstrated that darunavir is excreted in milk and at high levels (1,000 mg/kg/day) resulted in toxicity. Studies in animals have demonstrated that cobicistat is excreted in milk. Because of both the

potential for HIV transmission and the potential for adverse reactions in breast-fed infants, mothers should be instructed not to breast-feed under any circumstances if they are receiving REZOLSTA.

Fertility
No human data on the effect of darunavir or cobicistat on fertility are available. There was no effect on mating or fertility in animals (see section 5.3). Based on animal studies, no effect on mating or fertility is expected with REZOLSTA.

4.7 Effects on ability to drive and use machines

REZOLSTA may have a minor influence on the ability to drive and use machines. Dizziness has been reported in some patients during treatment with regimens containing darunavir administered with cobicistat and should be borne in mind when considering a patient's ability to drive or operate machinery

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of REZOLSTA is based on available clinical trial data from darunavir boosted with either cobicistat or ritonavir, from cobicistat and from post-marketing data from darunavir/ritonavir.

As REZOLSTA contains darunavir and cobicistat, the adverse reactions associated with each of the individual compounds may be expected.

The most frequent adverse reactions reported in the pooled data of the Phase 3 study GS-US-216-130 and the REZOLSTA arm of Phase 3 study TMC114FD2HTX3001 were diarrhoea (23%), nausea (17%), rash (13%), and headache (10%). Serious adverse reactions were diabetes mellitus, (drug) hypersensitivity, immune reconstitution inflammatory syndrome, rash, Stevens-Johnson syndrome, and vomiting. All of these serious ADRs occurred in one (0.1%) subject except for rash in 4 (0.6%) subjects.

The most frequent adverse reactions reported during the darunavir/ritonavir clinical development program and as spontaneous reports are diarrhoea, nausea, rash, headache, and vomiting. The most frequent serious reactions are acute renal failure, myocardial infarction, immune reconstitution inflammatory syndrome, thrombocytopenia, osteonecrosis, diarrhoea, hepatitis, and pyrexia.

In the 96 week analysis, the safety profile of darunavir/ritonavir 800/100 mg once daily in treatment-naïve subjects was similar to that seen with darunavir/ritonavir 600/100 mg twice daily in treatment-experienced subjects except for nausea which was observed more frequently in treatment-naïve subjects. This was driven by mild intensity nausea.
Tabulated list of adverse reactions
Adverse reactions are listed by system organ class (SOC) and frequency category. Within each frequency category, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and not known (frequency cannot be estimated from the available data).

Adverse reactions with darunavir/cobicistat in adult patients

MedDRA system organ class Frequency category	Adverse reaction
Immune system disorders	
Common	(drug) hypersensitivity
Uncommon	immune reconstitution inflammatory syndrome

Metabolism and nutrition disorders	
Common	anorexia, , hypercholesterolaemia, hypertriglyceridaemia,
Uncommon	diabetes mellitus, dyslipidaemia, hyperglycaemia, hyperlipidaemia
Psychiatric disorders	
Common	abnormal dreams
Nervous system disorders	
Very common	headache
Gastrointestinal disorders	
Very common	diarrhoea, nausea
Common	vomiting, abdominal pain, abdominal distension, dyspepsia, flatulence,
Uncommon	pancreatitis acute, pancreatic enzymes increased
Hepatobiliary disorders	
Common	hepatic enzyme increased
Uncommon	hepatitis*, cytolytic hepatitis*
Skin and subcutaneous tissue disorders	
Very common	rash (including macular, maculopapular, papular, erythematous, pruritic rash, generalised rash, and allergic dermatitis)
Common	pruritus,
Uncommon	Stevens-Johnson syndrome[#], angioedema, urticaria
Rare	drug reaction with eosinophilia and systemic symptoms*,
Not known	toxic epidermal necrolysis*, acute generalised exanthematous pustulosis*
Musculoskeletal and connective tissue disorders	
Common	myalgia
Uncommon	osteonecrosis*
Reproductive system and breast disorders	
Uncommon	gynaecomastia*
General disorders and administration site conditions	
Common	fatigue, asthenia
Investigations	
Common	increased blood creatinine

* These adverse drug reactions have not been reported in clinical trial experience with darunavir/cobicistat but have been noted with darunavir/ritonavir treatment and could be expected with darunavir/cobicistat too.

[#] When also taking into account the clinical trial data of DRV/COBI/emtricitabine/tenofovir alafenamide, Stevens-Johnson syndrome occurred rarely (in 1 out of 2,551 subjects) consistent with the DRV/rtv clinical trial program (see Severe skin reactions in Section 4.4).

Description of selected adverse reactions

Rash

In clinical trials with darunavir/ritonavir and darunavir/cobicistat, rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing (see

section 4.4). The pooled data of a single-arm trial investigating darunavir 800 mg once daily in combination with cobicistat 150 mg once daily and other antiretrovirals and one arm of a trial in which REZOLSTA 800/150 mg once daily and other antiretrovirals were administered, showed that 1.9% of patients discontinued treatment due to rash.

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

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

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Immune reconstitution inflammatory syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Bleeding in haemophiliac patients
There have been reports of increased spontaneous bleeding in haemophiliac patients receiving antiretroviral protease inhibitors (see section 4.4).

Decrease estimated creatinine clearance
Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of renal tubular secretion of creatinine. An increase in serum creatinine due to the inhibitory effect of cobicistat generally does not exceed 0.4 mg/dl.

The effect of cobicistat on serum creatinine was investigated in a Phase I trial in subjects with normal renal function (eGFR ≥ 80 mL/min, n = 12) and mild to moderate renal impairment (eGFR:50-79 mL/min, n = 18). Change of estimated glomerular filtration rate calculated by Cockcroft-Gault method ($eGFR_{CG}$) from baseline was observed within 7 days after start 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 and did not affect the actual glomerular filtration rate, as determined by the clearance of probe drug iohexol.

In the Phase III single-arm trial (GS-US-216-130), a decrease in $eGFR_{CG}$ was noted at week 2, which remained stable through week 48. The mean $eGFR_{CG}$ change from baseline was –9.6 mL/min at week 2, and –9.6 mL/min at week 48. In the REZOLSTA arm of Phase III trial TMC114FD2HTX3001, mean $eGFR_{CG}$ change from baseline was -11.1 mL/min at week 48 and mean $eGFR_{cystatin\ C}$ change from baseline was +2.9 mL/min/1.73 m² at week 48.

For more information consult the cobicistat Summary of Product Characteristics.

Paediatric population
The safety and efficacy of REZOLSTA in paediatric patients aged 3 to 17 years has not been established (see sections 4.4 and 5.3).

Other special populations

Patients co-infected with hepatitis B and/or hepatitis C virus
Limited information is available on the use of REZOLSTA in patients co-infected with hepatitis B and/or C virus. Among 1,968 treatment-experienced patients receiving darunavir co-administered with ritonavir 600/100 mg twice daily, 236 patients were co-infected with hepatitis B or C. Co-infected patients were more likely to have baseline and treatment emergent hepatic transaminase elevations than those without chronic viral hepatitis (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.

4.9 Overdose

Human experience of acute overdose with REZOLSTA or darunavir in combination with cobicistat is limited. Single doses up to 3,200 mg of darunavir as oral solution alone and up to 1,600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

There is no specific antidote for overdose with REZOLSTA. Treatment of overdose with REZOLSTA 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, antivirals for treatment of HIV infection, combinations ATC code: J05AR14

Mechanism of action
Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (K_D of 4.5 x 10^{-12}M). It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles.

Cobicistat is a mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as darunavir, where bioavailability is limited and half-life is shortened due to CYP3A-dependent metabolism.

Antiviral activity *in vitro*
Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM.

These EC_{50} values are well below the 50% cellular toxicity concentration range of 87 µM to > 100 µM.

Cobicistat has no detectable antiviral activity against HIV-1 and does not antagonise the antiviral effect of darunavir.

Resistance

In vitro selection of darunavir-resistant virus from wild type 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.

The resistance profile of REZOLSTA is driven by darunavir. Cobicistat does not select any HIV resistance mutations, due to its lack of antiviral activity. The resistance profile of REZOLSTA is supported by two Phase III trials conducted with darunavir/ritonavir in treatment-naïve (ARTEMIS) and treatment-experienced (ODIN) patients and the analysis of 48 week data from trial GS-US-216-130 in treatment-naïve and treatment-experienced patients.

Low rates of developing resistant HIV-1 virus were observed in ART-naïve patients who are treated for the first time with REZOLSTA or darunavir/ritonavir 800/100 mg once daily in combination with other ART, and in ART-experienced patients with no darunavir RAMs receiving REZOLSTA or darunavir/ritonavir 800/100 mg once daily in combination with other ART. The table below shows the development of HIV-1 protease mutations and loss of susceptibility to HIV PIs in virologic failures at endpoint in the GS-US-216-130, ARTEMIS and ODIN trials.

	GS-US-216-130[a]		ARTEMIS[b]	ODIN[b]	
	Treatment-naïve darunavir/cobicistat 800/150 mg once daily N = 295	Treatment-experienced darunavir/cobicistat 800/150 mg once daily N = 18	Treatment-naïve darunavir/ritonavir 800/100 mg once daily N = 343	Treatment-experienced darunavir/ritonavir 800/100 mg once daily N = 294	Treatment-experienced darunavir/ritonavir 600/100 mg twice daily N = 296
Number of subjects with virologic failure and genotype data that develop mutations[c] at endpoint, n/N					
Primary (major) PI mutations	0/8	1/7	0/43	1/60	0/42
PI RAMs	2/8	1/7	4/43	7/60	4/42
Number of subjects with virologic failure and phenotype data that show a loss of susceptibility to PIs at endpoint compared to baseline[d], n/N					
HIV PI					
darunavir	0/8	0/7	0/39	1/58	0/41
amprenavir	0/8	0/7	0/39	1/58	0/40
atazanavir	0/8	0/7	0/39	2/56	0/40
indinavir	0/8	0/7	0/39	2/57	0/40
lopinavir	0/8	0/7	0/39	1/58	0/40
saquinavir	0/8	0/7	0/39	0/56	0/40
tipranavir	0/8	0/7	0/39	0/58	0/41

[a] Virologic failures selected for resistance testing were defined as: never suppressed: HIV-1 RNA < 1 $\log_{10}$ reduction from baseline and ≥ 50 copies/mL at week 8, confirmed at the following visit; rebound: HIV-1 RNA < 50 copies/mL followed by confirmed HIV-1 RNA to ≥ 400 copies/mL or confirmed > 1 $\log_{10}$ HIV-1 RNA increase from the nadir; discontinuations with HIV-1 RNA ≥ 400 copies/mL at last visit

[b] Virologic failures based on TLOVR non-VF censored algorithm (HIV-1 RNA > 50 copies/mL)

[c] IAS-USA lists

[d] In GS-US-216-130 baseline phenotype was not available

Cross-resistance

In the virologic failures of the GS-US-216-130 trial no cross-resistance with other HIV PIs was observed. Refer to the table above for information on ARTEMIS and ODIN.

Clinical results

The antiretroviral effect of REZOLSTA is due to the darunavir component. The activity of cobicistat as a pharmacokinetic enhancer to darunavir has been demonstrated in pharmacokinetic trials. In these pharmacokinetic trials, 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 REZOLSTA is bioequivalent to darunavir 800 mg once daily in combination with cobicistat 150 mg once daily co-administered as single medicinal products (see section 5.2).

The evidence of efficacy of REZOLSTA once daily is based on the analysis of 48 week data from trial GS-US-216-130 in ART-naïve and ART-experienced patients, trial TMC114FD2HTX3001 in ART-naïve patients, and two Phase III trials ARTEMIS and ODIN conducted with darunavir/ritonavir 800/100 mg q.d. in ART-naïve and ART-experienced patients, respectively.

Description of clinical studies of REZOLSTA in adults

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

GS-US-216-130 is a single-arm, open-label, Phase III 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 optimised background regimen (OBR) 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 ≥ 1,000 copies/mL. The table below shows the efficacy data of the 48 week analyses from the GS-US-216-130 trial:

	GS-US-216-130		
Outcomes at Week 48	Treatment-naïve darunavir/cobicistat 800/150 mg once daily + OBR N = 295	Treatment-experienced darunavir/cobicistat 800/150 mg once daily + OBR N = 18	All subjects darunavir/cobicistat 800/150 mg once daily + OBR N = 313
HIV-1 RNA < 50 copies/mL[a]	245 (83.1%)	8 (44.4%)	253 (80.8%)
mean HIV-1 RNA log change from baseline (log_{10} copies/mL)	-3.01	-2.39	-2.97
CD4+ cell count mean change from baseline[b]	+174	+102	+170

[a] Imputations according to the TLOVR algorithm

[b] Last Observation Carried Forward imputation

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

TMC114FD2HTX3001 is a randomised, active-controlled, double blind, Phase III trial to evalate the efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide versus darunavir/cobicistat fixed-dose combination + emtricitabine/tenofovir disoproxil fumarate. In the darunavir/cobicistat fixed-dose combination treament arm, 363 HIV-1 infected, adult, treatment-naïve patients were treated.

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 darunavir/cobicistat arm of the TMC114FD2HTX3001 trial:

	TMC114FD2HTX3001 (darunavir/cobicistat arm)
Outcomes at Week 48	**Treatment-naïve darunavir/cobicistat 800/150 mg once daily + emtricitabine/tenofovir disoproxil fumarate N = 363**
HIV-1 RNA < 50 copies/mL[a]	321 (88.4%)
Virologic failure[a]	12 (3.3%)
No virologic data in 48-week window[a]	30 (8.3%)
CD4+ cell count mean change from baseline[b]	+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

Description of clinical studies of darunavir/ritonavir in adults

Efficacy of darunavir 800 mg once daily co-administered with 100 mg ritonavir once daily in ART-naïve patients

The evidence of efficacy of darunavir/ritonavir 800/100 mg once daily is based on the analyses of 192 week data from the randomised, controlled, open-label Phase III trial ARTEMIS in antiretroviral treatment-naïve HIV-1 infected patients comparing darunavir/ritonavir 800/100 mg once daily 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 once daily and emtricitabine 200 mg once daily.

The table below shows the efficacy data of the 48 week and 96 week analyses from the ARTEMIS trial:

ARTEMIS						
	Week 48[a]			Week 96[b]		
Outcomes	darunavir/ ritonavir 800/100 mg once daily N = 343	lopinavir/ ritonavir 800/200 mg per day N = 346	Treatment difference (95% CI of difference)	darunavir/ ritonavir 800/100 mg once daily N = 343	lopinavir/ ritonavir 800/200 mg per day N = 346	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/mL[c] All patients	83.7% (287)	78.3% (271)	5.3% (-0.5; 11.2)[d]	79.0% (271)	70.8% (245)	8.2% (1.7; 14.7)[d]
With baseline HIV-RNA < 100,000	85.8% (194/226)	84.5% (191/226)	1.3% (-5.2; 7.9)[d]	80.5% (182/226)	75.2% (170/226)	5.3% (-2.3; 13.0)[d]
With baseline HIV-RNA ≥ 100,000	79.5% (93/117)	66.7% (80/120)	12.8% (1.6; 24.1)[d]	76.1% (89/117)	62.5% (75/120)	13.6% (1.9; 25.3)[d]
With baseline CD4+ cell count < 200	79.4% (112/141)	70.3% (104/148)	9.2% (-0.8; 19.2)[d]	78.7% (111/141)	64.9% (96/148)	13.9% (3.5; 24.2)[d]
With baseline CD4+ cell count ≥ 200	86.6% (175/202)	84.3% (167/198)	2.3% (-4.6; 9.2)[d]	79.2% (160/202)	75.3% (149/198)	4.0% (-4.3; 12.2)[d]
median CD4+ cell count change from baseline (x 10^6/l)[e]	+137	+141		+171	+188	

[a] Data based on analyses at week 48
[b] Data based on analyses at week 96
[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

Non-inferiority in virologic response to the darunavir/ritonavir treatment, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/mL, was demonstrated (at the pre-defined 12% non-inferiority margin) for both Intent-To-Treat (ITT) and On Protocol (OP) populations in the 48 week analysis. These results were confirmed in the analyses of data at 96 weeks of treatment in the ARTEMIS trial. These results were sustained up to 192 weeks of treatment in the ARTEMIS trial.

Efficacy of darunavir 800 mg once daily co-administered with 100 mg ritonavir once daily in ART-experienced patients
ODIN is a Phase III, randomised, open-label trial comparing darunavir/ritonavir 800/100 mg once daily versus darunavir/ritonavir 600/100 mg twice daily in ART-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 screening HIV-1 RNA > 1,000 copies/mL. Efficacy analysis is based on 48 weeks of treatment (see table below). Both arms used an optimised background regimen (OBR) of ≥ 2 NRTIs.

ODIN			
	Week 48		
Outcomes	darunvir/ritonavir 800/100 mg once daily + OBR N = 294	darunvir/ritonavir 600/100 mg twice daily + OBR N = 296	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/mL[a]	72.1% (212)	70.9% (210)	1.2% (-6.1; 8.5)[b]
With Baseline HIV-1 RNA (copies/mL)			
< 100,000	77.6% (198/255)	73.2% (194/265)	4.4% (-3.0; 11.9)
≥ 100,000	35.9% (14/39)	51.6% (16/31)	-15.7% (-39.2; 7.7)
With Baseline CD4+ cell count (x 10^6/l)			
≥ 100	75.1% (184/245)	72.5% (187/258)	2.6% (-5.1; 10.3)
< 100	57.1% (28/49)	60.5% (23/38)	-3.4% (-24.5; 17.8)
With HIV-1 clade			
Type B	70.4% (126/179)	64.3% (128/199)	6.1% (-3.4; 15.6)
Type AE	90.5% (38/42)	91.2% (31/34)	-0.7% (-14.0, 12.6)
Type C	72.7% (32/44)	78.8% (26/33)	-6.1% (-2.6, 13.7)
Other[c]	55.2% (16/29)	83.3% (25/30)	-28.2% (-51.0, -5.3)
mean CD4+ cell count change from baseline (x 10^6/l)[e]	+108	+112	-5[d] (-25; 16)

[a] Imputations according to the TLOVR algorithm
[b] Based on a normal approximation of the difference in % response
[c] Clades A1, D, F1, G, K, CRF02_AG, CRF12_BF, and CRF06_CPX
[d] Difference in means
[e] Last Observation Carried Forward imputation

At 48 weeks, virologic response, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/mL, with darunavir/ritonavir 800/100 mg once daily treatment was demonstrated to be non-inferior (at the pre-defined 12% non-inferiority margin) compared to darunavir/ritonavir 600/100 mg twice daily for both ITT and OP populations.

REZOLSTA should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA ≥ 100,000 copies/mL or CD4+ cell count < 100 cells x 10^6/l (see sections 4.2 and 4.4). Limited data is available in patients with HIV-1 clades other than B.

5.2 Pharmacokinetic properties

Darunavir exposure was shown to be comparable in a bioavailability trial between REZOLSTA and darunavir/ritonavir 800/100 mg q.d. at steady-state and fed conditions in healthy subjects.
The bioequivalence between REZOLSTA and darunavir/cobicistat 800/150 mg co-administered as single agents was established under fed and fasted conditions in healthy subjects.

Absorption

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

Darunavir was rapidly absorbed following oral administration of REZOLSTA in healthy volunteers. Maximum plasma concentration of darunavir in the presence of cobicistat is generally achieved within 3 to 4.5 hours. Following oral administration of REZOLSTA in healthy volunteers, maximum plasma concentrations of cobicistat were observed 2 to 5 hours post-dose.

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

Distribution

Darunavir
Darunavir is approximately 95% bound to plasma protein. Darunavir binds primarily to plasma α_1-acid glycoprotein.
Following intravenous administration, the volume of distribution of darunavir alone was 88.1 ± 59.0 l (Mean ± SD) and increased to 131 ± 49.9 l (Mean ± SD) in the presence of 100 mg twice-daily ritonavir.

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

Biotransformation

Darunavir
In vitro experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolised by the hepatic CYP system and almost exclusively by isozyme CYP3A4. A ^{14}C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir with ritonavir dose was due to the parent active substance. 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 wild type HIV.

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

Elimination

Darunavir
After a 400/100 mg ^{14}C-darunavir with 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 terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir.
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.

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 plasma half-life of cobicistat following administration of REZOLSTA is approximately 3-4 hours.

Special populations

Paediatric population
The pharmacokinetics of REZOLSTA in paediatric patients have not been investigated.

Elderly
Darunavir
Limited information is available in this population. Population pharmacokinetic analysis in HIV infected patients showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV infected patients (n = 12, age ≥ 65 years) (see section 4.4). However, only limited data were available in patients above the age of 65 years.

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

Gender
Darunavir
Population pharmacokinetic analysis showed a slightly higher darunavir exposure (16.8%) in HIV infected females compared to males. This difference is not clinically relevant.

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

Renal impairment
REZOLSTA has not been investigated in patients with renal impairment.

Darunavir
Results from a mass balance study with ^{14}C-darunavir with ritonavir showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine unchanged.

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 sections 4.2 and 4.4).

Cobicistat
A trial 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
REZOLSTA has not been investigated in patients with hepatic impairment.

Darunavir
Darunavir is primarily metabolised and eliminated by the liver. In a multiple dose trial with darunavir/ritonavir (600/100 mg) twice daily, it was demonstrated that the total plasma concentrations 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. However, unbound darunavir concentrations were approximately 55% (Child-Pugh Class A) and 100% (Child-Pugh Class B) higher, respectively. The clinical relevance of this increase is unknown, therefore, darunavir/ritonavir should be used with caution. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see sections 4.2, 4.3 and 4.4).

Cobicistat
Cobicistat is primarily metabolised and eliminated by the liver. A trial 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 REZOLSTA 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 darunavir and cobicistat (refer to sections 4.4 and 4.8).

Pregnancy and postpartum
Treatment with REZOLSTA during pregnancy results in low darunavir exposure. In women receiving REZOLSTA during the second 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 third trimester of pregnancy, total darunavir C_{max}, AUC_{24h} and C_{min} values were 37%, 50% and 89% lower, respectively, as compared with postpartum. The unbound fraction was also substantially reduced, including around 90% reductions of C_{min} levels. The main cause of these low exposures is a marked reduction in cobicistat exposure as a consequence of pregnancy-associated enzyme induction (see below).

Pharmacokinetic results of total darunavir after administration of darunavir/cobicistat 800/150 mg once daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy, and postpartum

Pharmacokinetics of total darunavir (mean ± SD)	**Second trimester of pregnancy N=7**	**Third trimester of pregnancy N=6**	**Postpartum (6-12 weeks) N=6**
C_{max}, ng/mL	4,340 ± 1,616	4,910 ± 970	7,918 ± 2,199
AUC_{24h}, ng.h/mL	47,293 ± 19,058	47,991 ± 9,879	99,613 ± 34,862
C_{min}, ng/mL	168 ± 149	184 ± 99	1,538 ± 1,344

The exposure to cobicistat was lower during pregnancy, potentially leading to suboptimal boosting of darunavir. During the second trimester of pregnancy, cobicistat C_{max}, AUC_{24h}, and C_{min} were 50%, 63%, and 83% lower, respectively, as compared with postpartum. During the third trimester of pregnancy, cobicistat C_{max}, AUC_{24h}, and C_{min}, were 27%, 49%, and 83% lower, respectively, as compared with postpartum.

5.3 Preclinical safety data

Darunavir
Animal toxicology studies have been conducted at exposures up to clinical exposure levels with darunavir alone, in mice, rats and dogs and in combination with ritonavir in rats and dogs.

In repeated-dose toxicology studies in mice, rats and dogs, there were only limited effects of treatment with darunavir. In rodents the target organs identified were the haematopoietic system, the blood coagulation system, liver and thyroid. A variable but limited decrease in red blood cell-related parameters was observed, together with increases in activated partial thromboplastin time.

Changes were observed in liver (hepatocyte hypertrophy, vacuolation, increased liver enzymes) and thyroid (follicular hypertrophy). In the rat, the combination of darunavir with ritonavir lead to a small increase in effect on RBC parameters, liver and thyroid and increased incidence of islet fibrosis in the pancreas (in male rats only) compared to treatment with darunavir alone. In the dog, no major toxicity findings or target organs were identified up to exposures equivalent to clinical exposure at the recommended dose.

In a study conducted in rats, the number of corpora lutea and implantations were decreased in the presence of maternal toxicity. Otherwise, there were no effects on mating or fertility with darunavir treatment up to 1,000 mg/kg/day and exposure levels below (AUC-0.5 fold) of that in human at the clinically recommended dose. Up to same dose levels, there was no teratogenicity with darunavir in rats and rabbits when treated alone nor in mice when treated in combination with ritonavir. The exposure levels were lower than those with the recommended clinical dose in humans. In a pre- and postnatal development assessment in rats, darunavir with and without ritonavir, caused a transient reduction in body weight gain of the offspring pre-weaning and there was a slight delay in the opening of eyes and ears. Darunavir in combination with ritonavir caused a reduction in the number of pups that exhibited the startle response on day 15 of lactation and a reduced pup survival during lactation. These effects may be secondary to pup exposure to the active substance via the milk and/or maternal toxicity. No post weaning functions were affected with darunavir alone or in combination with ritonavir. In juvenile rats receiving darunavir up to days 23-26, increased mortality was observed with convulsions in some animals. Exposure in plasma, liver and brain was considerably higher than in adult rats after comparable doses in mg/kg between days 5 and 11 of age. After day 23 of life, the exposure was comparable to that in adult rats. The increased exposure was likely at least partly due to immaturity of the drug-metabolising enzymes in juvenile animals. No treatment related mortalities were noted in juvenile rats dosed at 1,000 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 REZOLSTA should not be used in paediatric patients below 3 years of age.

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1,000 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 and thyroid tumours 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 when co-administered with ritonavir 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.

After 2 years administration of darunavir at exposures at or below the human exposure, kidney changes were observed in mice (nephrosis) and rats (chronic progressive nephropathy).

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
Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. No teratogenic effects were observed in rats and rabbit developmental toxicity studies. In rats, ossification changes in the spinal column and sternebrae of fetuses occurred at a dose that produced significant maternal toxicity.

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

A long term carcinogenicity study of cobicistat in rats revealed tumourigenic potential specific for this species, that is regarded as of no relevance for humans. A long term carcinogenicity study in mice did not show any carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Silicified microcrystalline cellulose
Colloidal silicon dioxide
Crospovidone (type B)
Hypromellose 2910 15 mPa.s;
Magnesium stearate

Tablet film-coat
Polyvinyl alcohol– partially hydrolysed
Titanium dioxide
Macrogol/ peg 3350
Talc
Iron oxide red
Iron oxide black

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
6 weeks after first opening

6.4 Special precautions for storage

. Do not store above 30°C

6.5 Nature and contents of container

White, high density polyethylene (HDPE) bottle containing 30 tablets, fitted with polypropylene (PP) child resistant closure with induction seal.

Pack size of one bottle.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Revised on 12-2021

Manufactured by: Janssen Cilag S.p.A, Via C. Janssen, Borgo S. Michele 04010, Latina, Italy, Italy
MAH: J-C Health Care Ltd., Kibbutz Shefayim 6099000, Israel