אושר 8.15

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Prezista 400mg, Prezista 600mg, Prezista 800mg:
Adult patients:
Prezista, co-administered with ritonavir (Prezista/rtv), and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV -1) infection for patients over 18 years of age.

Prezista 75mg, Prezista 150mg:
Adult patients:
Prezista, co-administered with ritonavir (Prezista/rtv), and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV -1) infection.
This indication is based on analyses of plasma HIV-1 RNA levels and CD4+ cell counts from 2 controlled phase 3 trials of 48 weeks duration in antiretroviral treatment - naive and treatment-experienced patients and 2 controlled phase 2 trials of 96 weeks duration in clinically advanced, treatment-experienced adult patients .

Pediatric patients:
Prezista, co-administered with ritonavir (Prezista/rtv), and with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in treatment-experienced pediatric patients 6 years of age and older .
This indication is based on 24 Week analyses of plasma HIV-1 RNA levels and CD4+ cell counts from an open-label phase 2 trial in antiretroviral treatment-experienced pediatric patients 6 to < 18 years of age.
In treatment-experienced adult and pediatric, the following points should be considered when initiating therapy with Prezista/rtv:
- Treatment history and, when available, genotypic or phenotypic testing, should guide the use of Prezista/rtv.
- The use of other active agents with Prezista/rtv is associated with a greater likelihood of treatment response.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Patients

PREZISTA must be co-administered with ritonavir to exert its therapeutic effect. Failure to correctly co-administer PREZISTA with ritonavir will result in plasma levels of darunavir that will be insufficient to achieve the desired antiviral effect and will alter some drug interactions.

Treatment-Naïve Adult Patients

The recommended oral dose of PREZISTA tablets is 800 mg taken with ritonavir 100 mg once daily and with food.

Treatment-Experienced Adult Patients

Treatment-Experienced Adult Patients	
With no darunavir resistance associated substitutions*	With at least one darunavir resistance associated substitution*
800 mg PREZISTA once daily with ritonavir 100 mg once daily and with food	600 mg PREZISTA twice daily taken with ritonavir 100 mg twice daily and with food

* V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V

For antiretroviral treatment-experienced patients genotypic testing is recommended. However, when genotypic testing is not feasible, PREZISTA/ritonavir 600/100 mg twice daily dosing is recommended.

2.2 Pediatric Patients (age 6 to < 18 years)

Do not use once daily dosing in pediatric patients.

Healthcare professionals should pay special attention to accurate dose selection of PREZISTA, transcription of the medication order, dispensing information and dosing instruction to minimize risk for medication errors, overdose, and underdose.

Prescribers should select the appropriate dose of PREZISTA/ritonavir for each individual child based on body weight (kg) and should not exceed the recommended dose for treatment-experienced adults.

Before prescribing PREZISTA, children weighing greater than or equal to 20 kg should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a tablet, the use of PREZISTA tablets may not be appropriate.

The recommended dose of PREZISTA/ritonavir for pediatric patients (6 to < 18 years of age and weighing at least (20 kg)) is based on body weight (see Table 1) and should not exceed the recommended treatment-experienced adult dose (PREZISTA/ritonavir 600/100 mg b.i.d.). PREZISTA tablets should be taken with ritonavir twice daily and with food.

Table 1: Recommended Dose for Pediatric Patients (6 to < 18 years of age) for PREZISTA Tablets with ritonavir		
Body Weight		Dose
(kg)		
≥ 20 kg – < 30 kg		375 mg PREZISTA/50 mg ritonavir twice daily
≥ 30 kg – < 40 kg		450 mg PREZISTA/60 mg ritonavir twice daily
≥ 40 kg		600 mg PREZISTA/100 mg ritonavir twice daily

Do not use PREZISTA /ritonavir in pediatric patients below 3 years of age [see Warnings and *Precautions (5.11) and Nonclinical Toxicology (12.2)*].
Prezista Tabs are intended only for pediatric patients ≥6years old weighing ≥20 Kg.

2.3 Missed dose(s)
If using the once daily regimen: in case a dose of PREZISTA and/or ritonavir was missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of PREZISTA and ritonavir with food as soon as possible. If this was noticed later than 12 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.
If using the twice daily regimen: in case a dose of PREZISTA and/or ritonavir was missed within 6 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of PREZISTA and ritonavir with food as soon as possible. If this was noticed later than 6 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

2.4 Patients with Hepatic Impairment
Darunavir is metabolised by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, PREZISTA should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir exposure and a worsening of its safety profile. Therefore, PREZISTA must not be used in patients with severe hepatic impairment (Child-Pugh Class C).

3 DOSAGE FORMS AND STRENGTHS
3.1 PREZISTA 75 mg Tablets
PREZISTA (darunavir) 75 mg tablets are supplied as white, caplet-shaped, film-coated tablets containing darunavir ethanolate equivalent to 75 mg of darunavir per tablet. Each tablet is debossed with “75” on one side and “TMC” on the other side.

3.2 PREZISTA 150 mg Tablets
PREZISTA (darunavir) 150 mg tablets are supplied as white, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 150 mg of darunavir per tablet. Each tablet is debossed with “150” on one side and “TMC,” on the other side.

3.4 PREZISTA 400 mg Tablets
PREZISTA (darunavir) 400 mg tablets are supplied as light orange, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 400 mg of darunavir per tablet. Each tablet is debossed with “400” on one side and “TMC” on the other side.

3.5 PREZISTA 600 mg Tablets
PREZISTA (darunavir) 600 mg tablets are supplied as orange, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 600 mg of darunavir per tablet. Each tablet is debossed with “600” on one side and “TMC” on the other side.

3.6 PREZISTA 800 mg Tablets
PREZISTA (darunavir) 800 mg tablets are supplied as dark red, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 800 mg of darunavir per tablet. Each tablet is debossed with “800” on one side and “T” on the other side.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.
Patients with severe (Child-Pugh Class C) hepatic impairment..

Co-administration of PREZISTA/ritonavir is contraindicated with drugs that are highly dependent on cytochrome P450 3A (CYP3A) isoform for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These drugs and other contraindicated drugs (which may lead to reduced efficacy of darunavir) are listed in Table 2 [*also see Drug Interactions (7.3)*, Table 3].

Table-2: Drugs That Are Contraindicated With PREZISTA/ritonavir

Drug Class	**Drugs within Class that are contraindicated with PREZISTA/ritonavir**	**Clinical comment**
Alpha 1adrenoreceptor antagonist	Alfuzosin	Potential for serious and/or life-threatening reactions such as hypotension.
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic	Pimozide , sertindole	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/hypnotics	Orally administered Midazolam, Triazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A. Co-administration of triazolam or orally administered midazolam with PREZISTA/ritonavir may cause large increases in the concentrations of these benzodiazepines. Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Herbal Products	St. John’s Wort (Hypericum perforatum)	Patients taking PREZISTA/ritonavir should not use products containing St. John’s wort because co-

		administration may result in reduced plasma concentrations of darunavir. This may result in loss of therapeutic effect and development of resistance.
HMG CoA Reductase Inhibitors	Lovastatin, Simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis. For dosing recommendation regarding atorvastatin and pravastatin, see Table 3: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction.
Antimycobacterial	Rifampin	Rifampin is a potent inducer of CYP450 metabolism. PREZISTA/ritonavir should not be used in combination with rifampin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
PDE-5 inhibitor	Sildenafil for treatment of pulmonary arterial hypertension , avanafil (PDE-5 inhibitors)	A safe and effective dose for the treatment of pulmonary arterial hypertension has not been established with PREZISTA/ritonavir.There is an increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope).
Anti Allergic	Astemizole, Terfenadine	
Anti HIV	Co-administration with the combination product lopinavir/ritonavir	
antiarrhythmics	amiodarone, bepridil, dronedarone, quinidine, ranolazine, systemic lidocaine	
	ticagrelor (antiplatelets)	
	colchicine when used in patients with renal and/or hepatic impairment (antigout)	
	Quetiapine	

Due to the need for co-administration of PREZISTA with ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications.

5 WARNINGS AND PRECAUTIONS

5.1 General

PREZISTA must be co-administered with ritonavir and food to achieve the desired antiviral effect. Failure to administer PREZISTA with ritonavir and food may result in a loss of efficacy of darunavir.

Please refer to ritonavir prescribing information for additional information on precautionary measures.

5.2 Hepatotoxicity

Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/rtv.
During the clinical development program (N=3,063), hepatitis was reported in 0.5% of patients receiving combination antiretroviral therapy with PREZISTA/rtv. 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 events. 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 PREZISTA/rtv 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 PREZISTA/rtv 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 PREZISTA/rtv, interruption or discontinuation of treatment should be considered promptly.

5.3 Severe Skin Reactions

During the clinical development program (n=3063), severe skin reactions, accompanied by fever and/or elevations of transaminases in some cases, have been reported in 0.4% of subjects. Stevens-Johnson Syndrome was rarely (<0.1%) reported during the clinical development program. During post-marketing experience toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis have been reported. Discontinue PREZISTA/rtv immediately if signs or symptoms of severe skin reactions develop. These can include but are not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Rash (all grades, regardless of causality) occurred in 10.3% of subjects treated with PREZISTA/rtv [*also see Adverse Reactions* (6)]. 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 subjects using PREZISTA/rtv was 0.5%.

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing PREZISTA/rtv + raltegravir compared to subjects receiving PREZISTA/rtv without raltegravir or raltegravir without PREZISTA/rtv. 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.

5.4 Sulfa Allergy

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

5.5 Drug Interactions

Initiation of PREZISTA/ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving PREZISTA/ritonavir, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of PREZISTA/ritonavir, respectively. These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life threatening, or fatal events from greater exposures of concomitant medications.
- Clinically significant adverse reactions from greater exposures of PREZISTA/ritonavir.
- Loss of therapeutic effect of PREZISTA/ritonavir and possible development of resistance.

See **Table 3** for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during PREZISTA/ritonavir therapy; review concomitant medications during PREZISTA/ritonavir therapy; and monitor for the adverse reactions associated with the concomitant drugs *[see Contraindications (4) and Drug Interactions (7)]*.

5.6 Diabetes Mellitus / Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor (PI) therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment

of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued PI therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between PI therapy and these events have not been established.

5.7 Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.8 Immune reconstitution syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including PREZISTA. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

In addition,reactivation of herpes simplex and herpes zoster has been observed in clinical studies with PREZISTA co-administered with low dose ritonavir.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of antiretroviral treatment.

5.9 Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with PIs. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with 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.

5.10 Resistance/Cross-Resistance

Because the potential for HIV cross-resistance among PIs has not been fully explored in PREZISTA/ritonavir treated patients, the effect therapy with PREZISTA will have on the activity of subsequently administered PIs is unknown [*see Microbiology (11.4)*].

5.11 Pediatric Patients

Do not administer PREZISTA/ritonavir in pediatric patients below 3 years of age in view of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age [*see Use in Specific Populations (8.1 and 8.3)*, *Clinical Pharmacology (11.3)*, and *Nonclinical Toxicology (12.2)*].

Prezista Tabs are intended only for pediatric patients ≥6years old weighing ≥20 Kg.

5.12 Osteonecrosis

Although the etiology 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.

5.13 Elderly

As limited information is available on the use of PREZISTA in patients aged 65 and over, caution should be exercised in the administration of PREZISTA in elderly patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy.

5.14 Renal impairment

No special precautions or dose adjustments are required in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by

haemodialysis or peritoneal dialysis. Therefore, no special precautions or dose adjustments are required in these patients

6 ADVERSE REACTIONS

Summary of the safety profile

During the clinical development program (N=2,613 treatment-experienced subjects who initiated therapy with PREZISTA/rtv 600/100 mg twice daily), 51.3% of subjects experienced at least one adverse reaction. The total mean treatment duration for subjects was 95.3 weeks. The most frequent adverse reactions reported in clinical trials and as spontaneous reports are diarrhoea, nausea, rash, headache and vomiting. The most frequent serious reactions are acute renal failure, myocardial infarction, immune reconstitution syndrome, thrombocytopenia, osteonecrosis, diarrhoea, hepatitis and pyrexia.

In the 96 week analysis, the safety profile of PREZISTA/rtv 800/100 mg once daily in treatment-naïve subjects was similar to that seen with PREZISTA/rtv 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. No new safety findings were identified in the 192 week analysis of the treatment-naive subjects in which the mean treatment duration of PREZISTA/rtv 800/100 mg once daily was 162.5 weeks.

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).

System Organ Class **Frequency category**	**Adverse reaction**
Infections and infestations	
uncommon	herpes simplex
Blood and lymphatic system disorders	
uncommon	thrombocytopenia, neutropenia, anaemia, leukopenia
rare	increased eosinophil count
Immune system disorders	
uncommon	immune reconstitution syndrome, (drug) hypersensitivity
Endocrine disorders	
uncommon	hypothyroidism, increased blood thyroid stimulating hormone
Metabolism and nutrition disorders	
common	lipodystrophy (including lipohypertrophy, lipodystrophy, lipoatrophy), diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia
uncommon	gout, anorexia, decreased appetite, decreased weight, increased weight,

	hyperglycaemia, insulin resistance, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase
Psychiatric disorders	
common	insomnia
uncommon	depression, disorientation, anxiety, sleep disorder, abnormal dreams, nightmare, decreased libido
rare	confusional state, altered mood, restlessness
Nervous system disorders	
common	headache, peripheral neuropathy, dizziness
uncommon	lethargy, paraesthesia, hypoaesthesia, dysgeusia,disturbance in attention, memory impairment,somnolence
rare	syncope, convulsion, ageusia, sleep phase rhythm disturbance
Eye disorders	
uncommon	conjunctival hyperaemia, dry eye
rare	visual disturbance
Ear and labyrinth disorders	
uncommon	vertigo
Cardiac disorders	
uncommon	myocardial infarction, angina pectoris, prolonged electrocardiogram QT, tachycardia
rare	acute myocardial infarction, sinus bradycardia,palpitations
Vascular disorders	
uncommon	hypertension, flushing
Respiratory, thoracic and mediastinal disorders	
uncommon	dyspnoea, cough, epistaxis, throat irritation
rare	rhinorrhoea
Gastrointestinal disorders	
Very common	diarrhoea
common	vomiting, nausea, abdominal pain, increased blood amylase, dyspepsia, abdominal distension, flatulence
uncommon	pancreatitis, gastritis, gastrooesophageal reflux disease, aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia
rare	stomatitis, haematemesis, cheilitis, dry lip, coated tongue
Hepatobiliary disorders	
common	increased alanine aminotransferase
uncommon	hepatitis, cytolytic hepatitis, hepatic

	steatosis,hepatomegaly, increased transaminase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase,increased gamma-glutamyltransferase, hepatotoxicity
Skin and subcutaneous tissue disorders	
common	rash (including macular, maculopapular, papular,erythematous and pruritic rash), pruritus
uncommon	angioedema, generalised rash, allergic dermatitis,urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, dry skin, nail pigmentation
rare	DRESS, Stevens-Johnson syndrome, erythema multiforme, dermatitis, seborrhoeic dermatitis, skin lesion, xeroderma
Not known	toxic epidermal necrolysis, acute generalized exanthematous pustulosis
Musculoskeletal and connective tissue disorders	
uncommon	myalgia, osteonecrosis, muscle spasms, muscular weakness, arthralgia, pain in extremity, osteoporosis, increased blood creatine phosphokinase
rare	musculoskeletal stiffness, arthritis, joint stiffness
Renal and urinary disorders	
uncommon	acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria
rare	decreased creatinine renal clearance
Reproductive system and breast disorders	
uncommon	erectile dysfunction, gynaecomastia
General disorders and administration site conditions	
common	asthenia, fatigue
uncommon	pyrexia, chest pain, peripheral oedema, malaise, feeling hot, irritability, pain
rare	chills, abnormal feeling, xerosis

Description of selected adverse reactions

Rash

In clinical trials, rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. In cases of severe skin reaction see the warning in section 5.3.

During the clinical development program of raltegravir in treatment-experienced patients, rash, irrespective of causality, was more commonly observed with regimens containing PREZISTA/ritonavir +raltegravir compared to those containing PREZISTA/ritonavir without raltegravir or raltegravir

without PREZISTA/ritonavir. Rash considered by the investigator to be drug-related occurred at similar rates. The exposure-adjusted rates of rash (all causality) were 10.9, 4.2, and 3.8 per 100 patient-years (PYR),respectively; and for drug-related rash were 2.4, 1.1, and 2.3 per 100 PYR, respectively. The rashes observed in clinical studies were mild to moderate in severity and did not result in discontinuation of therapy .

Lipodystrophy
Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) .

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

Musculoskeletal abnormalities
Increased CPK, myalgia, myositis and rarely, rhabdomyolysis have been reported with the use of 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 .

Immune reconstitution 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) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment .

Bleeding in haemophiliac patients
There have been reports of increased spontaneous bleeding in haemophiliac patients receiving antiretroviral protease inhibitors .

Paediatric population
The safety assessment in paediatric patients is based on the 48-week analysis of safety data from three Phase II trials. The following patient populations were evaluated:
* 80 ART-experienced HIV-1 infected paediatric patients aged from 6 to 17 years and weighing at least 20 kg who received PREZISTA tablets with low dose ritonavir twice daily in combination with other antiretroviral agents.
* 21 ART-experienced HIV-1 infected paediatric patients aged from 3 to < 6 years and weighing 10 kg to < 20 kg (16 participants from 15 kg to < 20 kg) who received PREZISTA oral suspension with low dose ritonavir twice daily in combination with other antiretroviral agents.
* 12 ART-naïve HIV-1 infected paediatric patients aged from 12 to 17 years and weighing at least 40 kg who received PREZISTA tablets with low dose ritonavir once daily in combination with other antiretroviral agents.

Overall, the safety profile in these paediatric patients was similar to that observed in the adult

population.

Other special populations
Patients co-infected with hepatitis B and/or hepatitis C virus
Among 1,968 treatment-experienced patients receiving PREZISTA 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 .

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

7 DRUG INTERACTIONS
See also *Contraindications (4)* and *Clinical Pharmacology (11.3)*.

7.1 Potential for PREZISTA/ritonavir to Affect Other Drugs
PREZISTA co-administered with ritonavir is an inhibitor of CYP3A and CYP2D6. Co-administration of PREZISTA and ritonavir with drugs that are primarily metabolized by CYP3A and CYP2D6 may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see Table **3**).

7.2 Potential for Other Drugs to Affect Darunavir
Darunavir and ritonavir are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir. Co-administration of darunavir and ritonavir and other drugs that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir (see Table **3**).

7.3 Established and Other Potentially Significant Drug Interactions

Darunavir and ritonavir are both inhibitors of the CYP3A isoform. Co-administration of darunavir and ritonavir 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.
PREZISTA co-administered with low dose ritonavir must 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). These medicinal products include amiodarone, bepridil, quinidine, systemic lidocaine, astemizole, alfuzosin, terfenadine, sildenafil (when used for the treatment of pulmonary arterial hypertension), avanafil ,quetiapine, midazolam administered orally, triazolam, cisapride, pimozide, sertindole, simvastatin, lovastatin and the ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine and methylergonovine), Rifampin, St. John's Wort (Hypericum perforatum), Co-administration with the combination product lopinavir/ritonavir.

Table **3**provides dosing recommendations as a result of drug interactions with PREZISTA/ritonavir. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 3: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction
[*See Clinical Pharmacology (11.3)* for Magnitude of Interaction, Tables 8 and 9]

Concomitant Drug Class: Drug Name	**Effect on Concentration of Darunavir or Concomitant Drug**	**Clinical Comment**
Integrase strand tranfer inhibitors		
Raltegravir		Some clinical studies 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. PREZISTA co-administered with low dose ritonavir and raltegravir can be used without dose adjustments.
Elvitegravir	elvitegravir AUC ↔ elvitegravir Cmin ↔ elvitegravir Cmax ↔ darunavir AUC ↔ darunavir Cmin 17% darunavir Cmax ↔	When PREZISTA co-administered with low dose ritonavir (600/100 mg twice daily) is used in combination with elvitegravir, the dose of elvitegravir should be 150 mg once daily. The pharmacokinetics and dosing recommendations for other doses of darunavir or with elvitegravir/cobicistat have not been established. Therefore, co-administration of PREZISTA with low dose ritonavir in doses other than 600/100 mg twice daily and elvitegravir is not recommended. Co-administration of PREZISTA with low dose ritonavir and elvitegravir in the presence of cobicistat is not recommended
HIV-1-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
didanosine	↔ darunavir ↔ didanosine	Didanosine should be administered one hour before or two hours after PREZISTA/ritonavir (which are administered with food).
HIV-1-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
indinavir (The reference regimen for indinavir was indinavir/ritonavir 800/100 mg twice daily.)	↑ darunavir ↑ indinavir	The appropriate dose of indinavir in combination with PREZISTA/ritonavir has not been established.
lopinavir/ritonavir	↓ darunavir ↔ lopinavir	Appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer lopinavir/ritonavir and PREZISTA, with or without ritonavir.
saquinavir	↓ darunavir ↔ saquinavir	Appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer saquinavir and PREZISTA, with or without ritonavir.
HIV-1-Antiviral Agents: CCR5 co-receptor antagonists		
maraviroc	↑ maraviroc	Maraviroc concentrations are increased when co-administered with PREZISTA/ritonavir. When used in combination with PREZISTA/ritonavir, the

		dose of maraviroc should be 150 mg twice daily.
ANAESTHETIC		
Alfentanil	Not studied. The metabolism of alfentanil is mediated via CYP3A, and may as such be inhibited by boosted PREZISTA.	The concomitant use with boosted PREZISTA may require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression.
Other Agents		
Antiarrhythmics: flecainide, propafenone Disopyramide Mexiletine digoxin	↑ antiarrhythmics ↑ digoxin	Concentrations of these drugs may be increased when co-administered with PREZISTA/ritonavir. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with PREZISTA/ritonavir. 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.
Anticoagulant: Apixaban Dabigatran etexilate Rivaroxaban	Not studied. Co-administration of PREZISTA with these anticoagulants may increase concentrations of the anticoagulant. (CYP3A and/or P-gp inhibition).	The use of PREZISTA co-administered with low dose ritonavir and these anticoagulants is not recommended.
Anticoagulant: warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations are decreased when co-administered with PREZISTA/ritonavir. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with PREZISTA/ritonavir.
Anticonvulsant: carbamazepine	↔ darunavir ↑ carbamazepine	The dose of either darunavir/ritonavir or carbamazepine does not need to be adjusted when initiating co-administration with darunavir/ritonavir and carbamazepine. Clinical monitoring of carbamazepine concentrations and its dose titration is recommended to achieve the desired clinical response.
Anticonvulsant: phenobarbital, phenytoin	Not studied. Phenobarbital and phenytoin are expected to decrease plasma concentrations of darunavir. (induction of CYP450 enzymes)	PREZISTA co-administered with low dose ritonavir should not be used in combination with these medicines.
Antidepressant:	↑ trazodone	Concomitant use of trazodone or

trazodone, desipramine	↑ desipramine	desipramine and PREZISTA/ritonavir may increase plasma concentrations of trazodone or desipramine which may lead to adverse events such as nausea, dizziness, hypotension and syncope. If trazodone or desipramine is used with PREZISTA/ritonavir, the combination should be used with caution, and a lower dose of trazodone or desipramine should be considered.
Antidepressant: Amitriptyline Desipramine Imipramine Nortriptyline Trazodone	Concomitant use of PREZISTA co-administered wirth low dose ritonavir and these antidepressants may increase concentrations of the antidepressant. (CYP2D6 and/or CYP3A inhibition).	Clinical monitoring is recommended when co-administering PREZISTA with low dose ritonavir with these antidepressants and a dose adjustment of the antidepressant may be needed.
Anti-infective: clarithromycin	↔darunavir ↑clarithromycin	No dose adjustment of the combination is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered: - For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50%. - For subjects with CLcr of < 30 mL/min, the dose of clarithromycin should be reduced by 75%.
Antifungals: ketoconazole, itraconazole, voriconazole	↑ketoconazole ↑darunavir ↑itraconazole (not studied) ↓voriconazole (not studied)	Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole, and darunavir/ritonavir may increase plasma concentration of darunavir. Plasma concentrations of ketoconazole or itraconazole may be increased in the presence of darunavir/ritonavir. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Plasma concentrations of voriconazole may be decreased in the presence of darunavir/ritonavir. Voriconazole should not be administered to patients receiving darunavir/ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Antifungals: Clotrimazole	Not studied. Concomitant systemic use of clotrimazole andboosted	Caution is warranted and clinical monitoring is recommended, when co-administration of clotrimazole is

	PREZISTAmay increase plasma concentrations of darunavir and/or clotrimazole. darunavir AUC24h ↑ 33% (based on population pharmacokinetic model)	required.
Antifungals: Fluconazole Posaconazole	Not studied. PREZISTA may increase antifungal plasma concentrations (P-gp inhibition) and posaconazole may increase darunavir concentrations. (CYP3A inhibition)	Caution is warranted and clinical monitoring is recommended.
Anti-gout: colchicine	↑colchicine	Treatment of gout-flares – co-administration of colchicine in patients on PREZISTA/ritonavir: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. Prophylaxis of gout-flares – co-administration of colchicine in patients on PREZISTA/ritonavir: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. Treatment of familial Mediterranean fever – co-administration of colchicine in patients on PREZISTA/ritonavir: maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day). Co-administration of PREZISTA/rtv with colchicine in patients with renal or hepatic impairment is contraindicated.
ANTIMYCOBACTERIAL: Rifapentine	Not studied. Rifapentine is strong CYP3A inducers and have been shown to cause profound decreases in concentrations of other protease inhibitors,which can result in virological failure and resistance development (CYP450 enzyme induction). During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with low dose ritonavir, a high frequency of liver reactions	The combination of rifapentine and boosted PREZISTA is not recommended.

	was seen with rifampicin.	
Antimycobacterial: rifabutin The reference regimen for rifabutin was 300 mg once daily	↑darunavir ↑rifabutin ↑25-O-desacetylrifabutin	Dose reduction of rifabutin by at least 75% of the usual dose (300 mg once daily) is recommended (i.e., a maximum dose of 150 mg every other day). Increased monitoring for adverse events is warranted in patients receiving this combination and further dose reduction of rifabutin may be necessary.
ANTINEOPLASTICS: Dasatinib Nilotinib Vinblastine Vincristine Everolimus	Not studied. PREZISTA is expected to increase these antineoplastic plasma concentrations. (CYP3A inhibition)	Concentrations of these medicinal products may be increased when co-administered with PREZISTA with low dose ritonavir resulting in the potential for increased adverse events usually associated with these agents. Caution should be exercised when combining one of these antineoplastic agents with PREZISTA with low dose ritonavir. Concominant use of everolimus and PREZISTA co-administered with low dose ritonavir is not recommended.
β-Blockers: metoprolol, timolol Carvedilol	↑beta-blockers	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PREZISTA/ritonavir.
Buspirone Clorazepate Diazepam Estazolam Flurazepam Midazolam (parenteral) Zoldipem	Not studied. Sedative/hypnotics are extensively metabolised by CYP3A.Co-administration with boosted PREZISTA may cause a large increase in the concentration of these medicines. If parenteral midazolam is co-administered with boosted PREZISTA it may cause a large increase in the concentration of this benzodiazepine. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels.	Clinical monitoring is recommended when co-administering boosted PREZISTA with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. If parenteral midazolam is co-administered with boosted PREZISTA, it should be done in an intensive care unit (ICU) 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.
Calcium Channel Blockers: felodipine, nifedipine, nicardipine Amlodipine Diltiazem Verapamil	↑calcium channel blockers	Plasma concentrations of calcium channel blockers may increase when PREZISTA/ritonavir are co-administered. Caution is warranted and clinical monitoring of patients is recommended.

CORTICOSTEROIDS Fluticasone Budesonide	In a clinical study where ritonavir 100 mg capsules twice daily were co-administered with 50 µg intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, fluticasone propionate plasma concentrations increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% CI 82-89%). Greater effects may be expected when fluticasone is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone; this could also occur with other corticosteroids metabolised via the P4503A pathway, e.g., budesonide. The effects of high fluticasone systemic exposure on ritonavir plasma levels are unknown	Concomitant administration of PREZISTA co-administered with low dose ritonavir and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid which is not a substrate for CYP3A (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids, progressive dose reduction may have to be performed over a longer period.
Prednisone	Not studied. Darunavir may increase plasma concentrations of prednisone. (CYP3A inhibition)	Concomitant use of PREZISTA with low dose ritonavir and prednisone may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Clinical monitoring is recommended when co-administering PREZISTA with low dose ritonavir with corticosteroids.
Corticosteroid: **Systemic:** dexamethasone	↓darunavir	Systemic dexamethasone induces CYP3A and can thereby decrease darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
Endothelin receptor antagonists: bosentan	↑bosentan	Co-administration of bosentan in patients on PREZISTA/ritonavir:

		In patients who have been receiving PREZISTA/ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. <u>Co-administration of PREZISTA/ritonavir in patients on bosentan:</u> Discontinue use of bosentan at least 36 hours prior to initiation of PREZISTA/ritonavir. After at least 10 days following the initiation of PREZISTA/ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
Hepatitis C Virus (HCV) Direct-Acting Agents: **NS3-4A protease inhibitors:** boceprevir telaprevir	↓darunavir ↓boceprevir ↓telaprevir	Concomitant administration of PREZISTA/ritonavir and boceprevir or telaprevir resulted in reduced steady-state exposures to darunavir and boceprevir or telaprevir. It is not recommended to co-administer boceprevir or telaprevir and PREZISTA/ritonavir.
Simeprevir	simeprevir AUC ↑ 159% simeprevir Cmin ↑ 358% simeprevir Cmax ↑ 79% darunavir AUC ↑ 18% darunavir Cmin ↑ 31% darunavir Cmax ↔ The dose of simeprevir in this interaction study was 50 mg when co-administered in combination with darunavir/ritonavir, compared to 150 mg in the simeprevir alone treatment group.	It is not recommended to co-administer boosted PREZISTA and simeprevir.
HMG-CoA Reductase Inhibitors: pravastatin, atorvastatin, rosuvastatin	↑pravastatin ↑atorvastatin ↑rosuvastatin	Titrate atorvastatin, pravastatin or rosuvastatin dose carefully and use the lowest necessary dose while monitoring for safety. Do not exceed atorvastatin 20 mg/day.
Lovastatin Simvastatin	Not studied. Lovastatin and simvastatin are expected to have markedly increased plasma concentrations when co-administered with boosted PREZISTA. (CYP3A inhibition)	Increased plasma concentrations of lovastatin or simvastatin may cause myopathy, including rhabdomyolysis. Concomitant use of boosted PREZISTA with lovastatin and simvastatin is therefore contraindicated
Immunosuppressants: cyclosporine, tacrolimus, sirolimus	↑immunosuppressants	Plasma concentrations of cyclosporine, tacrolimus or sirolimus may be increased when co-administered with PREZISTA/ritonavir. Therapeutic concentration monitoring of the immunosuppressive agent is recommended

Everolimus		when co-administered with PREZISTA/ritonavir. Concomitant use of everolimus and boosted PREZISTA is not recommended.
Inhaled beta agonist: salmeterol	↑salmeterol	Concurrent administration of salmeterol and PREZISTA/ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Narcotic Analgesic/Treatment of Opioid Dependence: methadone, buprenorphine, buprenorphine/naloxone	↓methadone ↔buprenorphine, naloxone ↑norbuprenorphine (metabolite)	No adjustment of methadone dosage is required when initiating co-administration of PREZISTA/ritonavir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients. No dose adjustment for buprenorphine or buprenorphine/naloxone is required with concurrent administration of PREZISTA/ritonavir. Clinical monitoring is recommended if PREZISTA/ritonavir and buprenorphine or buprenorphine/naloxone are coadministered.
Neuroleptics: risperidone, thioridazine Perphenazine	↑neuroleptics	A dose decrease may be needed for these drugs when co-administered with PREZISTA/ritonavir.
Oral Contraceptives/estrogen: ethinyl estradiol, norethindrone	↓ethinyl estradiol ↓norethindrone	Plasma concentrations of ethinyl estradiol are decreased due to induction of its metabolism by ritonavir. Alternative methods of nonhormonal contraception are recommended.
PDE-5 inhibitors: sildenafil, vardenafil, tadalafil	↑PDE-5 inhibitors (only the use of sildenafil at doses used for treatment of erectile dysfunction has been studied with PREZISTA/ritonavir)	Co-administration with PREZISTA/ritonavir may result in an increase in PDE-5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances and priapism. <u>Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH):</u> -Use of sildenafil is contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) [*see Contraindications (4)*]. -The following dose adjustments are recommended for use of tadalafil with PREZISTA/ritonavir: <u>Co-administration of tadalafil in patients on PREZISTA/ritonavir:</u>

		In patients receiving PREZISTA/ritonavir 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 PREZISTA/ritonavir in patients on tadalafil: Avoid use of tadalafil during the initiation of PREZISTA/ritonavir. Stop tadalafil at least 24 hours prior to starting PREZISTA/ritonavir. After at least one week following the initiation of PREZISTA/ritonavir, 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: 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.
Selective Serotonin Reuptake Inhibitors (SSRIs): sertraline, paroxetine	↔darunavir ↓sertraline ↓paroxetine	If sertraline or paroxetine is co-administered with PREZISTA/ritonavir, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with PREZISTA/ritonavir should be monitored for antidepressant response.

Antimalarials:

An interaction trial between PREZISTA/rtv (600/100 mg b.i.d.) and artemether/lumefantrine (80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours) showed an increase in exposure to lumefantrine by 2.75-fold, while exposure to darunavir was not affected. The exposure to artemether and its active metabolite, dihydroartemisinin, decreased by 16% and 18%, respectively. The combination of PREZISTA and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.

In addition to the drugs included in Table **3**, the interaction between PREZISTA/ritonavir and the following drugs were evaluated in clinical studies and no dose adjustments are needed for either drug [see *Clinical Pharmacology (11.3)*]: atazanavir, efavirenz, etravirine, nevirapine, , ranitidine, rilpivirine, and tenofovir disoproxil fumarate.
Using cross-trial comparisons to historical pharmacokinetic data, dolutegravir did not appear to affect the pharmacokinetics of darunavir. Darunavir/ritonavir had no clinically significant effect on the pharmacokinetics of dolutegravir.

Proton Pump Inhibitors
Omeprazole, pantoprazole, rabeprazole, Esomeprazole, Lansoprazole

Co-administration of omeprazole (20 mg q.d.) and PREZISTA/rtv (400/100 mg b.i.d.) did not affect the exposure to darunavir. PREZISTA and proton pump inhibitors can be co-administered without dose adjustment

Other nucleoside reverse transcriptase inhibitors (NRTIs): Based on the different elimination pathways of the other NRTIs (zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir) that are primarily renally excreted, no drug interactions are expected for these drugs and PREZISTA/ritonavir.

Other PIs: The co-administration of PREZISTA/ritonavir and PIs other than lopinavir/ritonavir, saquinavir, atazanavir, and indinavir has not been studied. Therefore, such co-administration is not recommended.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
Delavirdine
Co-administration of PREZISTA/rtv and delavirdine may increase darunavir and delavirdine concentrations (inhibition of CYP3A). The appropriate doses of PREZISTA/rtv and delavirdine have not been established. The combination of PREZISTA/rtv and delavirdine is not recommended.

Antacids
e.g. Aluminium/magnesium hydroxide, calcium carbonate
No interaction is expected between antacids and PREZISTA/rtv. PREZISTA/rtv and antacids can be used concomitantly without dose adjustments.

H_2-Receptor antagonists
e.g. Cimetidine, famotidine, nizatidine, ranitidine
Co-administration of ranitidine (150 mg b.i.d.) and PREZISTA/rtv (400/100 mg b.i.d.) did not affect the exposure to darunavir. PREZISTA/rtv can be co-administered with H2-receptor antagonists without dose adjustments.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C: PREZISTA should be used during pregnancy only if the potential benefit justifies the potential risk.

No adequate and well-controlled studies have been conducted in pregnant women. Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice and rats in the presence or absence of ritonavir as well as in rabbits with darunavir alone. In these studies, darunavir exposures (based on AUC) were higher in rats (3-fold), whereas in mice and rabbits, exposures were lower (less than 1-fold) compared to those obtained in humans at the recommended clinical dose of darunavir boosted with ritonavir.

In the rat pre-and postnatal development study, a reduction in pup body weight gain was observed with darunavir alone or in combination with ritonavir during lactation. This was due to exposure of pups to drug substances via the milk. Sexual development, fertility and mating performance of offspring were not affected by maternal treatment with darunavir alone or in combination with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

In the juvenile toxicity study where rats were directly dosed with darunavir, deaths occurred from post-natal day 5 through 11 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) of 0.1 of the human plasma exposure levels.

8.2 Nursing Mothers
Although it is not known whether darunavir is secreted in human milk, darunavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving PREZISTA**.

8.3 Pediatric Use
Do not administer PREZISTA/ritonavir in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age [*see Warnings and Precautions (5.11), Use in Specific Populations (8.1), Clinical Pharmacology (11.3) and Nonclinical Toxicology (12.2)*].

8.4 Fertility
No human data on the effect of darunavir on fertility are available. There was no effect on mating or fertility with darunavir treatment in rats

8.5 Effects on ability to drive and use machines
PREZISTA in combination with ritonavir has no or negligible influence on the ability to drive and use machines. However, dizziness has been reported in some patients during treatment with regimens containing PREZISTA co-administered with low dose ritonavir and should be borne in mind when considering a patient's ability to drive or operate machinery.

Prezista Tabs are intended only for pediatric patients ≥6years old weighing ≥20 Kg.

The safety, pharmacokinetic profile, and virologic and immunologic responses of PREZISTA/ritonavir were evaluated in treatment-experienced HIV-1-infected pediatric subjects 6 to < 18 years of age and weighing at least 44 lbs (20 kg) [*see Adverse Reactions (6.6)*, *Clinical Pharmacology (11.3) and Clinical Studies (13.4)*]. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults [*see Adverse Reactions (6.6)*]. Please see *Dosage and Administration (2.2)* for dosing recommendations for pediatric subjects 6 to < 18 years of age and weighing at least 44 lbs (20 kg).

8.4 Geriatric Use
Clinical studies of PREZISTA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of PREZISTA in elderly patients reflecting the greater frequency of decreased hepatic function, and of concomitant disease or other drug therapy [*see Clinical Pharmacology (11.3)*].

8.5 Hepatic Impairment
No dose adjustment of PREZISTA/ritonavir is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of PREZISTA/ritonavir in subjects with severe hepatic impairment, therefore, PREZISTA/ritonavir is not recommended for use in patients with severe hepatic impairment [*see Dosage and Administration (2.3) and Clinical Pharmacology (11.3)*].

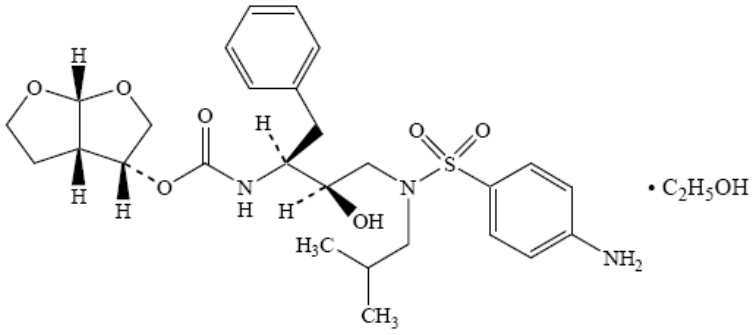
8.6 Renal Impairment
Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n=20). No pharmacokinetic data are available in HIV-1-infected patients with severe renal impairment or end stage renal disease; however, because the renal clearance of darunavir is limited, a decrease in total body clearance is not expected in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis [*see Clinical Pharmacology (11.3)*].

9 OVERDOSAGE
Human experience of acute overdose with PREZISTA/ritonavir 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.
No specific antidote is available for overdose with PREZISTA. Treatment of overdose with PREZISTA consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. In general gastric lavage should not be performed more than 1 hour after
ingestion of an overdose

Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since PREZISTA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

10 DESCRIPTION

PREZISTA (darunavir) is an inhibitor of the human immunodeficiency virus (HIV-1) protease.
PREZISTA (darunavir), in the form of darunavir ethanolate, has the following chemical name: [(1*S*,2*R*)-3-[[(4-aminophenyl) sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*] furan-3-yl ester monoethanolate. Its molecular formula is C27H37N3O7S • C2H5OH and its molecular weight is 593.73. Darunavir ethanolate has the following structural formula:



Darunavir ethanolate is a white to off-white powder with a solubility of approximately 0.15 mg/mL in water at 20°C.

PREZISTA 75 mg tablets are available as white, caplet-shaped, film-coated tablets for oral administration.
PREZISTA 150 mg tablets are available as white, oval-shaped, film-coated tablets for oral administration.
PREZISTA 600 mg tablets are available as orange, oval-shaped, film-coated tablets for oral administration.
PREZISTA 400 mg is available as a light orange, oval-shaped, film-coated tablet for oral administration.
PREZISTA 800 mg tablets are available as dark red, oval-shaped, film-coated tablets for oral administration.

Each 75 mg tablet contains darunavir ethanolate equivalent to 75 mg of darunavir. Each 150 mg tablet contains darunavir ethanolate equivalent to 150 mg of darunavir. Each 400 mg tablet contains darunavir ethanolate equivalent to 400 mg of darunavir. Each 600 mg tablet contains darunavir ethanolate equivalent to 600 mg of darunavir. Each 800 mg tablet contains darunavir ethanolate equivalent to 800 mg of darunavir.

During storage, partial conversion from ethanolate to hydrate may occur; however, this does not affect product quality or performance.

Each 75mg 150mg 400mg 600mg tablet also contains the inactive ingredients colloidal anhydrous silica crospovidone, magnesium stearate, and PROSOLV SMCC. The 75 and 150 mg tablet film coating, OPADRY® White, contains polyethylene glycol 3350, polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide. The 400 and 600 mg tablet film coating, OPADRY® Light Orange and OPADRY® Orange, respectively, contains FD&C Yellow No. 6, polyethylene glycol, polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide.

Each 800mg tablet also contain inactive ingredients: hypromellose 2910 15 mPa.s, silicified microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate and OPADRY II DARK RED 85F150004 (contains polyvinyl alcohol-partially hydrolyzed, macrogol 3350, macrogol 4000, titanium dioxide, talc, iron oxide red.

All dosages for PREZISTA are expressed in terms of the free form of darunavir.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Darunavir is an HIV antiviral drug [*see Clinical Pharmacology (11.4)*].

11.2 Pharmacodynamics
In an open-label, randomized, placebo- and active-controlled, four-way crossover trial, 40 healthy subjects were administered supratheraputic doses of darunavir/ritonavir 1600/100 mg once daily and 800/100 mg twice daily for seven days.

At the mean maximum darunavir concentration of 6599 ng/mL observed in this study, the mean increase in QTcF was 2.2 ms with a 90% two-sided confidence interval (CI) of -2.0 to 6.3 ms. When evaluating the 2-sided 90% CI on the time-matched mean changes in QTcF versus placebo control, the upper bounds of both darunavir/ritonavir groups never exceeded the 10 ms boundary. In the setting of this trial, darunavir/ritonavir did not appear to prolong the QTc interval.

11.3 Pharmacokinetics
Pharmacokinetics in Adults
General
Darunavir is primarily metabolized by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir. When a single dose of PREZISTA 600 mg was given orally in combination with 100 mg ritonavir twice daily, there was an approximate 14-fold increase in the systemic exposure of darunavir. Therefore, PREZISTA should only be used in combination with 100 mg of ritonavir to achieve sufficient exposures of darunavir.

The pharmacokinetics of darunavir, co-administered with low dose ritonavir (100 mg), has been evaluated in healthy adult volunteers and in HIV-1-infected subjects. Table **4**displays the population pharmacokinetic estimates of darunavir after oral administration of PREZISTA/ritonavir 600/100 mg twice daily [based on sparse sampling in 285 patients in study TMC114-C214, 278 patients in Study TMC114-C229 and 119 patients (integrated data) from Studies TMC114-C202 and TMC114-C213] and PREZISTA/ritonavir 800/100 mg once daily [based on sparse sampling in 335 patients in Study TMC114-C211 and 280 patients in Study TMC114-C229] to HIV-1-infected patients.

Table 4: Population Pharmacokinetic Estimates of Darunavir at PREZISTA/ritonavir 800/100 mg once daily(Study TMC114-C211, 48 Week Analysis and Study TMC114-C229 48 week analysis) and PREZISTA/ritonavir 600/100 mg twice daily(Study TMC114-C214, 48 Week Analysis ,Study TMC114-229, 48 Week Analysis and Integrated data from Studies TMC114-C213 and TMC114-C202, Primary 24-Week Analysis)

Parameter	**StudyTMC114-C211 PREZISTA/ritonavir 800/100 mg once daily N = 335**	**Study TMC114-C229 PREZISTA/ ritonavir 800/100 mg once daily N = 280**	**Study TMC114-C214 PREZISTA /ritonavir 600/100 mg twice daily N = 285**	**Study TMC114-C229 PREZISTA/ ritonavir 600/100 mg twice daily N = 278**	**Studies TMC114-C213 and TMC114-C202 (integrated data) PREZISTA/ritonavir 600/100 mg twice daily N =119**
AUC_{24h} (ng·h/mL)*					
Mean ± Standard Deviation	93026 ± 27050	93334±28626	116796 ± 33594	114302±32681	124698 ± 32286
Median (Range)	87854 (45000-219240)	87788 (45456-236920)	111632 (64874-355360)	109401 (48934±323820)	123336 (67714-212980)
C_{0h} (ng/mL)					
Mean ± Standard Deviation	2282 ± 1168	2160±1201	3490 ± 1401	3386±1372	3578 ± 1151

Median (Range)	2041 (368-7242)	1896 (184-7881)	3307 (1517-13198)	3197 (250-11865)	3539 (1255-7368)
N = number of subjects with data. *AUC_{24h} is calculated as AUC_{12h}*2					

Absorption and Bioavailability
Darunavir, co-administered with 100 mg ritonavir twice daily, was absorbed following oral administration with a Tmax of approximately 2.5-4 hours. The absolute oral bioavailability of a single 600 mg dose of darunavir alone and after co-administration with 100 mg ritonavir twice daily was 37% and 82%, respectively. *In vivo* data suggests that darunavir/ritonavir is an inhibitor of the p-glycoprotein (p-gp) transporters.

Effects of Food on Oral Absorption
When administered with food, the C_{max} and AUC of darunavir, co-administered with ritonavir, is approximately 40% higher relative to the fasting state. Therefore, PREZISTA tablets, co-administered with ritonavir, should always be taken with food. Within the range of meals studied, darunavir exposure is similar. The total caloric content of the various meals evaluated ranged from 240 Kcal (12 gms fat) to 928 Kcal (56 gms fat).

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

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

Elimination
A mass balance study in healthy volunteers showed that after single dose administration of 400 mg ^{14}C-darunavir, co-administered with 100 mg ritonavir, approximately 79.5% and 13.9% of the administered dose of ^{14}C-darunavir was recovered in the feces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when co-administered with ritonavir. After intravenous administration, the clearance of darunavir, administered alone and co-administered with 100 mg twice daily ritonavir, was 32.8 L/h and 5.9 L/h, respectively.

Special Populations

Hepatic Impairment
Darunavir is primarily metabolized by the liver. The steady-state pharmacokinetic parameters of darunavir were similar after multiple dose co-administration of PREZISTA/ritonavir 600/100 mg twice daily to subjects with normal hepatic function (n=16), mild hepatic impairment (Child-Pugh Class A, n=8), and moderate hepatic impairment (Child-Pugh Class B, n=8). The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been evaluated [*see Dosage and Administration (2.2) and Use in Specific Populations (8.4)*].
Hepatitis B or Hepatitis C Virus Co-infection
The 48-week analysis of the data from Studies TMC114-C211 and TMC114-C214 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.

Renal Impairment
Results from a mass balance study with ^{14}C-darunavir/ritonavir showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine as unchanged drug. As darunavir and ritonavir are highly

bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n=20). There are no pharmacokinetic data available in HIV-1-infected patients with severe renal impairment or end stage renal disease [*see Use in Specific Populations (8.5)*].

Gender
Population pharmacokinetic analysis showed higher mean darunavir exposure in HIV-infected females compared to males. This difference is not clinically relevant.

Race
Population pharmacokinetic analysis of darunavir in HIV-infected subjects indicated that race had no apparent effect on the exposure to darunavir.

Geriatric Patients
Population pharmacokinetic analysis in HIV-infected subjects showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV-infected subjects (n = 12, age ≥ 65) [*see Use in Specific Populations (8.3)*].

Pediatric Patients

The pharmacokinetics of darunavir in combination with ritonavir in 92 antiretroviral treatment-experienced HIV-1-infected pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg showed that the administered weight-based dosages resulted in darunavir exposure that was comparable to the exposures achieved in treatment-experienced adults receiving PREZISTA/ritonavir 600/100 mg twice daily *[see Dosage and Administration (2.2)].*

Table 5: Population Pharmacokinetic Estimates of Darunavir Exposure (Study TMC114-C212 and Study TMC114-C228) Following Administration of Doses in Tables 1 and 2

Parameter	**Study TMC114-C212 PREZISTA/ ritonavir twice daily N = 74**	**Study TMC114-C228 PREZISTA/ ritonavir twice daily***	
		10 to less than 15 kg‡ N = 10	**15 to less than 20 kg§ N = 12**
AUC_{24h} (ng·h/mL) †			
Mean ± Standard Deviation	126377 ± 34356	137896±51420	157760±54080
Median (Range)	127340 (67054-230720)	124044 (89688-261090)	132698 (112310-294840)
C0h (ng/mL)			
Mean ± Standard Deviation	3948 ± 1363	4510±2031	4848± 2143

Median (Range)	3888 (1836-7821)	4126 (2456-9361)	3927(3046-10292)

N = number of subjects with data.
* Subjects may have contributed pharmacokinetic data to both the 10 kg to less than 15 kg weight group and the 15 kg to less than 20 kg weight group.
† AUC_{24h} is calculated as AUC_{12h}*2
‡
Calculated from individual pharmacokinetic parameters estimated for Week 2 and Week 4, based on the Week 48 analysis that evaluated a darunavir dose of 20 mg/kg twice daily with ritonavir 3 mg/kg twice daily.

§ The 15 kg to less than 20 kg weight group received 380 mg (3.8 mL) PREZISTA oral suspension twice daily with 48 mg (0.6 mL) ritonavir oral solution twice daily in TMC114-C228.-Calculated from individual pharmacokinetic parameters estimated for Week 2 post-dose adjustment visit; Week 24 and Week 48 based on the -Week 48 analysis that evaluated a darunavir dose of 380 mg twice daily.

Drug Interactions

[*See also Contraindications (4)*, *Warnings and Precautions (5.5), and Drug Interactions (7)*.]

Darunavir co-administered with ritonavir is an inhibitor of CYP3A and CYP2D6. Co-administration of darunavir and ritonavir with drugs primarily metabolized by CYP3A and CYP2D6 may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events.

Darunavir and ritonavir are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir. Co-administration of darunavir and ritonavir and other drugs that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir.

Drug interaction studies were performed with darunavir and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of darunavir on the AUC, C_{max}, and C_{min} values are summarized in Table **6** (effect of other drugs on darunavir) and Table **7** (effect of darunavir on other drugs). For information regarding clinical recommendations, *see Drug Interactions (7)*.

Several interaction studies have been performed with a dose other than the recommended dose of the co-administered drug or darunavir; however, the results are applicable to the recommended dose of the co-administered drug and/or darunavir.

Table 6: Drug Interactions: Pharmacokinetic Parameters for Darunavir in the Presence of Co-administered Drugs

Co-Administered Drug	**Dose/Schedule**		**N**	**PK**	**LS Mean Ratio (90% CI) of Darunavir Pharmacokinetic Parameters With/Without Co-administered Drug No Effect =1.00**		
	Co-Administered Drug	**Darunavir/ ritonavir**			**C_{max}**	**AUC**	**C_{min}**
Co-Administration With Other HIV Protease Inhibitors							
Atazanavir	300 mg q.d.*		13	↔			

		400/100 mg b.i.d. †			1.02 (0.96-1.09)	1.03 (0.94-1.12)	1.01 (0.88-1.16)
Indinavir	800 mg b.i.d.	400/100 mg b.i.d.	9	↑	1.11 (0.98-1.26)	1.24 (1.09-1.42)	1.44 (1.13-1.82)
Lopinavir/ Ri onavir	400/100 mg b.i.d. 533/133.3 mg b.i.d.	1200/100 mg b.i.d.‡ 1200 mg b.i.d.‡	14 15	↓ ↓	0.79 (0.67-0.92) 0.79 (0.64-0.97)	0.62 (0.53-0.73) 0.59 (0.50-0.70)	0.49 (0.39-0.63) 0.45 (0.38-0.52)
Saquinavir hard gel capsule	1000 mg b.i.d.	400/100 mg b.i.d.	14	↓	0.83 (0.75-0.92)	0.74 (0.63-0.86)	0.58 (0.47-0.72)
Co-Administration With Other HIV Antiretrovirals							
Didanosine	400 mg q.d.	600/100 mg b.i.d.	17	↔	0.93 (0.86-1.00)	1.01 (0.95-1.07	1.07 (0.95-1.21)
Efaviren	600 mg q.d.	300/100 mg b.i.d.	12	↓	0.85 (0.72-1.00)	0.87 (0.75-1.01)	0.69 (0.54-0.87)
Etravirine	200 mg b.i.d.	600/100 mg b.i.d.	15	↔	1.11 (1.01-1.22)	1.15 (1.05-1.2)	1.02 (0.90-1.17)
Nevir pin e	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.40 § (1.14-1.73)	1.24 § (0.97-1.57)	1.02 § (0.79-1.32)
Rilpivirine	150 mg q.d.	800/100 mg q.d.	15	↔	0.90 (0.81-1.00)	0.89 (.81-0.99)	0.89 (0.68-1.16)
Tenofovir Disoproxil Fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.16 (0.94-1.42)	1.21 (0.95-1.54)	1.24 (0.90-1.69)
Co-Administration With HCV NS3-4A Protease Inhibitors							
Boceprevir ^	800 mg three times daily	600/100 mg b.i.d.	11	↓	0.64 (0.58-0.71)	0.56 (0.51-0.61)	0.41 (0.38-0.45)
Telaprevir	750 mg every 8 hours 1125 mg every 12 hours	600/100 mg b.i.d. 600/100 mg b.i.d.	11‖ 15	↓ ↓	0.60 (0.56-0.64) 0.53 (0.47 0.59)	0.60 (0.57-0.63) 0.49 (0.43-	0.58 (0.52-0.64) 0.42 (0.35-

						0.55)	0.51)
Co-Administration With Other Drugs							
Artemether/Lumefantrine	80/480mg (6 doses at 0, 8,24,36,48 and 60 hours)	600/100 mg b.i.d.	14	↔	1.00 (0.93-1.07)	0.96 (0.90-1.03)	0.87 (0.77-0.98)
Carbamazepine	200 mg b.i.d.	600/100 mg b.i.d.	16	↔	1.04 (0.93-1.16)	0.99 (0.90-1.08)	0.85 (0.73-1.00)
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	7	↔	0.83 (0.72-0.96)	0.87 (0.75-1.01)	1.01 (0.81-1.26)
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	14	↑	1.21 (1.04-1.40)	1.42 (1.23-1.65)	1.73 (1.39-2.14)
Omeprazole	20 mg q.d.	400/100 mg b.i.d.	16	↔	1.02 (0.95-1.09)	1.04 (0.96-1.13)	1.08 (0.93-1.25)
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↔	0.97 (0.92-1.02)	1.02 (0.95-1.10)	1.07 (0.96-1.19)
Ranitidine	150 mg b.i.d.	400/100 g b.i.d.	16	↔	0.96 (0.89-.05)	0.95 (0.90-1.01)	0.94 (0.90-0.99)
Rifabutin	150 mg q.o.d. ¶	600/100 mg b.i.d.	11	↑	1.42 (1.21-1.67)	1.57 (1.28-1.93)	1.75 (1.28-2.37)
Sertraline	50 mg q.d.	400/ 00 mg b.i.d.	13	↔	1.01 (0 89-1.14)	0.98 (0.84-1.14)	0.94 (0.76-1.16)

N = number of subjects with data
* q.d. = once daily
† b.i.d. = twice daily
‡ The pharmacokinetic parameters of darunavir in this study were compared with the pharmacokinetic parameters following administration of darunavir/ritonavir 600/100 mg b.i.d.
§ Ratio based on between-study comparison.
¶ q.o.d. = every other day
^ AUC is $AUC_{(0\text{-last})}$; N = 10 for C_{min} in the reference arm
‖ N = 14 for C_{max}

Table 7: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Darunavir/Ritonavir

Co-Administered Drug	Dose/Schedule		N	PK	LS Mean Ratio (90% CI) of Co-Administered Drug Pharmacokinetic Parameters With/Without Darunavir No effect =1.00		
	Co-Administered Drug	Darunavir / ritonavir			C_{max}	AUC	C_{min}
Co-Administration With Other HIV Protease Inhibitors							
Atazanavir	300 mg q.d.* /100 mg ritonavir q.d. when administered alone 300 mg q.d. when administered with darunavir/ ritonavir	400/100 mg b.i.d. †	13	↔	0.89 (0.78-1.01)	1.08 (0.94-1.24)	1.52 (0.99-2.34)
Indinavir	800 mg b.i.d. /100 mg ritonavir b.i.d. when administered alone 800 mg b.i.d. when administered with darunavir/ ritonavir	400/100 mg b.i.d.	9	↑	1.08 (0.95-1.22)	1.23 (1.06-1.42)	2.25 (1.63-3.10)
Lopinavir/ Ritonavir	400/100 mg b.i.d.‡	1200/100 mg b.i.d.	14	↔	0.98 (0.78-1.22)	1.09 (0.86-1.37)	1.23 (0.90-1.69)
	533/133.3 mg b.i.d.‡	1200 mg b.i.d.	15	↔	1.11 (0.96-1.30)	1.09 (0.96-1.24)	1.13 (0.90-1.42)
Saquinavir hard gel capsule	1000 mg b.i.d. /100 mg ritonavir b.i.d. when administered alone 1000 mg b.i.d. when administered with darunavir/ ritonavir	400/100 mg b.i.d.	12	↔	0.94 (0.78-1.13)	0.94 (0.76-1.17)	0.82 (0.52-1.30)

Co-Administration With Other HIV Antiretrovirals							
Didanosine	400 mg q. .	600/100 mg b.i.d.	17	↔	0.84 (0.59-1.20)	0.91 (0.75-1.10)	-
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	↑	1.15 (0.97-1.35)	1.21 (1.08-1.36)	1.17 (1.01-1.36)
Etravirine	100 mg b.i.d.	600/100 mg b.i.d.	14	↓	0.68 (0.57-0.82)	0.63 (0.54-0.73)	0.51 (0.44-0.61)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.18 (1.02 - 1.37)	1.27 (1.12 - 1.44)	1.47 (1.20 - 1.82)
Rilpivirine	150 mg q d.	800/100 mg q.d.	14	↑	1.79 (1.56-2.06)	2.30 (1.98-2.67)	2.78 (2.39-3.24)
Tenofovir Disoproxil Fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.24 (1.08-1.42)	1.22 (1.10-1.35)	1.37 (1.19-1.57)
Maraviroc	150 mg b.i.d.	600/100 mg b.i.d.	12	↑	2.29 (1.46-3.59)	4.05 (2.94-5.59)	8.00 (6.35-10.1)
Maraviroc	150 mg b.i.d.	600/100 mg b.i.d. with 200 mg b.i.d. etravirine	10	↑	1.77 (1.20-2.60)	3.10 (2.57-3.7)	5.27 (4.51-6.15)
Co-Administration With HCV NS3-4A Protease Inhibitors							
Boceprevir	800 mg three times daily	600/100 mg b.i.d.	12	↓	0.75 (0.67-0.85)	0.68 (0.65-0.72)	0.65 (0.56-0.76)
Telaprevir	750 mg every 8 hours	600/100 mg b.i.d.	11‖	↓	0.64 (0.61-0.67)	0.65 (0.61-0.69)	0.68 (0.63-0.74)
Co-Administration With Other Drugs							
Atorvastatin	40 mg q.d. when administered alone 10 mg q.d. when administered with darunavir/ ri onavir	300/100 mg b.i.d.	15	↑	0.56 (0.48-0.67)	0.85 (0.76-0.97)	1.81 (1.37-2.40)

Artemether	80 mg single dose	600/100 mg b.i.d.	15	↓	0.85 (0.68-1.05)	0.91 (0.78-1.06)	-
Dihydroartemisinin			15	↑	1.06 (0.82-1.39)	1.12 (0.96-1.30)	-
Artemether	Artemether/ lumefantrine 80/480 mg (6 doses at 0, 8, 24, 36, 48, and 60 hours)	600/100 mg b.i.d.	15	↓	0.82 (0.61-1.11)	0.84 (0.69-1.02)	0.97 (0.90-1.05)
Dihydroartemisinin			15	↓	0.82 (0.66-1.01)	0.82 (0.74-0.91)	1.00 (0.82-1.22)
Lumefantrine			15	↑	1.65 (1.49-1.83)	2.75 (2.46-3.08)	2.26 (1.92-2.67)
Buprenorphine/ Naloxone	8/2 mg to 16/4 mg q.d.	600/100 mg b.i.d.	17	↔	0.92 § (0.79-1.08)	0.89 § (0.78-1.02)	0.98 § (0.82-1.16)
Norbuprenorphine			17	↑	1.36 (1.06-1.74)	1.46 (1.15-1.85)	1.71 (1.29-2.27)
Carbamazepine	200 mg b.i.d.	600/100 mg b.i.d.	16	↑	1.43 (1.34-1.53)	1.45 (1.35-1.57)	1.54 (1.41-1.68)
Carbamazepine epoxide			16	↓	0.46 (0.43-0.49)	0.46 (0. 4-0.49)	0.48 (0.45-0.51)
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↑	1.26 (1.03-1.54)	1.57 (1.35-1.84)	2.74 (2.30-3.26)
Dextromethorphan	30 mg	600/100 mg b.i.d	12	↑	2.27 (1.59-3.26)	2.70 (1.80-4.05)	-
Dextrorphan				↓	0.87 (0.77-0.98)	0.96 (0.90-1.03)	-
Digoxin	0.4 mg	600/100 mg b.i.d.	8	↑	1.15 (0.89-1.48)	1.36 (0.81-2.27)	-
Ethinyl estradiol (EE)	Ortho-Novum 1/35 (35 µg EE / 1 mg NE)	600/100 mg b.i.d.	11	↓	0.68 (0.61-0.74)	0.56 (0.50-0.63)	0.38 (0.27-0.54)
Norethindrone (NE			11	↓	0.90 (0.83-0.97)	0.86 (0.75-0.98)	0.70 (0.51-0.97)
Ketoconazole	200 mg b.i.d.	40 /100 mg b.i.d.	15	↑	2.11 (1.81-2.44)	3.12 (2.65-3.68)	9.68 (6.44-14.55)

R-Methadone	55-150 mg q.d.	600/100 mg b.i.d.	16	↓	0.76 (0.71-0.81)	0.84 (0.78-0.91)	0.85 (0.77-0.94)
Omeprazole	40 mg single dose	600/100 mg b.i.d.	12	↓	0.66 (0.48-0.90)	0.58 (0.50-0.66)	-
5-hydroxy meprazole				↓	0.93 (0.71-1.21)	0.84 (0.77-0.92)	-
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↓	0.64 (0.59-0.71)	0.61 (0.56-0.66)	0.63 (0.55-0.73)
Pravastatin	40 mg single dose	600/100 mg b.i.d.	14	↑	1.63 (0.95-2.82)	1.81 (1.23-2.66)	–
Rifabutin	150 mg q.o.d. ¶ when administered with PREZISTA/ritonavir	600/100 mg b.i.d. #	11	↑	0.72 (0.55-0.93)	0.93 (0.80-1.09)	1.64 (1.48-1.81)
25-*O*-desacetyl-rifabutin	300 mg q.d. when administered alone		11	↑	4.77 (4.04-5.63)	9.81 (8.09-11.9)	27.1 (22.2-33.2)
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↓	0.56 (0.49-0.63)	0.51 (0.46-0.58)	0.51 (0.45-0.57)
Sildenafil	100 mg (single dose) administered alone 25 mg (single dose) when administered with darunavir/ ritonavir	400/100 mg b.i.d.	16	↑	0.62 (0.55-0.70)	0.97 (0.86-1.09)	–
S-warfarin	10 mg single dose	600/100 mg b.i.d.	12	↓	0.92 (0.86-0.97)	0.79 (0.73-0.85)	–
7-OH-S-warfarin			12	↑	1.42 (1.24-1.63)	1.23 (0.97-1.57)	–

N = number of subjects with data;- = no information available
* q.d. = once daily
† b.i.d. = twice daily
‡ The pharmacokinetic parameters of lopinavir in this study were compared with the pharmacokinetic parameters following administration of lopinavir/ritonavir 400/100 mg b.i.d.
§ ratio is for buprenorphine; mean C_{max} and AUC_{24} for naloxone were comparable when buprenorphine/naloxone was administered with or without PREZISTA/ritonavir
¶ q.o.d. = every other day
# In comparison to rifabutin 300 mg q.d.
‖ N = 14 for Cmax
A cocktail study was conducted in 12 healthy volunteers to evaluate the effect of steady state pharmacokinetics of darunavir/ritonavir on the activity of CYP2D6 (using dextromethorphan as probe substrate), CYP2C9 (using warfarin as probe substrate), and CYP2C19 (using omeprazole as probe substrate). The pharmacokinetic results are shown in Table 7.

11.4 Microbiology

Mechanism of Action

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

Antiviral Activity

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity in cell culture against a broad panel of HIV-1 group M (A, B, C, D, E, F, G), and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM. The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum. Darunavir did not show antagonism when studied in combination with the PIs amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir, the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine, the NNRTIs delavirdine, rilpivirine, efavirenz, etravirine, or nevirapine, and the fusion inhibitor enfuvirtide.

Resistance

Cell Culture: HIV-1 isolates with a decreased susceptibility to darunavir have been selected in cell culture and obtained from subjects treated with darunavir/ritonavir. Darunavir-resistant virus derived in cell culture from wild-type HIV had 21- to 88-fold decreased susceptibility to darunavir and developed 2 to 4 of the following amino acid substitutions S37D, R41E/T, K55Q, H69Q, K70E, T74S, V77I, or I85V in the protease. Selection in cell culture of darunavir resistant HIV-1 from nine HIV-1 strains harboring multiple PI resistance-associated mutations resulted in the overall emergence of 22 mutations in the protease gene, coding for amino acid substitutions L10F, V11I, I13V, I15V, G16E, L23I, V32I, L33F, S37N, M46I, I47V, I50V, F53L, L63P, A71V, G73S, L76V, V82I, I84V, T91A/S, and Q92R, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were the most prevalent. These darunavir-resistant viruses had at least eight protease substitutions and exhibited 50- to 641-fold decreases in darunavir susceptibility with final EC_{50} values ranging from 125 nM to 3461 nM.

Clinical studies of PREZISTA/ritonavir in treatment-experienced subjects: In a pooled analysis of the 600/100 mg PREZISTA/ritonavir twice daily arms of Studies TMC114-C213, TMC114-C202, TMC114-C215, and the control arms of etravirine studies TMC125-C206 and TMC125-C216, the amino acid substitutions V32I and I54L or M developed most frequently on PREZISTA/ritonavir in 41% and 25%, respectively, of the treatment-experienced subjects who experienced virologic failure, either by rebound or by never being suppressed (< 50 copies/mL). Other substitutions that developed frequently in PREZISTA/ritonavir virologic failure isolates occurred at amino acid positions V11I, I15V, L33F, I47V, I50V, and L89V. These amino acid substitutions were associated with decreased susceptibility to darunavir; 90% of the virologic failure isolates had a > 7-fold decrease in susceptibility to darunavir at failure. The median darunavir phenotype (fold change from reference) of the virologic failure isolates was 4.3-fold at baseline and 85-fold at failure. Amino acid substitutions were also observed in the protease cleavage sites in the Gag polyprotein of some PREZISTA/ritonavir virologic failure isolates. In Study

TMC114-C212 of treatment-experienced pediatric subjects, the amino acid substitutions V32I, I54L and L89M developed most frequently in virologic failures on PREZISTA/ritonavir.
In the 96-week as-treated analysis of the Phase 3 Study TMC114-C214, the percent of virologic failures (never suppressed, rebounders and discontinued before achieving suppression) was 21% (62/298) in the group of subjects receiving PREZISTA/ritonavir 600/100 mg twice daily compared to 32% (96/297) of subjects receiving lopinavir/ritonavir 400/100 mg twice daily. Examination of subjects who failed on PREZISTA/ritonavir 600/100 mg twice daily and had post-baseline genotypes and phenotypes showed that 7 subjects (7/43; 16%) developed PI substitutions on darunavir/ritonavir treatment resulting in decreased susceptibility to darunavir. Six of the 7 had baseline PI resistance-associated substitutions and baseline darunavir phenotypes > 7. The most common emerging PI substitutions in these virologic failures were V32I, L33F, M46I or L, I47V, I54L, T74P and L76V. These amino acid substitutions were associated with 59- to 839-fold decreased susceptibility to darunavir at failure. Examination of individual subjects who failed in the comparator arm on lopinavir/ritonavir and had post-baseline genotypes and phenotypes showed that 31 subjects (31/75; 41%) developed substitutions on lopinavir treatment resulting in decreased susceptibility to lopinavir (> 10-fold) and the most common substitutions emerging on treatment were L10I or F, M46I or L, I47V or A, I54V and L76V. Of the 31 lopinavir/ritonavir virologic failure subjects, 14 had reduced susceptibility (> 10-fold) to lopinavir at baseline.

In the 48-week analysis of the Phase 3 Study TMC114-C229, the number of virologic failures (including those who discontinued before suppression after Week 4) was 26% (75/294) in the group of subjects receiving PREZISTA/ritonavir 800/100 mg once daily compared to 19% (56/296) of subjects receiving PREZISTA/ritonavir 600/100 mg twice daily. Examination of isolates from subjects who failed on PREZISTA/ritonavir 800/100 mg once daily and had post-baseline genotypes showed that 8 subjects (8/60; 13%) had isolates that developed IAS-USA defined PI resistance-associated substitutions compared to 5 subjects (5/39; 13%) on PREZISTA/ritonavir 600/100 mg twice daily. Isolates from 2 subjects developed PI resistance associated substitutions associated with decreased susceptibility to darunavir; 1 subject isolate in the PREZISTA/ritonavir 800/100 mg once daily arm, developed substitutions V32I, M46I, L76V and I84V associated with a 24-fold decreased susceptibility to darunavir, and 1 subject isolate in the PREZISTA/ritonavir 600/100 mg twice daily arm developed substitutions L33F and I50V associated with a 40-fold decreased susceptibility to darunavir. In the PREZISTA/ritonavir 800/100 mg once daily and PREZISTA/ritonavir 600/100 mg twice daily groups, isolates from 7 (7/60, 12%) and 4 (4/42, 10%) virologic failures, respectively, developed decreased susceptibility to an NRTI included in the treatment regimen.

Clinical studies of PREZISTA/ritonavir in treatment-naive subjects: In the 192-week as-treated analysis censoring those who discontinued before Week 4 of the Phase 3 Study TMC114-C211, the percentage of virologic failures (never suppressed, rebounders and discontinued before achieving suppression) was 22% (64/288) in the group of subjects receiving PREZISTA/ritonavir 800/100 mg once daily compared to 29% (76/263) of subjects receiving lopinavir/ritonavir 800/200 mg per day. In the PREZISTA/ritonavir arm, emergent PI resistance-associated substitutions were identified in 11 of the virologic failures with post-baseline genotypic data (n=43) .

However, none of the darunavir virologic failures had a decrease in darunavir susceptibility (> 7-fold change) at failure. In the comparator lopinavir/ritonavir arm, emergent PI resistance-associated substitutions were identified in 17 of the virologic failures with post-baseline genotypic data (n=53), but none of the lopinavir/ritonavir virologic failures had decreased susceptibility to lopinavir (> 10-fold change) at failure. The reverse transcriptase M184V substitution and resistance to emtricitabine, which was included in the fixed background regimen, was identified in 4 virologic failures from the PREZISTA/ritonavir arm and 7 virologic failures in the lopinavir/ritonavir arm.

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

Darunavir-resistant viruses were not susceptible to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir or saquinavir in cell culture. However, six of nine darunavir-resistant viruses selected in cell culture from PI-resistant viruses showed a fold change in EC_{50} values < 3 for tipranavir, indicative of limited cross-resistance

between darunavir and tipranavir. In Studies TMC114-C213, TMC114-C202, and TMC114-C215, 34% (64/187) of subjects in the darunavir/ritonavir arm whose baseline isolates had decreased susceptibility to tipranavir (tipranavir fold change > 3) achieved < 50 copies/mL serum HIV-1 RNA levels at Week 96. Of the viruses isolated from subjects experiencing virologic failure on PREZISTA/ritonavir 600/100 mg twice daily (> 7 fold change), 41% were still susceptible to tipranavir and 10% were susceptible to saquinavir while less than 2% were susceptible to the other protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir or nelfinavir).

In Study TMC114-C214, the 7 darunavir/ritonavir virologic failures with reduced susceptibility to darunavir at failure were also resistant to the approved PIs (fos) amprenavir, atazanavir, lopinavir, indinavir, and nelfinavir at failure. Six of these 7 were resistant to saquinavir and 5 were resistant to tipranavir. Four of these virologic failures were already PI-resistant at baseline. .

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

Baseline Genotype/Phenotype and Virologic Outcome Analyses
Genotypic and/or phenotypic analysis of baseline virus may aid in determining darunavir susceptibility before initiation of PREZISTA/ritonavir 600/100 mg twice daily therapy. The effect of baseline genotype and phenotype on virologic response at 96 weeks was analyzed in as-treated analyses using pooled data from the Phase 2b studies (Studies TMC114-C213, TMC114-C202, and TMC114-C215) (n=439). The findings were confirmed with additional genotypic and phenotypic data from the control arms of etravirine Studies TMC125-C206 and TMC125C-216 at Week 24 (n=591).

Diminished virologic responses were observed in subjects with 5 or more baseline IAS-defined primary protease inhibitor resistance-associated substitutions (D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, L76V, V82A/F/L/S/T, I84V, N88S, L90M) (see Table **8**).

Table 8: Response to PREZISTA/ritonavir 600/100mg twice daily by Baseline Number of IAS-Defined Primary PI Resistance-Associated Substitutions: As-treated Analysis of Studies TMC114-C213, TMC114-C202, and TMC114-C215

	Studies TMC114-C213, TMC114-C202, TMC114-C215 < 50 copies/mL at Week 96 N=439		
# IAS-Defined Primary PI Substitutions	**Overall**	**De Novo ENF**	**Re-Used/No ENF**
All	44% (192/439)	54% (61/112)	40% (131/327)
0 - 4	50% (162/322)	58% (49/85)	48% (113/237)
5	22% (16/74)	47% (9/19)	13% (7/55)
≥ 6	9% (3/32)	17% (1/6)	8% (2/26)

IAS Primary PI Substitutions (2008): D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, L76V, V82A/F/L/S/T, I84V, N88S, L90M

The presence at baseline of two or more of the substitutions V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V was associated with a decreased virologic response to PREZISTA/ritonavir. In subjects not taking enfuvirtide de novo, the proportion of subjects achieving viral load < 50 plasma HIV RNA copies/mL at 96 weeks was 59%, 29%, and 12% when the baseline genotype had 0-1, 2 and ≥ 3 of these substitutions, respectively.

Baseline darunavir phenotype (shift in susceptibility relative to reference) was shown to be a predictive factor of virologic outcome. Response rates assessed by baseline darunavir phenotype are shown in Table **9**. These baseline phenotype groups are based on the select patient populations in the Studies TMC114-C213, TMC114-C202, and TMC114-C215, and are not meant to represent definitive clinical susceptibility breakpoints for

PREZISTA/ritonavir. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to darunavir.

Table 9: Response (HIV-1 RNA < 50 copies/mL at Week 96) to PREZISTA/ritonavir 600/100 mg twice daily by Baseline Darunavir Phenotype and by Use of Enfuvirtide (ENF): As-treated Analysis of Studies TMC114-C213, TMC114-C202, and TMC114-C215

	Proportion of Subjects with < 50 copies/mL at Week 96 N=417		
Baseline DRV Phenotype	**All**	**De Novo ENF**	**Re-Used/ No ENF**
Overall	175/417 (42%)	61/112 (54%)	131/327 (40%)
0 - 7	148/270 (55%)	44/65 (68%)	104/205 (51%)
> 7 - 20	16/53 (30%)	7/17 (41%)	9/36 (25%)
> 20	11/94 (12%)	6/23 (26%)	5/71 (7%)

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis and Mutagenesis

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. A dose-related increase in the incidence of hepatocellular adenomas and carcinomas were observed in males and females of both species as well as an increase in thyroid follicular cell adenomas in male rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to darunavir (based on AUC) were between 0.4- and 0.7-fold (mice) and 0.7-and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg once daily).

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

Impairment of Fertility

No effects on fertility or early embryonic development were observed with darunavir in rats and darunavir has shown no teratogenic potential in mice or rats (in the presence or absence of ritonavir) and rabbits.

12.2 Animal Toxicology and/or Pharmacology

In juvenile rats single doses of darunavir (20 mg/kg to 160 mg/kg at ages 5-11 days) or multiple doses of darunavir (40 mg/kg to 1000 mg/kg at age 12 days) caused mortality. The mortalities were associated with convulsions in some of the animals. 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 after a single dose of darunavir at 1000 mg/kg on day 26 of age or after repeat dosing at 500 mg/kg from day 23 to 50 of age. The exposures and toxicity profile in the older animals (day 23 or day 26) 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, do not administer PREZISTA/ritonavir in pediatric patients below 3 years of age.

13 CLINICAL STUDIES

13.1 Description of Adult Clinical Studies

The evidence of efficacy of PREZISTA/ritonavir is based on the analyses of 192-week data from a randomized, controlled open-label Phase 3 trial in treatment-naïve (TMC114-C211) HIV-1-infected adult subjects and 96-week data from a randomized, controlled, open-label Phase 3 trial in antiretroviral treatment-experienced (TMC114-C214) HIV-1-infected adult subjects. In addition, 96-week data are included from 2 randomized, controlled Phase 2b trials, TMC114-C213 and TMC114-C202, in antiretroviral treatment-experienced HIV-1-infected adult subjects.

13.2 Treatment-Naïve Adult Subjects

Study TMC114-C211

Study TMC114-C211 is a randomized, controlled, open-label Phase 3 trial comparing PREZISTA/ritonavir 800/100 mg once daily versus lopinavir/ritonavir 800/200 mg per day (given as a twice daily or as a once daily regimen) in antiretroviral treatment-naïve HIV-1-infected adult subjects. Both arms used a fixed background regimen consisting of tenofovir disoproxil fumarate 300 mg once daily (TDF) and emtricitabine 200 mg once daily (FTC).

HIV-1-infected subjects who were eligible for this trial had plasma HIV-1 RNA ≥ 5000 copies/mL. Randomization was stratified by screening plasma viral load (HIV-1 RNA < 100,000 copies/mL or ≥ 100,000 copies/mL) and screening CD4+ cell count (< 200 cells/mm^3 or ≥ 200 cells/mm^3). Virologic response was defined as a confirmed plasma HIV-1 RNA viral load < 50 copies/mL. Analyses included 689 subjects in Study TMC114-C211 who had completed 192 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the PREZISTA/ritonavir arm and the lopinavir/ritonavir arm (see Table **10**). Table **10**compares the demographic and baseline characteristics between subjects in the PREZISTA/ritonavir 800/100 mg once daily arm and subjects in the lopinavir/ritonavir 800/200 mg per day arm in Study TMC114-C211.

Table 10: Demographic and Baseline Characteristics of Subjects in Study TMC114-C211

	Randomized Study TMC114-C211	
	PREZISTA/ritonavir 800/100 mg once daily + TDF/FTC N = 343	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC N = 346**
Demographic Characteristics		
Median Age (years) (range, years)	34 (18-70)	33 (19-68)
Sex		
Male	70%	70%
Female	30%	30%
Race		
White	40%	45%
Black	23%	21%
Hispanic	23%	22%
Asian	13%	11%
Baseline Characteristics		
Mean Baseline Plasma HIV-1 RNA (log_{10} copies/mL)	4.86	4.84
Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)	228 (4-750)	218 (2-714)
Percentage of Patients with Baseline Viral Load ≥ 100,000 copies/mL	34%	35%
Percentage of Patients with Baseline CD4+ Cell Count < 200 cells/mm^3	41%	43%

Week 192 outcomes for subjects on PREZISTA/ritonavir 800/100 mg once daily from Study TMC114-C211 are shown in Table **11**.

Table 11: Virologic Outcome of Randomized Treatment of Study TMC114-C211 at 96 Weeks

	PREZISTA/ ritonavir 800/100 mg once daily + TDF/FTC N = 343	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC N = 346**
Virologic success HIV-1 RNA < 50 copies/mL	70%*	61%
Virologic failure†	12%	15%
No virologic data at Week 192 window‡		
Reasons		
Discontinued study due to adverse event or death§	5%	13%
Discontinued study for other reasons¶	13%	12%
Missing data during window‡ but on study	<1%	0%

N = total number of subjects with data
* 95% CI: 1.9; 16.1

† Includes patients who discontinued prior to Week 96 for lack or loss of efficacy and patients who are ≥ 50 copies in the 96-week window and patients who had a change in their background regimen that was not permitted by the protocol
‡ Window 90-102 Weeks
§ Includes patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window
¶ Other includes: withdrew consent, loss to follow-up, etc., if the viral load at the time of discontinuation was < 50 copies/mL

In Study TMC114-C211 at 192 weeks of treatment, the median increase from baseline in CD4+ cell counts was 258 cells/mm3 in the PREZISTA/ritonavir 800/100 mg once daily arm and 263 cells/mm3 in the lopinavir/ritonavir 800/200 mg per day arm. Of the PREZISTA/ritonavir subjects with a confirmed virologic response of < 50 copies/mL at Week 48, 81% remained undetectable at Week 192 versus 68% with lopinavir/ritonavir. In the 192 week analysis, statistical superiority of the PREZISTA/ritonavir regimen over the lopinavir/ritonavir regimen was demonstrated for both ITT and OP populations.

13.3 Treatment-Experienced Adult Subjects

Study TMC114-C229
Study TMC114-C229 is a randomized, open-label trial comparing PREZISTA/ritonavir 800/100 mg once daily to PREZISTA/ritonavir 600/100 mg twice daily in treatment-experienced HIV-1-infected patients with screening genotype resistance test showing no darunavir resistance associated substitutions (i.e. V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V) and a screening viral load of greater than 1,000 HIV-1 RNA copies/mL. Both arms used an optimized background regimen consisting of greater than or equal to 2 NRTIs selected by the investigator.
HIV-1-infected subjects who were eligible for this trial were on a highly active antiretroviral therapy regimen (HAART) for at least 12 weeks. Virologic response was defined as a confirmed plasma HIV-1 RNA viral load less than 50 copies/mL. Analyses included 590 subjects who had completed 48 weeks of treatment or discontinued earlier.

Table **12**compares the demographic and baseline characteristics between subjects in the PREZISTA/ritonavir 800/100 mg once daily arm and subjects in the PREZISTA/ritonavir 600/100 mg twice daily arm in Study TMC114-C229. No imbalances between the 2 arms were noted.

Table 12: Demographic and Baseline Characteristics of Subjects in Study TMC114-C229

	Randomized Study TMC114-C229	
	PREZISTA/ritonavir 800/100 mg once daily + OBR N = 294	**PREZISTA/ritonavir 600/100 mg twice daily + OBR N = 296**
Demographic Characteristics		
Median Age (years) (range, years)	40 (18-70)	40 (18-77)
Sex		
Male	61%	67%
Female	39%	33%
Race		
White	35%	37%
Black	28%	24%
Hispanic	16%	20%
Asian	16%	14%
Baseline Characteristics		
Mean Baseline Plasma HIV-1 RNA (log_{10} copies/mL)	4.19	4.13
Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)	219 (24-1306)	236 (44-864)
Percentage of Patients with Baseline Viral Load ≥ 100,000 copies/mL	13%	11%
Percentage of Patients with Baseline CD4+ Cell Count < 200 cells/mm^3	43%	39%
Median Darunavir Fold Change (range)*	0.50 (0.1-1.8)	0.50 (0.1-1.9)
Median Number of Resistance-Associated† :		
PI mutations	3	4
NNRTI mutations	2	1
NRTI mutations	1	1
Percentage of Subjects Susceptible to All Available PIs at Baseline	88%	86%
Percentage of Subjects with Number of Baseline Primary Protease Inhibitor Mutations† :		
0	84%	84%
1	8%	9%
2	5%	4%
≥ 3	3%	2%
Median Number of ARVs Previously Used‡:		
NRTIs	3	3
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	1	1

* Based on phenotype (Antivirogram®)
† Johnson VA, Brun-Vézinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: December 2008. Top HIV Med 2008; 16(5): 138-145
‡ Only counting ARVs, excluding low-dose ritonavir

Week 48 outcomes for subjects on PREZISTA/ritonavir 800/100 mg once daily from Study TMC114-C229 are shown in Table 13.

Table 13: **Virologic Outcome of Randomized Treatment of Study TMC114-C229 at 48 Weeks**

	Randomized Study TMC114-C229	
	PREZISTA/ritonavir 800/100 mg once daily + OBR N = 294	**PREZISTA/ritonavir 600/100 mg twice daily + OBR N = 296**
Virologic success HIV-1 RNA < 50 copies/mL	69%	69%
Virologic failure*	26%	23%
No virologic data at Week 48 window†		
Reasons		
Discontinued study due to adverse event or death‡	3%	4%
Discontinued study for other reasons§	2%	3%
Missing data during window† but on study	0%	< 1%

N = total number of subjects with data

* Includes patients who discontinued prior to Week 48 for lack or loss of efficacy, patients who are ≥ 50 copies in the 48-week window, patients who had a change in their background regimen that was not permitted in the protocol (provided the switch occurred before the earliest onset of an AE leading to permanent stop of study medication) and patients who discontinued for reasons other than AEs/death and lack or loss of efficacy (provided their last available viral load was detectable (HIV RNA ≥ 50 copies/mL).

† Window 42-54 Weeks

‡ Patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

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

The mean increase from baseline in CD4+ cell counts was comparable for both treatment arms (108 cells/mm3 and 112 cells/mm3 in the PREZISTA/ritonavir 800/100 mg once daily arm and the PREZISTA/ritonavir 600/100 mg twice daily arm, respectively).

Study TMC114-C214

Study TMC114-C214 is a randomized, controlled, open-label Phase 3 trial comparing PREZISTA/ritonavir 600/100 mg twice daily versus lopinavir/ritonavir 400/100 mg twice daily in antiretroviral treatment-experienced, lopinavir/ritonavir-naïve HIV-1-infected adult subjects. Both arms used an optimized background regimen (OBR) consisting of at least 2 antiretrovirals (NRTIs with or without NNRTIs).

HIV-1-infected subjects who were eligible for this trial had plasma HIV-1 RNA > 1000 copies/mL and were on a highly active antiretroviral therapy regimen (HAART) for at least 12 weeks. Virologic response was defined as a confirmed plasma HIV-1 RNA viral load < 400 copies/mL. Analyses included 595 subjects in Study TMC114-C214 who had completed 96 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the PREZISTA/ritonavir arm and the lopinavir/ritonavir arm (see Table 14). Table 14 compares the demographic and baseline characteristics between subjects in the PREZISTA/ritonavir 600/100 mg twice daily arm and subjects in the lopinavir/ritonavir 400/100 mg twice daily arm in Study TMC114-C214.

Table 14: **Demographic and Baseline Characteristics of Subjects in Study TMC114-C214**

	Randomized Study TMC114-C214	
	PREZISTA/ritonavir 600/100 mg twice daily + OBR N = 298	**lopinavir/ritonavir 400/100 mg twice daily + OBR N = 297**
Demographic Characteristics		
Median Age (years) (range, years)	40 (18-68)	41 (22-76)
Sex		
Male	77%	81%
Female	23%	19%
Race		
White	54%	57%
Black	18%	17%
Hispanic	15%	15%
Asian	9%	9%
Baseline Characteristics		
Mean Baseline Plasma HIV-1 RNA (log_{10} copies/mL)	4.33	4.28
Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)	235 (3-831)	230 (2-1096)
Percentage of Patients with Baseline Viral Load ≥ 100,000 copies/mL	19%	17%
Percentage of Patients with Baseline CD4+ Cell Count < 200 cells/mm^3	40%	40%
Median Darunavir Fold Change (range)	0.60 (0.10-37.40)	0.60 (0.1-43.8)
Median Lopinavir Fold Change (range)	0.70 (0.40-74.40)	0.80 (0.30-74.50)
Median Number of Resistance-Associated*:		
PI mutations	4	4
NNRTI mutations	1	1
NRTI mutations	2	2
Percentage of Subjects with Number of Baseline Primary Protease Inhibitor Mutations*:		
≤ 1	78%	80%
2	8%	9%
≥ 3	13%	11%
Median Number of ARVs Previously Used†:		
NRTIs	4	4
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	1	1
Percentage of Subjects Resistant‡ to All Available§ PIs at Baseline, excluding Darunavir	2%	3%

* Johnson VA, Brun-Vezinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: Fall 2006. Top

HIV Med 2006; 14(3): 125-130
† Only counting ARVs, excluding low-dose ritonavir
‡ Based on phenotype (Antivirogram™)
§ Commercially available PIs at the time of study enrollment

Week 96 outcomes for subjects on PREZISTA/ritonavir 600/100 mg twice daily from Study TMC114-C214 are shown in Table 15.

Table 15: Virologic Outcome of Randomized Treatment of Study TMC114-C214 at 96 Weeks

	PREZISTA /ritonavir 600/100 mg twice daily + OBR N = 298	**lopinavir/ritonavir 400/100 mg twice daily + OBR N = 297**
Virologic success HIV-1 RNA < 50 copies/mL	58%	52%
Virologic failure*	26%	33%
No virologic data at Week 96 window†		
Reasons		
Discontinued study due to adverse event or death‡	7%	8%
Discontinued study for other reasons§	8%	7%
Missing data during window† but on study	1%	< 1%

N = total number of subjects with data
* Includes patients who discontinued prior to Week 96 for lack or loss of efficacy and patients who are ≥ 50 copies in the 96 week window and patients who had a change in their OBR that was not permitted by the protocol.
† Window 90-102 Weeks
‡ Includes patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
§ Other includes: withdrew consent, loss to follow-up, etc., if the viral load at the time of discontinuation was < 50 copies/mL.

In Study TMC114-C214 at 96 weeks of treatment, the median increase from baseline in CD4+ cell counts was 81 cells/mm^3 in the PREZISTA/ritonavir 600/100 mg twice daily arm and 93 cells/mm^3 in the lopinavir/ritonavir 400/100 mg twice daily arm.

Studies TMC114-C213 and TMC114-C202
Studies TMC114-C213 and TMC114-C202 are randomized, controlled, Phase 2b trials in adult subjects with a high level of PI resistance consisting of 2 parts: an initial partially-blinded, dose-finding part and a second long-term part in which all subjects randomized to PREZISTA/ritonavir received the recommended dose of 600/100 mg twice daily.

HIV-1-infected subjects who were eligible for these trials had plasma HIV-1 RNA > 1000 copies/mL, had prior treatment with PI(s), NNRTI(s) and NRTI(s), had at least one primary PI mutation (D30N, M46I/L, G48V, I50L/V, V82A/F/S/T, I84V, L90M) at screening, and were on a stable PI-containing regimen at screening for at least 8

weeks. Randomization was stratified by the number of PI mutations, screening viral load, and the use of enfuvirtide.

The virologic response rate was evaluated in subjects receiving PREZISTA/ritonavir plus an OBR versus a control group receiving an investigator-selected PI(s) regimen plus an OBR. Prior to randomization, PI(s) and OBR were selected by the investigator based on genotypic resistance testing and prior ARV history. The OBR consisted of at least 2 NRTIs with or without enfuvirtide. Selected PI(s) in the control arm included: lopinavir in 36%, (fos)amprenavir in 34%, saquinavir in 35% and atazanavir in 17%; 98% of control subjects received a ritonavir boosted PI regimen out of which 23% of control subjects used dual-boosted PIs. Approximately 47% of all subjects used enfuvirtide, and 35% of the use was in subjects who were ENF-naïve. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1 $\log_{10}$ versus baseline.

In the pooled analysis for TMC114-C213 and TMC114-C202, demographics and baseline characteristics were balanced between the PREZISTA/ritonavir arm and the comparator PI arm (see Table 16). Table 16 compares the demographic and baseline characteristics between subjects in the PREZISTA/ritonavir 600/100 mg twice daily arm and subjects in the comparator PI arm in the pooled analysis of Studies TMC114-C213 and TMC114-C202.

Table 16**: Demographic and Baseline Characteristics of Subjects in the Studies TMC114-C213 and TMC114C-202 (Pooled Analysis)**

	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/ritonavir 600/100 mg twice daily + OBR N = 131	**Comparator PI(s) + OBR N = 124**
Demographic Characteristics		
Median Age (years) (range, years)	43 (27-73)	44 (25-65)
Sex		
Male	89%	88%
Female	11%	12%
Race		
White	81%	73%
Black	10%	15%
Hispanic	7%	8%
Baseline Characteristics		
Mean Baseline Plasma HIV-1 RNA ($\log_{10}$ copies/mL)	4.61	4.49
Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)	153 (3-776)	163 (3-1274)
Percentage of Patients with Baseline Viral Load > 100,000 copies/mL	24%	29%
Percentage of Patients with Baseline CD4+ Cell Count < 200 cells/mm^3	67%	58%
Median Darunavir Fold Change	4.3	3.3
Median Number of Resistance-Associated*: PI mutations NNRTI mutations	12 1 5	12 1 5

NRTI mutations		
Percentage of Subjects with Number of Baseline Primary Protease Inhibitor Mutations*: ≤ 1 2 ≥ 3	 8% 22% 70%	 9% 21% 70%
Median Number of ARVs Previously Used†: NRTIs NNRTIs PIs (excluding low-dose ritonavir)	 6 1 5	 6 1 5
Percentage of Subjects Resistant† to All Available‡ PIs at Baseline, excluding Tipranavir and Darunavir	63%	61%
Percentage of Subjects with Prior Use of Enfuvirtide	20%	17%
* Johnson VA, Brun-Vezinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: Fall 2006. Top HIV Med 2006; 14(3): 125-130 † Based on phenotype (Antivirogram™) ‡ Commercially available PIs at the time of study enrollment		

Week 96 outcomes for subjects on the recommended dose PREZISTA/ritonavir 600/100 mg twice daily from the pooled Studies TMC114-C213 and TMC114-C202 are shown in Table 17.

Table 17**: Outcomes of Randomized Treatment Through Week 96 of the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)**

	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/ritonavir 600/100 mg twice daily + OBR N=131	**Comparator PI + OBR N=124**
Virologic Responders confirmed at least 1 $\log^{10}$ HIV-1 RNA below baseline through Week 96 (< 50 copies/mL at Week 96)	57% (39%)	10% (9%)
Virologic failures	29%	80%
Lack of initial response*	8%	53%
Rebounder†	17%	19%
Never Suppressed‡	4%	8%
Death or discontinuation due to adverse events	9%	3%
Discontinuation due to other reasons	5%	7%
* Subjects who did not achieve at least a confirmed 0.5 $\log_{10}$ HIV-1 RNA drop from baseline at Week 12 † Subjects with an initial response (confirmed 1 $\log_{10}$ drop in viral load), but without a confirmed 1 $\log_{10}$ drop in viralload at Week 96 ‡ Subjects who never reached a confirmed 1 $\log_{10}$ drop in viral load before Week 96		

In the pooled Studies TMC114-C213 and TMC114-C202 through 48 weeks of treatment, the proportion of subjects with HIV-1 RNA < 400 copies/mL in the arm receiving PREZISTA/ritonavir 600/100 mg twice daily compared to the comparator PI arm was 55.0% and 14.5%, respectively. In addition, the mean changes in plasma HIV-1 RNA from baseline were –1.69 $\log_{10}$ copies/mL in the arm receiving PREZISTA/ritonavir 600/100

mg twice daily and – 0.37 log_{10} copies/mL for the comparator PI arm. The mean increase from baseline in CD4+ cell counts was higher in the arm receiving PREZISTA/ritonavir 600/100 mg twice daily (103 cells/mm^3) than in the comparator PI arm (17 cells/mm^3).

13.4 Pediatric Patients
The pharmacokinetic profile, safety and antiviral activity of PREZISTA/ritonavir were evaluated in 2 randomized, open-label, multicenter studies.

Study TMC114-C212
Treatment-experienced pediatric subjects between the ages of 6 and less than 18 years and weighing at least 20 kg were stratified according to their weight (greater than or equal to 20 kg to less than 30 kg, greater than or equal to 30kg to less than 40 kg, greater than or equal to 40 kg) and received PREZISTA tablets with either ritonavir capsules or oral solution plus background therapy consisting of at least two non-protease inhibitor antiretroviral drugs. Eighty patients were randomized and received at least one dose of PREZISTA/ritonavir. Pediatric subjects who were at risk of discontinuing therapy due to intolerance of ritonavir oral solution (e.g., taste aversion) were allowed to switch to the capsule formulation. Of the 44 pediatric subjects taking ritonavir oral solution, 23 subjects switched to the 100 mg capsule formulation and exceeded the weight-based ritonavir dose without changes in observed safety.
The 80 randomized pediatric subjects had a median age of 14 (range 6 to less than 18 years), and were 71% male, 54% Caucasian, 30% Black, 9% Hispanic and 8% other. The mean baseline plasma HIV-1 RNA was 4.64 log_{10} copies/mL, and the median baseline CD4+ cell count was 330 cells/mm^3 (range: 6 to 1505 cells/mm^3). Overall, 38% of pediatric subjects had baseline plasma HIV-1 RNA 100,000 copies/mL. Most pediatric subjects (79%) had previous use of at least one NNRTI and 96% of pediatric subjects had previously used at least one PI. Seventy-seven pediatric subjects (96%) completed the 24-week period. Of the patients who discontinued, one patient discontinued treatment due to an adverse event. An additional 2 patients discontinued for other reasons, one patient due to compliance and another patient due to relocation.
The proportion of pediatric subjects with HIV-1 RNA less than 400 copies/mL and less than 50 copies/mL was 64% and 50%, respectively. The mean CD4+ cell count increase from baseline was 117 cells/mm^3.

Study TMC114-C228
Treatment-experienced pediatric subjects between the ages of 3 and less than 6 years and weighing greater than or equal to 10 kg to less than 20 kg received PREZISTA oral suspension with ritonavir oral solution plus background therapy consisting of at least two active non-protease inhibitor antiretroviral drugs. Twenty-one subjects received at least one dose of PREZISTA/ritonavir.
The 21 subjects had a median age of 4.4 years (range 3 to less than 6 years), and were 48% male, 57% Black, 29%, Caucasian and 14% other. The mean baseline plasma HIV-1 was 4.34 log_{10} copies/mL, the median baseline CD4+ cell count was 927 x 10^6 cells/l (range: 209 to 2,429 x 10^6 cells/l) and the median baseline CD4+ percentage was 27.7% (range: 15.6% to 51.1%). Overall, 24% of subjects had a baseline plasma HIV-1 RNA greater than or equal to 100,000 copies/mL. All subjects had used greater than or equal to 2 NRTIs, 62% of subjects had used greater than or equal to 1 NNRTI and 76% had previously used at least one HIV PI.
Twenty subjects (95%) completed the 24 week period. One subject prematurely discontinued treatment due to vomiting assessed as related to ritonavir.
The proportion of subjects with HIV-1 RNA less than 50 copies/mL and less than 400 copies/mL was 57% and 81%, respectively. The mean change in CD4+ percentage from baseline was 4%. The mean change in CD4+ cell count from baseline was 109 x 10^6 cells/L.

14 HOW SUPPLIED/STORAGE AND HANDLING

PREZISTA (darunavir) 75 mg tablets are supplied as white, caplet-shaped, film-coated tablets containing darunavir ethanolate equivalent to 75 mg of darunavir per tablet. Each tablet is debossed with “75” on one side and “TMC” on the other side.
PREZISTA (darunavir) 150 mg tablets are supplied as white, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 150 mg of darunavir per tablet. Each tablet is debossed with “150” on one side and “TMC” on the other side.

PREZISTA (darunavir) 400 mg tablets are supplied as light orange, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 400 mg of darunavir per tablet. Each tablet is debossed with “400” on one side and “TMC” on the other side.
PREZISTA (darunavir) 600 mg tablets are supplied as orange, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 600 mg of darunavir per tablet. Each tablet is debossed with “600” on one side and “TMC” on the other side.
PREZISTA (darunavir) 800 mg tablets are supplied as dark red, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 800 mg of darunavir per tablet. Each tablet is debossed with “800” on one side and “T” on the other side.

PREZISTA tablets are packaged in bottles in the following configuration:

75 mg tablets—bottles of 480
150 mg tablets—bottles of 240
400 mg tablets—bottles of 60
600 mg tablets—bottles of 60
800 mg tablets - bottles of 30

Storage:
Store PREZISTA tablets at 15°-30°C (59°-86°F).
Shelf life after first opening: prezista 400mg, prezista 600 mg – 1 month
Prezista 800 mg – 3 months

15 PATIENT COUNSELING INFORMATION

A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with PREZISTA.** A Patient Package Insert for PREZISTA is available for patient information.

15.1 General

PREZISTA is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using PREZISTA.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

***Do not share needles or other injection equipment.**

***Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**

***Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

***Do not breastfeed.** We do not know if PREZISTA can be passed to the baby through breast milk and whether it could harm the baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

15.2 Instructions for Use
General
Patients should be advised to take PREZISTA and ritonavir with food every day as prescribed. Patients should be instructed to swallow whole tablets with a drink such as water or milk. PREZISTA must always be used with ritonavir) in combination with other antiretroviral drugs. Patients should not alter the dose of either PREZISTA or ritonavir discontinue ritonavir, or discontinue therapy with PREZISTA without consulting their physician.

Patients Taking PREZISTA Once Daily
If a patient misses a dose of PREZISTA or ritonavir by more than 12 hours, the patient should be told to wait and then take the next dose of PREZISTA and ritonavir at the regularly scheduled time. If the patient misses a dose of PREZISTA or ritonavir by less than 12 hours, the patient should be told to take PREZISTA and ritonavir immediately, and then take the next dose of PREZISTA and ritonavir at the regularly scheduled time. If a dose of PREZISTA or ritonavir is skipped, the patient should not double the next dose. Inform the patient that he or she should not take more or less than the prescribed dose of PREZISTA or ritonavir.

Patients Taking PREZISTA Twice Daily
If a patient misses a dose of PREZISTA or ritonavir by more than 6 hours, the patient should be told to wait and then take the next dose of PREZISTA and ritonavir at the regularly scheduled time. If the patient misses a dose of PREZISTA or ritonavir by less than 6 hours, the patient should be told to take PREZISTA and ritonavir immediately, and then take the next dose of PREZISTA and ritonavir at the regularly scheduled time. If a dose of PREZISTA or ritonavir is skipped, the patient should not double the next dose. Inform the patient that he or she should not take more or less than the prescribed dose of PREZISTA or ritonavir.

15.3 Hepatotoxicity
Patients should be informed that Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA co-administered with 100 mg of ritonavir. Monitor liver function before and during therapy, especially in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases. Post-marketing cases of liver injury, including some fatalities, have been reported. Patients should be advised about the signs and symptoms of liver problems. These may include jaundice of the skin or eyes, dark (tea colored) urine, pale colored stools, nausea, vomiting, loss of appetite, or pain, aching or sensitivity in the right upper quadrant of the abdomen.

15.4 Severe Skin Reactions
Patients should be informed that skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome and toxic epidermal necrolysis, have been reported with PREZISTA co-administered with 100 mg of ritonavir. Patients should be advised to discontinue PREZISTA/ritonavir 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.

15.5 Drug Interactions
PREZISTA/ritonavir may interact with many drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort.
Patients receiving estrogen-based contraceptives should be instructed to use alternate contraceptive measures during therapy with PREZISTA/ritonavir because hormonal levels may decrease.

15.6 Fat Redistribution
Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including PREZISTA/ritonavir, and that the cause and long-term health effects of these conditions are not known at this time.

Manufacturer: Janssen Cilag SpA, Latina, Italy
Registration holder: J-C Health Care Ltd. Kibbutz Shefayim, 60990, Israel