Darunavir Tablets
089-2025-01
2102629

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DARUNAVIR TABLETS safely and effectively. See Full Prescribing Information for DARUNAVIR TABLETS.

DARUNAVIR tablets, for oral use

Initial U.S. Approval: 2006

INDICATIONS AND USAGE

Darunavir tablets are a human immunodeficiency virus (HIV-1) protease inhibitor indicated for the treatment of HIV-1 infection in adult and pediatric patients 3 years of age and older. Darunavir tablets must be co-administered with ritonavir (darunavir tablets/ritonavir) and with other antiretroviral agents. (1)

DOSAGE AND ADMINISTRATION

- Testing:
  - In treatment-experienced patients, treatment history genotypic and/or phenotypic testing is recommended prior to initiation of therapy with darunavir tablets/ritonavir to assess drug susceptibility of the HIV-1 virus (2.1, 12.4)
  - Monitor serum liver chemistry tests before and during therapy with darunavir tablets/ritonavir. (2.1, 2.2, 5.2)
- Treatment-naïve adult patients and treatment-experienced adult patients with no darunavir resistance associated substitutions: 800 mg (one 800 mg tablet) taken with ritonavir 100 mg once daily and with food. (2.3)
- Treatment-experienced adult patients with at least one darunavir resistance associated substitution: 600 mg (one 600 mg tablet) taken with ritonavir 100 mg twice daily and with food. (2.3)
- Pregnant patients: 600 mg (one 600 mg tablet) taken with ritonavir 100 mg twice daily and with food. (2.4)
- Pediatric patients (3 to less than 18 years of age and weighing at least 10 kg): dosage of darunavir tablets and ritonavir is based on body weight and should not exceed the adult dose. Darunavir tablets should be taken with ritonavir and with food. (2.5)
- Darunavir tablets/ritonavir is not recommended for use in patients with severe hepatic impairment. (2.6)

DOSAGE FORMS AND STRENGTHS

- Tablets: 600 mg, and 800 mg (3)

CONTRAINDICATIONS

- Co-administration of darunavir tablets/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). (4)

WARNINGS AND PRECAUTIONS

- Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with darunavir/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. (5.2)
- Skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms and acute generalized exanthematous pustulosis, have been reported. Discontinue treatment if severe reaction develops. (5.3)
- Use with caution in patients with a known sulfonamide allergy. (5.4)
- Patients may develop new onset diabetes mellitus or hyperglycemia. Initiation or dose adjustments of insulin or oral hypoglycemic agents may be required. (5.6)
- Patients may develop redistribution/accumulation of body fat or immune reconstitution syndrome. (5.7, 5.8)
- Patients with hemophilia may develop increased bleeding events. (5.9)
- Darunavir/ritonavir is not recommended in pediatric patients below 3 years of age in view of toxicity and mortality observed in juvenile rats dosed with darunavir up to days 23 to 26 of age. (5.10)

ADVERSE REACTIONS

- The most common clinical adverse drug reactions to darunavir/ritonavir (incidence greater than or equal to 5%) of at least moderate intensity (greater than or equal to Grade 2) were diarrhea, nausea, rash, headache, abdominal pain and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Annora Pharma Private Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Co-administration of darunavir/ritonavir with other drugs can alter the concentrations of other drugs and other drugs may alter the concentrations of darunavir. The potential drug-drug interactions must be considered prior to and during therapy. (4, 5.5, 7, 12.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Total darunavir exposures were generally lower during pregnancy compared to postpartum period. The reduction in darunavir exposures during pregnancy were greater for once daily dosing compared to the twice daily dosing regimen. (8.1, 12.3)
- Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. (8.2)
- Pediatrics: Not recommended for patients less than 3 years of age. (8.4)

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

Revised: 01/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Darunavir tablets, co-administered with ritonavir (darunavir tablets/ritonavir), in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adult and pediatric patients 3 years of age and older *[see Use in Specific Populations (8.4) and Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of darunavir tablets/ritonavir

In treatment-experienced patients, treatment history, genotypic and/or phenotypic testing is recommended to assess drug susceptibility of the HIV-1 virus *[see Microbiology (12.4)]*. Refer to *Dosage and Administration (2.3), (2.4) and (2.5)* for dosing recommendations.

Appropriate laboratory testing such as serum liver biochemistries should be conducted prior to initiating therapy with darunavir tablets/ritonavir *[see Warnings and Precautions (5.2)]*.

2.2 Monitoring During Treatment with darunavir tablets/ritonavir

Patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases should be monitored for elevation in serum liver biochemistries, especially during the first several months of darunavir tablets/ritonavir treatment *[see Warnings and Precautions (5.2)]*.

2.3 Recommended Dosage in Adult Patients

Darunavir tablets must be co-administered with ritonavir to exert its therapeutic effect. Failure to correctly co-administer darunavir tablets 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.

Patients who have difficulty swallowing darunavir tablets can use the 100 mg per mL darunavir oral suspension.

Treatment-Naïve Adult Patients

The recommended oral dose of darunavir is 800 mg (one 800 mg tablet or 8 mL of the oral suspension) taken with ritonavir 100 mg (one 100 mg tablet or capsule or 1.25 mL of a 80 mg per mL ritonavir oral solution) once daily and with food. An 8 mL darunavir tablets dose should be taken as two 4 mL administrations with the included oral dosing syringe.

Treatment-Experienced Adult Patients

The recommended oral dosage for treatment-experienced adult patients is summarized in Table 1.

Baseline genotypic testing is recommended for dose selection. However, when genotypic testing is not feasible, darunavir tablets 600 mg taken with ritonavir 100 mg twice daily is recommended.

Table 1: Recommended darunavir tablets/ritonavir Dosage in Treatment-Experienced Adult Patients

Baseline Resistance	Formulation and Recommended Dosing: Darunavir tablets with ritonavir tablets or capsule	Formulation and Recommended Dosing: Darunavir oral suspension (100 mg/mL) with ritonavir oral solution (80 mg/mL)
With no darunavir resistance associated substitutions[a]	One 800 mg darunavir tablet with one 100 mg ritonavir tablet/capsule, taken once daily with food	8 mL[b] darunavir oral suspension with 1.25 mL ritonavir oral solution, taken once daily with food
With at least one darunavir resistance associated substitutions[a], or with no baseline resistance information	One 600 mg darunavir tablet with one 100 mg ritonavir tablet/capsule, taken twice daily with food	6 mL darunavir oral suspension with 1.25 mL ritonavir oral solution, taken twice daily with food

[a] V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V
[b] An 8 mL darunavir dose should be taken as two 4 mL administrations with the included oral dosing syringe.

2.4 Recommended Dosage During Pregnancy

The recommended dosage in pregnant patients is darunavir tablets 600 mg taken with ritonavir 100 mg twice daily with food.

Darunavir tablets 800 mg taken with ritonavir 100 mg once daily should only be considered in certain pregnant patients who are already on a stable darunavir tablets 800 mg with ritonavir 100 mg once daily regimen prior to pregnancy, are virologically suppressed (HIV-1 RNA less than 50 copies per mL), and in whom a change to twice daily darunavir tablets 600 mg with ritonavir 100 mg may compromise tolerability or compliance.

2.5 Recommended Dosage in Pediatric Patients (age 3 to less than 18 years)

Healthcare professionals should pay special attention to accurate dose selection of darunavir tablets, 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 darunavir tablets/ritonavir for each individual child based on body weight (kg) and should not exceed the recommended dose for adults.

Before prescribing darunavir tablets, children weighing greater than or equal to 15 kg should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a tablet, the use of darunavir oral suspension should be considered.

The recommended dose of darunavir tablets/ritonavir for pediatric patients (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see Tables 2, 3, 4, and 5) and should not exceed the recommended adult dose. Darunavir tablets should be taken with ritonavir and with food.

The recommendations for the darunavir tablets/ritonavir dosage regimens were based on pediatric clinical trial data and population pharmacokinetic modeling and simulation *[see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]*.

Dosing Recommendations for Treatment-Naïve Pediatric Patients or Antiretroviral Treatment-Experienced Pediatric Patients with No Darunavir Resistance Associated Substitutions

Pediatric Patients Weighing At Least 10 kg but Less than 15 kg

The weight-based dose in antiretroviral treatment-naïve pediatric patients or antiretroviral treatment-experienced pediatric patients with no darunavir resistance associated substitutions is darunavir 35 mg/kg once daily with ritonavir 7 mg/kg once daily using the following table:

Table 2: Recommended Dose for Pediatric Patients Weighing 10 kg to Less Than 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Darunavir Resistance Associated Substitutions[a]

Body weight (kg)	Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL) — Dose: once daily with food
Greater than or equal to 10 kg to less than 11 kg	Darunavir 3.6 mL[b] (350 mg) with ritonavir 0.8 mL (64 mg)
Greater than or equal to 11 kg to less than 12 kg	Darunavir 4 mL[b] (385 mg) with ritonavir 0.8 mL (64 mg)
Greater than or equal to 12 kg to less than 13 kg	Darunavir 4.2 mL (420 mg) with ritonavir 1 mL (80 mg)
Greater than or equal to 13 kg to less than 14 kg	Darunavir 4.6 mL[b] (455 mg) with ritonavir 1 mL (80 mg)
Greater than or equal to 14 kg to less than 15 kg	Darunavir 5 mL[b] (490 mg) with ritonavir 1.2 mL (96 mg)

[a] darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V
[b] The 350 mg, 385 mg, 455 mg and 490 mg darunavir dose for the specified weight groups were rounded up for suspension dosing convenience to 3.6 mL, 4 mL, 4.6 mL and 5 mL, respectively.

Pediatric Patients Weighing At Least 15 kg

Pediatric patients weighing at least 15 kg can be dosed with darunavir oral tablet(s) or suspension using the following table:

Table 3: Recommended Dose for Pediatric Patients Weighing At Least 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Darunavir Resistance Associated Substitutions[a]

Body weight (kg)	Formulation: Darunavir tablet(s) and ritonavir capsules or tablets (100 mg) — Dose: once daily with food	Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL) — Dose: once daily with food
Greater than or equal to 15 kg to less than 30 kg	Darunavir tablets 600 mg with ritonavir 100 mg	Darunavir 6 mL (600 mg) with ritonavir 1.25 mL (100 mg)
Greater than or equal to 30 kg to less than 40 kg	Darunavir tablets 675 mg with ritonavir 100 mg	Darunavir 6.8 mL[bc] (675 mg) with ritonavir 1.25 mL (100 mg)
Greater than or equal to 40 kg	Darunavir tablets 800 mg with ritonavir 100 mg	Darunavir 8 mL[c] (800 mg) with ritonavir 1.25 mL (100 mg)

[a] darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V
[b] The 675 mg dose using darunavir tablets for this weight group is rounded up to 6.8 mL for suspension dosing convenience.
[c] The 6.8 mL and 8 mL darunavir dose should be taken as two (3.4 mL or 4 mL respectively) administrations with the included oral dosing syringe.

Dosing Recommendations for Treatment-Experienced Pediatric Patients with At Least One Darunavir Resistance Associated Substitutions

Pediatric Patients Weighing At Least 10 kg but Less than 15 kg

The weight-based dose in antiretroviral treatment-experienced pediatric patients with at least one darunavir resistance associated substitution is darunavir 20 mg/kg twice daily with ritonavir 3 mg/kg twice daily using the following table:

Table 4: Recommended Dose for Pediatric Patients Weighing 10 kg to Less Than 15 kg Who are Treatment-Experienced with At Least One Darunavir Resistance Associated Substitution[a]

Body weight (kg)	Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL) — Dose: twice daily with food
Greater than or equal to 10 kg to less than 11 kg	Darunavir 2 mL (200 mg) with ritonavir 0.4 mL (32 mg)
Greater than or equal to 11 kg to less than 12 kg	Darunavir 2.2 mL (220 mg) with ritonavir 0.4 mL (32 mg)
Greater than or equal to 12 kg to less than 13 kg	Darunavir 2.4 mL (240 mg) with ritonavir 0.5 mL (40 mg)
Greater than or equal to 13 kg to less than 14 kg	Darunavir 2.6 mL (260 mg) with ritonavir 0.5 mL (40 mg)
Greater than or equal to 14 kg to less than 15 kg	Darunavir 2.8 mL (280 mg) with ritonavir 0.6 mL (48 mg)

[a] darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

Pediatric Patients Weighing At Least 15 kg

Pediatric patients weighing at least 15 kg can be dosed with darunavir oral tablet(s) or suspension using the following table:

Table 5: Recommended Dose for Pediatric Patients Weighing At Least 15 kg Who are Treatment-Experienced with At Least One Darunavir Resistance Associated Substitution[a]

Body weight (kg)	Formulation: Darunavir tablet(s) and ritonavir tablets, capsules (100 mg) or oral solution (80 mg/mL) — Dose: twice daily with food	Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL) — Dose: twice daily with food
Greater than or equal to 15 kg to less than 30 kg	Darunavir tablets 375 mg with ritonavir 0.6 mL (48 mg)	Darunavir 3.8 mL (375 mg)[b] with ritonavir 0.6 mL (48 mg)
Greater than or equal to 30 kg to less than 40 kg	Darunavir tablets 450 mg with ritonavir 0.75 mL (60 mg)	Darunavir 4.6 mL (450 mg)[b] with ritonavir 0.75 mL (60 mg)
Greater than or equal to 40 kg	Darunavir tablets 600 mg with ritonavir 100 mg	Darunavir 6 mL (600 mg) with ritonavir 1.25 mL (100 mg)

[a] darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V
[b] The 375 mg and 450 mg dose using darunavir tablets for this weight group is rounded up to 3.8 mL and 4.6 mL for suspension dosing convenience.

The use of darunavir tablets/ritonavir in pediatric patients below 3 years of age is not recommended *[see Warnings and Precautions (5.10) and Use in Specific Populations (8.4)]*.

2.6 Not Recommended in Patients with Severe Hepatic Impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment. No data are available regarding the use of darunavir tablets/ritonavir when co-administered to subjects with severe hepatic impairment; therefore, darunavir tablets/ritonavir is not recommended for use in patients with severe hepatic impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

600 mg: Yellow, oval shaped, biconvex, film-coated tablets debossed with 'V' on one side and '5' on the other side.

800 mg: Yellow, oval shaped, biconvex, film-coated tablets debossed with 'V' on one side and '7' on the other side.

4 CONTRAINDICATIONS

Co-administration of darunavir tablets/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). Examples of these drugs and other contraindicated drugs (which may lead to reduced efficacy of darunavir) are listed below *[see Drug Interactions (7.3)]*. Due to the need for co-administration of darunavir tablets with ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications.

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Anti-gout: colchicine, in patients with renal and/or hepatic impairment
- Antimycobacterial: rifampin
- Antipsychotics: lurasidone, pimozide
- Cardiac Disorders: dronedarone, ivabradine, ranolazine
- Ergot derivatives, e.g. dihydroergotamine, ergotamine, methylergonovine
- Herbal product: St. John's wort (*Hypericum perforatum*)
- Hepatitis C direct acting antiviral: elbasvir/grazoprevir
- Lipid modifying agents: lomitapide, lovastatin, simvastatin
- Opioid Antagonist: naloxegol
- PDE-5 inhibitor: sildenafil when used for treatment of pulmonary arterial hypertension
- Sedatives/hypnotics: orally administered midazolam, triazolam

5 WARNINGS AND PRECAUTIONS

5.1 Importance of Co-administration with Ritonavir

Darunavir must be co-administered with ritonavir and food to achieve the desired antiviral effect. Failure to administer darunavir 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 darunavir/ritonavir. During the clinical development program (N = 3063), hepatitis was reported in 0.5% of patients receiving combination therapy with darunavir/ritonavir. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse events.

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

Appropriate laboratory testing should be conducted prior to initiating therapy with darunavir/ritonavir 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 darunavir/ritonavir treatment.

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

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 (less than 0.1%) reported during the clinical development program. During post-marketing experience toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis have been reported. Discontinue darunavir/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.

Rash (all grades, regardless of causality) occurred in 10.3% of subjects treated with darunavir/ritonavir *[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 darunavir/ritonavir was 0.5%.

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

5.4 Sulfa Allergy

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

5.5 Risk of Serious Adverse Reactions due to Drug Interactions

Initiation of darunavir/ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving darunavir/ritonavir, may increase plasma concentrations of medications metabolized by CYP3A and reduce plasma concentrations of active metabolite(s) formed by CYP3A.

Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of darunavir/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 darunavir/ritonavir.
- Loss of therapeutic effect of the concomitant medications from lower exposures of active metabolite(s).
- Loss of therapeutic effect of darunavir/ritonavir and possible development of resistance from lower exposures of darunavir/ritonavir.

See Table 10 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 darunavir/ritonavir therapy; review concomitant medications during darunavir/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 darunavir. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

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

5.9 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 between PI therapy and these episodes has not been established.

5.10 Not Recommended in Pediatric Patients Below 3 Years of Age

Darunavir/ritonavir in pediatric patients below 3 years of age is not recommended 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 8.4) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

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

- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Severe Skin Reactions *[see Warnings and Precautions (5.3)]*
- Diabetes Mellitus/Hyperglycemia *[see Warnings and Precautions (5.6)]*
- Fat Redistribution *[see Warnings and Precautions (5.7)]*
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.8)]*
- Hemophilia *[see Warnings and Precautions (5.9)]*

Due to the need for co-administration of darunavir with ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Treatment Naïve-Adults: TMC114-C211

The safety assessment is based on all safety data from the Phase 3 trial TMC114-C211 comparing darunavir/ritonavir 800/100 mg once daily versus lopinavir/ritonavir 800/200 mg per day in 689 antiretroviral treatment-naïve HIV-1-infected adult subjects. The total mean exposure for subjects in the darunavir/ritonavir 800/100 mg once daily arm and in the lopinavir/ritonavir 800/200 mg per day arm was 162.5 and 153.5 weeks, respectively.

The majority of the adverse drug reactions (ADRs) reported during treatment with darunavir/ritonavir 800/100 mg once daily were mild in severity. The most common clinical ADRs to darunavir/ritonavir 800/100 mg once daily (greater than or equal to 5%) of at least moderate intensity (greater than or equal to Grade 2) were diarrhea, headache, abdominal pain and rash. 2.3% of subjects in the darunavir/ritonavir arm discontinued treatment due to ADRs.

ADRs to darunavir/ritonavir 800/100 mg once daily of at least moderate intensity (greater than or equal to Grade 2) in antiretroviral treatment-naïve HIV-1-infected adult subjects are presented in Table 6 and subsequent text below the table.

Table 6: Selected Clinical Adverse Drug Reactions to darunavir/ritonavir 800/100 mg Once Daily[a] of at Least Moderate Intensity (≥ Grade 2) Occurring in ≥ 2% of Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects (Trial TMC114-C211)

System organ class, preferred term, %	Darunavir/ritonavir 800/100 mg once daily + TDF/FTC N=343	lopinavir/ritonavir 800/200 mg per day + TDF/FTC N=346
Gastrointestinal Disorders		
Abdominal pain	6%	6%
Diarrhea	9%	16%
Nausea	4%	4%
Vomiting	2%	4%
General Disorders and Administration Site Conditions		
Fatigue	< 1%	3%
Metabolism and Nutrition Disorders		
Anorexia	2%	< 1%
Nervous System Disorders		
Headache	7%	6%
Skin and Subcutaneous Tissue Disorders		
Rash	6%	7%

N = total number of subjects per treatment group; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate
[a] Excluding laboratory abnormalities reported as ADRs.

Less Common Adverse Reactions

Treatment-emergent ADRs of at least moderate intensity (greater than or equal to Grade 2) occurring in less than 2% of antiretroviral treatment-naïve subjects receiving darunavir/ritonavir 800/100 mg once daily are listed below by body system:

Gastrointestinal Disorders: acute pancreatitis, dyspepsia, flatulence

General Disorders and Administration Site Conditions: asthenia

Hepatobiliary Disorders: acute hepatitis (e.g., acute hepatitis, cytolytic hepatitis, hepatotoxicity)

Immune System Disorders: (drug) hypersensitivity, immune reconstitution syndrome

Metabolism and Nutrition Disorders: diabetes mellitus

Musculoskeletal and Connective Tissue Disorders: myalgia, osteonecrosis

Psychiatric Disorders: abnormal dreams

Skin and Subcutaneous Tissue Disorders: angioedema, pruritus, Stevens-Johnson Syndrome, urticaria

Laboratory Abnormalities

Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-naïve adult subjects treated with darunavir/ritonavir 800/100 mg once daily are presented in Table 7.

Table 7: Grade 2 to 4 Laboratory Abnormalities Observed in Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects[a] (Trial TMC114-C211)

Laboratory parameter %	Limit	Darunavir/ritonavir 800/100 mg once daily + TDF/FTC	lopinavir/ritonavir 800/200 mg per day + TDF/FTC
Biochemistry			
Alanine Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	9%	9%
Grade 3	> 5.0 to ≤ 10.0 X ULN	3%	3%
Grade 4	> 10.0 X ULN	< 1%	3%
Aspartate Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	7%	10%
Grade 3	> 5.0 to ≤ 10.0 X ULN	4%	2%
Grade 4	> 10.0 X ULN	1%	3%
Alkaline Phosphatase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	1%	1%
Grade 3	> 5.0 to ≤ 10.0 X ULN	0%	< 1%
Grade 4	> 10.0 X ULN	0%	0%
Hyperbilirubinemia			
Grade 2	> 1.5 to ≤ 2.5 X ULN	< 1%	5%
Grade 3	> 2.5 to ≤ 5.0 X ULN	< 1%	< 1%
Grade 4	> 5.0 X ULN	0%	0%
Triglycerides			
Grade 2	5.65 to 8.48 mmol/L 500 to 750 mg/dL	3%	10%
Grade 3	8.49 to 13.56 mmol/L 751 to 1200 mg/dL	2%	5%
Grade 4	> 13.56 mmol/L > 1200 mg/dL	1%	1%
Total Cholesterol			
Grade 2	6.20 to 7.77 mmol/L 240 to 300 mg/dL	23%	27%
Grade 3	> 7.77 mmol/L > 300 mg/dL	1%	5%
Low-Density Lipoprotein Cholesterol			
Grade 2	4.13 to 4.90 mmol/L 160 to 190 mg/dL	14%	12%
Grade 3	≥ 4.91 mmol/L ≥ 191 mg/dL	9%	6%
Elevated Glucose Levels			
Grade 2	6.95 to 13.88 mmol/L 126 to 250 mg/dL	11%	10%
Grade 3	13.89 to 27.75 mmol/L 251 to 500 mg/dL	1%	< 1%
Grade 4	> 27.75 mmol/L > 500 mg/dL	0%	0%
Pancreatic Lipase			
Grade 2	> 1.5 to ≤ 3.0 X ULN	3%	2%
Grade 3	> 3.0 to ≤ 5.0 X ULN	< 1%	1%
Grade 4	> 5.0 X ULN	0%	< 1%
Pancreatic Amylase			
Grade 2	> 1.5 to ≤ 2.0 X ULN	5%	2%
Grade 3	> 2.0 to ≤ 5.0 X ULN	5%	4%
Grade 4	> 5.0 X ULN	0%	< 1%

N = total number of subjects per treatment group; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate
[a] Grade 4 data not applicable in Division of AIDS grading scale.

Treatment-Experienced Adults: TMC114-C214

The safety assessment is based on all safety data from the Phase 3 trial TMC114-C214 comparing darunavir/ritonavir 600/100 mg twice daily versus lopinavir/ritonavir 400/100 mg twice daily in 595 antiretroviral treatment-experienced HIV-1-infected adult subjects. The total mean exposure for subjects in the darunavir/ritonavir 600/100 mg twice daily arm and in the lopinavir/ritonavir 400/100 mg twice daily arm was 80.7 and 76.4 weeks, respectively.

The majority of the ADRs reported during treatment with darunavir/ritonavir 600/100 mg twice daily were mild in severity. The most common clinical ADRs to darunavir/ritonavir 600/100 mg twice daily (greater than or equal to 5%) of at least moderate intensity (greater than or equal to Grade 2) were diarrhea, nausea, rash, abdominal pain and vomiting. 4.7% of subjects in the darunavir/ritonavir arm discontinued treatment due to ADRs.

ADRs to darunavir/ritonavir 600/100 mg twice daily of at least moderate intensity (greater than or equal to Grade 2) in antiretroviral treatment-experienced HIV-1-infected adult subjects are presented in Table 8 and subsequent text below the table.

Table 8: Selected Clinical Adverse Drug Reactions to darunavir/ritonavir 600/100 mg Twice Daily[a] of at Least Moderate Intensity (≥ Grade 2) Occurring in ≥ 2% of Antiretroviral Treatment-Experienced HIV-1-Infected Adult Subjects (Trial TMC114-C214)

System organ class, preferred term, %	Darunavir/ritonavir 600/100 mg twice daily + OBR N=298	lopinavir/ritonavir 400/100 mg twice daily + OBR N=297
Gastrointestinal Disorders		
Abdominal distension	2%	< 1%
Abdominal pain	6%	3%
Diarrhea	14%	20%
Dyspepsia	2%	1%
Nausea	7%	6%
Vomiting	5%	3%
General Disorders and Administration Site Conditions		
Asthenia	3%	1%
Fatigue	2%	1%
Metabolism and Nutrition Disorders		
Anorexia	2%	2%
Diabetes mellitus	2%	< 1%
Nervous System Disorders		
Headache	3%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	7%	3%

N = total number of subjects per treatment group; OBR = optimized background regimen
[a] Excluding laboratory abnormalities reported as ADRs.

Less Common Adverse Reactions

Treatment-emergent ADRs of at least moderate intensity (greater than or equal to Grade 2) occurring in less than 2% of antiretroviral treatment-experienced subjects receiving darunavir/ritonavir 600/100 mg twice daily are listed below by body system:

Gastrointestinal Disorders: acute pancreatitis, flatulence

Musculoskeletal and Connective Tissue Disorders: myalgia

Psychiatric Disorders: abnormal dreams

Skin and Subcutaneous Tissue Disorders: pruritus, urticaria

Laboratory Abnormalities

Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with darunavir/ritonavir 600/100 mg twice daily are presented in Table 9.

Artwork information

Customer	Camber	Market	USA
Dimensions (mm)	480 x 900 mm	Non Printing Colors	Die cut
Pharma Code No.	Front-345 & Back-346		
Printing Colours	Black		

Others: Pharma code position and Orientation are tentative, will be changed based on folding size.