568-2023-04

10829

Darunavir Tablets

2D

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

----RECENT MAJOR CHANGES----

Contraindications (4) 4/2022

----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:
  - o 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)
  - o 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 (two 400 mg tablets) 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: 400 mg , and 600 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 Hetero Labs 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: 04/2023

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.

[illegible]

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

[illegible]

ARTWORK SPECIFICATION

Customer/Market	Camber Pharmaceutical — **Country**: US
Dimensions	480x900 mm
Pharma Code No.	Front: 10829, Back: 10830
Colours	1 (Black)
Spec.	Printed on 28 GSM Bible paper, front & back side printing.
If Any	Position of the pharma code and product name will change as per folding machine feasibility.

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Note: The above table format is for specification purpose only. Refer approved specification for final details. Version : 01

Darunavir/ritonavir was well tolerated during pregnancy and postpartum. There were no new clinically relevant safety findings compared with the known safety profile of darunavir/ritonavir in HIV-1-infected adults.

Among the 31 infants with HIV test results available data, born to the 31 HIV-infected pregnant women who completed trial through delivery or postpartum period, all 31 infants had test results that were negative for HIV-1 at the time of delivery and/or through 16 weeks postpartum. All 31 infants received antiretroviral prophylactic treatment containing zidovudine.

Based on prospective reports to the APR of over 980 exposures to darunavir- containing regimens during pregnancy resulting in live births (including over 660 exposed in the first trimester and over 320 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.6.% (95% CI: 2.3% to 5.3.%) with first trimester exposure to darunavir-containing regimens and 2.5% (95% CI: 1.1% to 4.8%) with second/third trimester exposure to darunavir-containing regimens.

Animal Data

Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice (doses up to 1000 mg/kg from gestation day (GD) 6 to15 with darunavir alone) and rats (doses up to 1000 mg/kg from GD 7 to 19 in the presence or absence of ritonavir) as well as in rabbits (doses up to 1000 mg/kg/day from GD 8 to 20 with darunavir alone). In these studies, darunavir exposures (based on AUC) were higher in rats (3-fold), whereas in mice and rabbits, exposures were lower (less than 1-fold) compared to those obtained in humans at the recommended clinical dose of darunavir boosted with ritonavir.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

There are no data on the presence of darunavir in human milk, the effects on the breastfed infant, or the effects on milk production. Darunavir is present in the milk of lactating rats *[see Data]*. Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving darunavir *[see Use in Specific Populations (8.4)]*.

Data

Animal Data

Studies in rats (with darunavir alone or with ritonavir) have demonstrated that darunavir is secreted in the milk. In the rat pre- and postnatal development study, a reduction in pup body weight gain was observed due to exposure of pups to drug substances via milk. The maximal maternal plasma exposures achieved with darunavir (up to 1000 mg/kg with ritonavir) were approximately 50% of those obtained in humans at the recommended clinical dose with ritonavir.

8.3 Females and Males of Reproductive Potential

Contraception

Use of darunavir may reduce the efficacy of combined hormonal contraceptives and the progestin only pill. Advise patients to use an effective alternative (non-hormonal) contraceptive method or add a barrier method of contraception. For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia *[see Drug Interactions (7.3)]*.

8.4 Pediatric Use

Darunavir/ritonavir is not recommended 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 (5.10), Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

The safety, pharmacokinetic profile, and virologic and immunologic responses of darunavir/ritonavir administered twice daily were evaluated in treatment-experienced HIV-1-infected pediatric subjects 3 to less than 18 years of age and weighting at least 10 kg. These subjects were evaluated in clinical trials TMC114-C212 (80 subjects, 6 to less than 18 years of age) and TMC114-228 (21 subjects, 3 to less than 6 years of age) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.4)]*. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults *[see Adverse Reactions (6.1)]*. Refer to *Dosage and Administration (2.5)* for twice-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

In clinical trial TMC114-C230, the safety, pharmacokinetic profile and virologic and immunologic responses of darunavir/ritonavir administered once daily were evaluated in treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years of age (12 subjects) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.4)]*. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults *[see Adverse Reactions (6.1)]*. Once daily dosing recommendations for pediatric patients 3 to less than 12 years of age were derived using population pharmacokinetic modeling and simulation. Although a darunavir/ritonavir once daily dosing pediatric trial was not conducted in children less than 12 years of age, there is sufficient clinical safety data to support the predicted darunavir exposures for the dosing recommendations in this age group *[see Clinical Pharmacology (12.3)]*. Please see *Dosage and Administration (2.5)* for once-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

Juvenile Animal Data

In a juvenile toxicity study where rats were directly dosed with darunavir (up to 1000 mg/kg), deaths occurred from post-natal day 5 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) 2 times the human plasma exposure levels.

8.5 Geriatric Use

Clinical studies of darunavir did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of darunavir in elderly patients, reflecting the greater frequency of decreased hepatic function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

No dosage adjustment of darunavir/ritonavir is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of darunavir/ritonavir in subjects with severe hepatic impairment. Therefore, darunavir/ritonavir is not recommended for use in patients with severe hepatic impairment *[see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)]*.

8.7 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 to 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 (12.3)]*.

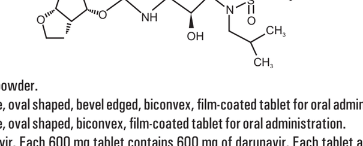
10 OVERDOSAGE

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

11 DESCRIPTION

Darunavir is an inhibitor of the human immunodeficiency virus (HIV-1) protease.

Darunavir, has the following chemical name: [(1*S*,2*R*-3-[[(4-Amino-phenyl)sulfonyl](2-methylpropylamino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamicacid(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]-furan-3-yl ester. Its molecular formula is $C_{27}H_{37}N_3O_7S$ and its molecular weight is 547.66. Darunavir has the following structural formula:



Darunavir is an off-white to pale brown colored powder.

Darunavir 400 mg tablets are available as orange, oval shaped, bevel edged, biconvex, film-coated tablet for oral administration.

Darunavir 600 mg tablets are available as orange, oval shaped, biconvex, film-coated tablet for oral administration.

Each 400 mg tablet contains 400 mg of darunavir. Each 600 mg tablet contains 600 mg of darunavir. Each tablet also contains the inactive ingredients colloidal silicon dioxide, crospovidone, magnesium stearate and silicified microcrystalline cellulose. The tablet film coating, Opadry II Orange, contains FD&C yellow #6/sunset yellow FCF aluminum lake, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Darunavir is an HIV-1 antiviral drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT/QTc study in 40 healthy subjects, darunavir/ritonavir doses of 1.33 times the maximum recommended dose did not affect the QT/QTc interval.

12.3 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 darunavir 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, darunavir 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 11 displays the population pharmacokinetic estimates of darunavir after oral administration of darunavir/ritonavir 600/100 mg twice daily (based on sparse sampling in 285 patients in trial TMC114-C214, 278 patients in trial TMC114-C229 and 119 patients [integrated data] from trials TMC114-C202 and TMC114-C213) and darunavir/ritonavir 800/100 mg once daily (based on sparse sampling in 335 patients in trial TMC114-C211 and 280 patients in trial TMC114-C229) to HIV-1-infected patients.

Table 11: Population Pharmacokinetic Estimates of Darunavir at Darunavir/ritonavir 800/100 mg Once Daily (Trial TMC114-C211, 48-Week Analysis and Trial TMC114-C229, 48-Week Analysis) and darunavir/ritonavir 600/100 mg Twice Daily (Trial TMC114-C214, 48-Week Analysis, Trial TMC114-C229, 48-Week Analysis and Integrated Data from Trials TMC114-C213 and TMC114-C202, Primary 24-Week Analysis)

	Darunavir/ritonavir 800/100 mg once daily		Darunavir/ritonavir 600/100 mg twice daily		
Parameter	TMC114-C211 N=335	TMC114-C229 N=280	TMC114-C214 N=285	TMC114-C229 N=278	TMC114-C213 + TMC114-C202 (integrated data) N=119
AUC_{24h} (ng.h/mL)[a]					
Mean ± Standard Deviation	93026 ± 27050	93334 ± 28626	116796 ± 33594	114302 ± 32681	124698 ± 32286
Median (Range)	87854 (45000 to 219240)	87788 (45456 to 236920)	111632 (64874 to 355360)	109401 (48934 to 323820)	123336 (67714 to 212980)
C_{0h} (ng/mL)					
Mean ± Standard Deviation	2282 ± 1168	2160 ± 1201	3490 ± 1401	3386 ± 1372	3578 ± 1151
Median (Range)	2041 (368 to 7242)	1896 (184 to 7881)	3307 (1517 to 13198)	3197 (250 to 11865)	3539 (1255 to 7368)

N = number of subjects with data

[a] 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 T_{max} of approximately 2.5 to 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 suggest that darunavir/ritonavir is an inhibitor of the P-glycoprotein (P-gp) transporters.

Effects of Food on Oral Absorption

When darunavir tablets were administered with food, the C_{max} and AUC of darunavir, co-administered with ritonavir, is approximately 40% higher relative to the fasting state. 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-1.

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 darunavir/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 (2.6) and Use in Specific Populations (8.6)]*.

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-1-infected subjects with moderate renal impairment (CrCL between 30 to 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 (8.7)]*.

Gender

Population pharmacokinetic analysis showed higher mean darunavir exposure in HIV-1-infected females compared to males. This difference is not clinically relevant.

Race

Population pharmacokinetic analysis of darunavir in HIV-1-infected subjects indicated that race had no apparent effect on the exposure to darunavir.

Geriatric Patients

Population pharmacokinetic analysis in HIV-1-infected subjects showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV-1-infected subjects (n=12, age greater than or equal to 65) *[see Use in Specific Populations (8.5)]*.

Pediatric Patients

Darunavir/ritonavir administered twice daily

The pharmacokinetics of darunavir in combination with ritonavir in 93 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 similar darunavir exposure when compared to the darunavir exposure achieved in treatment-experienced adults receiving darunavir/ritonavir 600/100 mg twice daily *[see Dosage and Administration (2.5)]*.

Darunavir/ritonavir administered once daily

The pharmacokinetics of darunavir in combination with ritonavir in 12 antiretroviral treatment-naïve HIV-1-infected pediatric subjects 12 to less than 18 years of age and weighing at least 40 kg receiving darunavir/ritonavir 800/100 mg once daily resulted in similar darunavir exposures when compared to the darunavir exposure achieved in treatment-naïve adults receiving darunavir/ritonavir 800/100 mg once daily *[see Dosage and Administration (2.5)]*.

Based on population pharmacokinetic modeling and simulation, the proposed darunavir/ritonavir once daily dosing regimens for pediatric patients 3 to less than 12 years of age is predicted to result in similar darunavir exposures when compared to the darunavir exposures achieved in treatment-naïve adults receiving darunavir/ritonavir 800/100 mg once daily *[see Dosage and Administration (2.5)]*.

The population pharmacokinetic parameters in pediatric subjects with darunavir/ritonavir administered once or twice daily are summarized in the table below:

Table 12: Population Pharmacokinetic Estimates of Darunavir Exposure (Trials TMC114-C230, TMC114-C212 and TMC114-C228) Following Administration of Doses in Tables 2 and 3

	Darunavir/ritonavir once daily	Darunavir/ritonavir twice daily		
			TMC114-C228[c]	
Parameter	TMC114-C230[a] N=12	TMC114-C212 N=74	10 to less than 15 kg[b] N=10	15 to less than 20 kg[d] N=13
AUC_{24h} (ng·h/mL)[e]				
Mean ± Standard Deviation	84390 ± 23587	126377 ± 34356	137896 ± 51420	157760 ± 54080
Median (Range)	86741 (35527 to 123325)	127340 (67054 to 230720)	124044 (89688 to 261090)	132698 (112310 to 294840)
C_{0h} (ng/mL)				
Mean ± Standard Deviation	2141 ± 865	3948 ±1363	4510 ± 2031	4848 ± 2143
Median (Range)	2234 (542 to 3776)	3888 (1836 to 7821)	4126 (2456 to 9361)	3927 (3046 to 10292)

N = number of subjects with data.

[a] Summary statistics for population pharmacokinetic parameter estimates for DRV after administration of DRV/rtv at 800/100 mg once daily in treatment-naïve HIV-1 infected subjects from 12 to < 18 years of age – Week-48 Analyses.

[b] 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.

[c] 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.

[d] The 15 kg to less than 20 kg weight group received 380 mg (3.8 mL) darunavir 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.

[e] AUC_{24h} is calculated as AUC_{12h}*2.

Pregnancy and Postpartum

The exposure to total darunavir and ritonavir after intake of darunavir/ritonavir 600/100 mg twice daily and darunavir/ritonavir 800/100 mg once daily as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum (see Table 13, Table 14 and Figure 1).

Table 13: Pharmacokinetic Results of Total Darunavir After Administration of darunavir/ritonavir at 600/100 mg Twice Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy and Postpartum

Pharmacokinetics of total darunavir (mean ± standard deviation)	2nd Trimester of pregnancy (n=12)[a]	3rd Trimester of pregnancy (n=12)	Postpartum (6 to 12 Weeks) (n=12)
C_{max}, ng/mL	4668 ± 1097	5328 ± 1631	6659 ± 2364
AUC_{24h}, ng·h/mL[b]	78740 ± 19194	91760 ± 34720	113780 ± 52680
C_{min}, ng/mL	1922 ± 825	2661 ± 1269	2851 ± 2216

[a] n=11 for AUC_{24h}

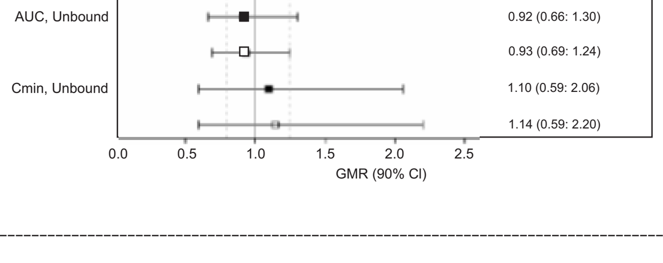
[b] AUC_{24h} is calculated as AUC_{12h}*2.

Table 14: Pharmacokinetic Results of Total Darunavir After Administration of darunavir/ritonavir at 800/100 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy and Postpartum

Pharmacokinetics of total darunavir (mean ± standard deviation)	2nd Trimester of pregnancy (n=17)	3rd Trimester of pregnancy (n=15)	Postpartum (6 to 12 Weeks) (n=16)
C_{max}, ng/mL	4964 ± 1505	5132 ± 1198	7310 ± 1704
AUC_{24h}, ng·h/mL	62289 ± 16234	61112 ± 13790	92116 ± 29241
C_{min}, ng/mL	1248 ± 542	1075 ± 594	1473 ± 1141

Due to an increase in the unbound fraction of darunavir during pregnancy compared to postpartum, unbound darunavir exposures were less reduced during pregnancy as compared to postpartum. Exposure reductions during pregnancy were greater for the once daily regimen as compared to the twice daily regimen (see Figure 1).

Figure 1: Pharmacokinetic Results (Within-Subject Comparison) of Total and Unbound Darunavir After Administration of darunavir/ritonavir at 600/100 mg Twice Daily or 800/100 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd and 3rd Trimester of Pregnancy Compared to Postpartum



Manufactured by:
HETERO™
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This Patient Information has been approved by the U.S. Food and Drug Administration.

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