



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	WARNINGS AND PRECAUTIONS Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with darunavir/ritonavir. Monitor liver function before and during	Table 9: Grade 2 to 4 Laboratory TMC114-C214)	Abnormalities Observed in Antiretrovi	ral Treatment-Experienced HIV-1	-Infected Adult Subjects [®] (Trial	Concomitant Drug Class Drug Name	Effect on Concentration of Darunavir Or Concomitant Drug	Clinical Comment
DARUNAVIR TABLETS. DARUNAVIR tablets, for oral use Initial U.S. Approval: 2006	 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) 	Laboratory parameter, %	Limit	Darunavir/ritonavir 600/100 mg twice daily + OBR	lopinavir/ritonavir 400/100 mg twice daily + OBR	vinblastine, vincristine		For vincristine and vinblastine, consideration should be given to temporarily withholding the ritonavir.containing antiretroviral regimen in patients who develop significant hematologic or
RECENT MAJOR CHANGES	 Symptoms and acute generalized exant nematous pustulosis, nave been reported. Discontinue treatment if severe reaction develops. (5.3) Use with caution in patients with a known sulfonamide allergy. (5.4) 	Biochemistry						gastrointestinal side effects when darunavir/ritonavir is
Contraindications (4) 4/2022	• Patients may develop new onset diabetes mellitus or hyperglycemia. Initiation or dose adjustments of insulin or oral hypoglycemic agents may be required. (5.6)	Alanine Aminotransferase						administered concurrently with vincristine or vinblastine. If the
INDICATIONS AND USAGE	 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) 	Grade 2	$>\!2.5$ to $\leq\!5.0$ X ULN	7%	5%			antiretroviral regimen must be withheld for a prolonged period, consideration should be given to initiating a revised regimen that
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)	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	Grade 3	> 5.0 to ≤ 10.0 X ULN	2%	2%			does not include a CYP3A or P-gp inhibitor.
DOSAGE AND ADMINISTRATION	darunavir up to days 23 to 26 of age. (5.10)	Grade 4 Aspartate Aminotransferase	>10.0 X ULN	1%	2%	Antipsychotics:		
Testing:	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	Grade 2	$>$ 2.5 to \leq 5.0 X ULN	6%	6%	lurasidone	↑ lurasidone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
 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) 	equal to Grade 2) were diarrhea, nausea, rash, headache, abdominal pain and vomiting. (6)	Grade 3	> 5.0 to ≤ 10.0 X ULN	2%	2%	pimozide	↑ pimozide	Co-administration is contraindicated due to potential for serious
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)	To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or	Grade 4	> 10.0 X ULN	<1%	2%			and/or life-threatening reactions such as cardiac arrhythmias.
Treatment-naïve adult patients and treatment-experienced adult patients with no darunavir resistance associated substitutions: 800 mg (two 400 mg	www.fda.gov/medwatch.	Alkaline Phosphatase	> 10.0 X OLIV	< 1/0	2 /0	quetiapine	↑ quetiapine	Initiation of darunavir with ritonavir in patients taking quetiapine: Consider alternative antiretroviral therapy to avoid increases in
tablets) taken with ritonavir 100 mg once daily and with food. (2.3)	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	Grade 2	>2.5 to ≤5.0 X ULN	< 1%	0%			quetiapine exposures. If co-administration is necessary, reduce
 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) 	darunavir. The potential drug-drug interactions must be considered prior to and during therapy. (4, 5.5, 7, 12.3)	Grade 3	> 5.0 to ≤ 10.0 X ULN	<1%	0% <1%			the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine
 Pregnant patients: 600 mg (one 600 mg tablet) taken with ritonavir 100 mg twice daily and with food. (2.4) 	USE IN SPECIFIC POPULATIONS	Grade 4	> 10.0 X ULN	0%	0%			prescribing information for recommendations on adverse reaction monitoring.
• 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	 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) 	Hvperbilirubinemia	> 10.0 X ULIN	070	0 /0			Initiation of quetiapine in patients taking darunavir with ritonavir:
not exceed the adult dose. Darunavir tablets should be taken with ritonavir and with food. (2.5)	Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. (8.2)		> 1 F 4: < 0 F V III N	< 10/	20/			Refer to the quetiapine prescribing information for initial dosing
Darunavir tablets/ritonavir is not recommended for use in patients with severe hepatic impairment. (2.6) DOSAGE FORMS AND STRENGTHS	Pediatrics: Not recommended for patients less than 3 years of age. (8.4)	Grade 2	> 1.5 to ≤ 2.5 X ULN	<1%	2%	tiiit	*	and titration of quetiapine. A decrease in the dose of antipsychotics that are metabolized by
Tablets: 400 mg , and 600 mg (3)	See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.	Grade 3	$>$ 2.5 to \leq 5.0 X ULN	<1%	<1%	e.g. perphenazine, risperidone, thioridazine	↑ antipsychotics	CYP3A or CYP2D6 may be needed when co-administered with
CONTRAINDICATIONS	Revised: 04/2023	Grade 4	>5.0 X ULN	<1%	0%			darunavir/ritonavir.
Co-administration of darunavir tablets/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated placeme appropriate tions are accessible with actions and/or life threatening wants/parameters/inindex/ (4)		Triglycerides	1	1		β-Blockers:	↑ hata blaskara	Clinical manitoring of noticate is successful to the
plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). (4)		Grade 2	5.65 to 8.48 mmol/L	10%	11%	e.g. carvedilol, metoprolol,	↑ beta-blockers	Clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with
			500 to 750 mg/dL	701	100/	timolol		darunavir/ritonavir and a lower dose of the beta blocker should be considered.
		Grade 3	8.49 to 13.56 mmol/L 751 to 1200 mg/dL	7%	10%	Calcium Channel Blockers:		DE CONSIDERED.
FULL PRESCRIBING INFORMATION: CONTENTS*	7.4 Drugs without Clinically Significant Interactions with Darunavir	Grade 4	> 13.56 mmol/L	3%	6%	amlodipine, diltiazem, felodipine,	↑ calcium channel blockers	Clinical monitoring of patients is recommended.
1 INDICATIONS AND USAGE	8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy		> 1200 mg/dL			nicardipine, nifedipine, verapamil		
2 DOSAGE AND ADMINISTRATION 2.1 Testing Prior to Initiation of darunavir tablets/ritonavir	8.2 Lactation	Total Cholesterol		1		Cardiac Disorders:		
2.2 Monitoring During Treatment with darunavir tablets/ritonavir	8.3 Females and Males of Reproductive Potential 8.4 Pediatric Use	Grade 2	6.20 to 7.77 mmol/L 240 to 300 mg/dL	25%	23%	ranolazine,	↑ ranolazine	Co-administration is contraindicated due to potential for serious
2.3 Recommended Dosage in Adult Patients 2.4 Recommended Dosage During Pregnancy	8.5 Geriatric Use	Grade 3	>7.77 mmol/L	10%	14%	ivabradine	↑ ivabradine	and/or life-threatening reactions.
2.5 Recommended Dosage in Pediatric Patients (age 3 to less than 18 years)	8.6 Hepatic Impairment		> 300 mg/dL			dronedarone	↑ dronedarone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
2.6 Not Recommended in Patients with Severe Hepatic Impairment	8.7 Renal Impairment 10 OVERDOSAGE	Low-Density Lipoprotein Cholestero	1			Other antiarrhythmics	A and and addression	
3 DOSAGE FORMS AND STRENGTHS	10 OVERDUSAGE	Grade 2	4.13 to 4.90 mmol/L 160 to 190 ma/dL	14%	14%	e.g. amiodarone, bepridil, disopyramide, flecainide, lidocaine	↑ antiarrhythmics	Therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with darunavir/ritonavir.
4 CONTRAINDICATIONS	12 CLINICAL PHARMACOLOGY	Grade 3	≥4.91 mmol/L	8%	9%	(systemic), mexiletine,		
5 WARNINGS AND PRECAUTIONS 5.1 Importance of Co-administration with Ritonavir	12 CLINICAL PHARMACULUGY 12.1 Mechanism of Action		≥ 191 mg/dL		- /-	propafenone, quinidine		
5.1 Importance of co-administration with Ritonavin 5.2 Hepatotoxicity	12.2 Pharmacodynamics	Elevated Glucose Levels	- 1			digoxin	↑ digoxin	The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for
5.3 Severe Skin Reactions	12.3 Pharmacokinetics 12.4 Microbiology	Grade 2	6.95 to 13.88 mmol/L 126 to 250 mg/dL	10%	11%			titration of digoxin dose to obtain the desired clinical effect.
5.4 Sulfa Allergy 5.5 Risk of Serious Adverse Reactions due to Drug Interactions	13 NONCLINICAL TOXICOLOGY	Grade 3	13.89 to 27.75 mmol/L	1%	<1%	Corticosteroids:		-
5.6 Diabetes Mellitus/Hyperglycemia	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Gibbe 5	251 to 500 mg/dL	170	< 1 /u	dexamethasone (systemic)	↓ darunavir	Co-administration of darunavir/ritonavir with systemic dexamethasone or other systemic corticosteroids that induce CYP3A may result in loss
5.7 Fat Redistribution 5.8 Immune Reconstitution Syndrome	14 CLINICAL STUDIES 14.1 Description of Adult Clinical Trials	Grade 4	>27.75 mmol/L	<1%	0%			of therapeutic effect and development of resistance to darunavir.
5.9 Hemophilia	14.2 Treatment-Naïve Adult Subjects	Pancreatic Lipase	> 500 mg/dL					Consider alternative corticosteroids.
5.10 Not Recommended in Pediatric Patients Below 3 Years of Age	14.3 Treatment-Experienced Adult Subjects 14.4 Pediatric Patients	Grade 2	$>$ 1.5 to \leq 3.0 X ULN	3%	4%	Corticosteroids primarily metabolized by CYP3A:	↑ corticosteroids	Co-administration with corticosteroids (all routes of administration) of
6 ADVERSE REACTIONS 6.1 Clinical Trials Experience	16 HOW SUPPLIED/STORAGE AND HANDLING	Grade 3	> 3.0 to ≤ 5.0 X ULN	2%	<1%	e.g.		which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression.
6.2 Postmarketing Experience	17 PATIENT COUNSELING INFORMATION	Grade 4	>5.0 X ULN	<1%	0%	betamethasone		Alternative corticosteroids including beclomethasone, prednisone, and
7 DRUG INTERACTIONS	*Sections or subsections omitted from the full prescribing information are not listed.	Pancreatic Amylase		27		budesonide ciclesonide		prednisolone (for which PK and/or PD are less affected by strong CYP3A
7.1 Potential for darunavir/ritonavir to Affect Other Drugs 7.2 Potential for Other Drugs to Affect Darunavir		Grade 2 Grade 3	> 1.5 to \leq 2.0 X ULN > 2.0 to \leq 5.0 X ULN	6% 7%	7% 3%	fluticasone		inhibitors relative to other steroids) should be considered, particularly for long term use.
7.2 Potential for Other Drugs to Affect Darunavir 7.3 Established and Other Potentially Significant Drug Interactions		Grade 4	>5.0 X ULN	0%	0%	methylprednisolone mometasone		
		N - total number of subjects per treatment	t group; OBR = optimized background regimen	•		triamcinolone		
		^a Grade 4 data not applicable in Division of A				Endothelin receptor antagonist:		
FULL PRESCRIBING INFORMATION	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	Serious ADRs				bosentan	↑ bosentan	<u>Co-administration of bosentan in patients on darunavir/ritonavir:</u> In patients who have been receiving darunavir/ritonavir for at
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	monitor for the adverse reactions associated with the concomitant drugs /see Contraindications (4) and Drug Interactions (7)].		oderate intensity (greater than or equal to Gra e pancreatitis, anorexia, asthenia, diabet					least 10 days, start bosentan at 62.5 mg once daily or every
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)].	5.6 Diabetes Mellitus/Hyperglycemia	hypercholesterolemia, hyperglycemia, hy	pertriglyceridemia, immune reconstitution s					other day based upon individual tolerability.
2 DOSAGE AND ADMINISTRATION	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	increased, rash, Stevens-Johnson Syndror	-					<u>Co-administration of darunavir/ritonavir in patients on bosentan:</u> Discontinue use of bosentan at least 36 hours prior to initiation
2.1 Testing Prior to Initiation of darunavir tablets/ritonavir	treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued PI therapy, hyperglycemia persisted in some	Patients Co-Infected with Hepatitis B and/ In subjects co-infected with hepatitis B or	<u>for Hepatitis C Virus</u> C virus receiving darunavir/ritonavir, the incid	ence of adverse events and clinical ch	emistry abnormalities was not higher			of darunavir/ritonavir. After at least 10 days following the
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.	cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between PI	than in subjects receiving darunavir/rito	navir who were not co-infected, except fo	increased hepatic enzymes (see W				initiation of darunavir/ritonavir, resume bosentan at 62.5 mg once
Appropriate laboratory testing such as serum liver biochemistries should be conducted prior to initiating therapy with darunavir tablets/ritonavir <i>(see Warnings and</i>	therapy and these events have not been established. 5.7 Fat Redistribution	pharmacokinetic exposure in co-infected s Clinical Trials Experience: Pediatric Patien	subjects was comparable to that in subjects wi	hout co-infection.		Errot doving times		daily or every other day based upon individual tolerability.
Precautions (5.2)].	Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast		i <u>ts</u> ombination with other antiretroviral agents i	n 3 Phase 2 trials. TMC114·C212, i	n which 80 antiretroviral treatment-	Ergot derivatives: e.g. dihydroergotamine,	↑ ergot derivatives	Co-administration is contraindicated due to potential for serious
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	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.		ects 6 to less than 18 years of age and weight			ergotamine,		and/or life-threatening reactions such as acute ergot toxicity
liver biochemistries, especially during the first several months of darunavir tablets/ritonavir treatment/see Warnings and Precautions (5.2)).	events are currently unknown. A causal relationship has not been established. 5.8 Immune Reconstitution Syndrome		diatric subjects 3 to less than 6 years of age ifected pediatric patients aged from 12 to les			methylergonovine		characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
2.3 Recommended Dosage in Adult Patients	Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including darunavir. During the initial phase of	C212 and C228 trials evaluated darunav	rir/ritonavir twice daily dosing and the TMC1			Hepatitis C virus (HCV):		งการแสนธิง อาน บนเฮา แจงนซึ่ง.
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.	combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic	Specific Populations (8.4) and Clinical Stud Frequency, type, and severity of ADRs in n	<i>dies (14.4)].</i> Jediatric subjects were comparable to those ob	served in adults		Direct-Acting Antivirals:		
Patients who have difficulty swallowing darunavir tablets can use the 100 mg per mL darunavir oral suspension.	infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.	TMC114-C212	ווסצפ סנון איז			elbasvir/grazoprevir	↑elbasvir/grazoprevir	Co-administration is contraindicated due to potential for the
Treatment-Naïve Adult Patients The recommended and does at down with it is 900 me (two 400 me tablets, or 9 mL of the analysis and supported by taken with site out 100 me (one 100 me tablet or cancele	Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) have also been reported to occur in the setting	Clinical ADRs to darunavir/ritonavir (all g	rades, greater than or equal to 3%), were vo	niting (13%), diarrhea (11%), abdom	inal pain (10%), headache (9%), rash	glecaprevir/pibrentasvir	↑ glecaprevir	increased risk of alanine transaminase (ALT) elevations.
The recommended oral dose of darunavir is 800 mg (two 400 mg tablets 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	of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of antiretroviral treatment.	(5%), nausea (4%), and fatigue (3%).	ro Al Tinereneed (Create 2, 20/ - C J- 4, 40/)	ACT increased (Crede 2: 1/1)	tio amulana increased (C 0. 4ª/	Aiceahicauthini curgeall	↑ pibrentasvir	Co-administration of darunavir/ritonavir with glecaprevir/ pibrentasviris not recommended.
included oral dosing syringe.	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.		re ALT increased (Grade 3: 3%; Grade 4: 1%), (Grade 3: 1%), total cholesterol increased (Gra					r · · · · · · · · · · · · · · · · · · ·
<u>Treatment-Experienced Adult Patients</u>	In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with Pls was continued or reintroduced if treatment had been	TMC114-C228				Herbal product: St. John's wort (<i>Hypericum</i>	l darunavir	
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	discontinued. A causal relationship between PI therapy and these episodes has not been established.	Clinical ADRs to darunavir/ritonavir (all gra (5%).	ades, greater than or equal to 5%), were diarr	nea (24%), vomiting (19%), rash (199	b), abdominal pain (5%), and anorexia	perforatum)	↓ darunavir	Co-administration is contraindicated due to potential for reduced plasma concentrations of darunavir, which may result in loss of
100 mg twice daily is recommended.	5.10 Not Recommended in Pediatric Patients Below 3 Years of Age	(5%). There were no Grade 3 or 4 laboratory abn	ormalities considered as ADRs in this trial					therapeutic effect and development of resistance.
Table 1: Recommended darunavir tablets/ritonavir Dosage in Treatment-Experienced Adult Patients	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 molling to 1000 molling) we to dow 23 to 25 of any logic line in Security and P. (Lond P. (Lond P. Land P. (Line and P.	TMC 11 4.C 230				Hormonal contraceptives:		

Included of a dusing synape. <u>Treatment-Experienced Adult Patients</u> Threecommended 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.

	Formulation and Recommended Dosing runavir tablets with ritonavir tablets or capsule Darunavir oral suspension (100 mg/mL) with ritonavir oral solution (80 mg/mL) darunavir tablets with one 100 mg ritonavir , taken once daily with food 8 mL ¹ darunavir oral suspension with 1.25 mL ritonavir oral suspension with the included oral dosing syringe. 600 mg taken with ritonavir 100 mg twice daily with food. 9 with the included oral dosing syringe. 600 mg taken with ritonavir 100 mg twice daily with food. 9 wears of ses selection of darunavir tablets, transcription of the medication order, dispensing information ses, and underdose. 12 big should be assessed for the ability to swallow tablets. If a child is unable to dide considered. patients (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see dose. Darunavir tablets should be taken with ritonavir and with food. upmens were based on pediatric clinical trial data and population pharmacokinetic modeling and ca	 6 ADVERSE REACTIONS The following adverse reactions are discuments of the patotoxicity (see Warnings and See Warning See Warning See Warning New See Warning See See See See See See See See See Se	assed in other sections of labeling: Precautions (5.2)/ greand Precautions (5.3)/ [see Warnings and Precautions (5.6), and Precautions (5.7)/ [see Warnings and Precautions (5.6), cautions (5.9)/ larunavir with ritonavir, please refer ler widely varying conditions, advers and may not reflect the rates observ in 689 antirentoviral treatment- ty arm and in the lopinavir/ritonavir 8 ons (ADRs) reported during treatment- ity arm and in the lopinavir/ritonavir 8 ons (ADRs) reported during treatment- ty arm and in the lopinavir/ritonavir 8 ons (ADRs) reported during treatment- ity arm and in the lopinavir/ritonavir 8 ons (ADRs) reported during treatment- ty arm and in the lopinavir/ritonavir 8 ons (ADRs) reported during treatment- tion (ADRs) reported during treatment- lison (ADRs) reported during treatment- and rash. 2.3% of subjects in the da once daily of at least moderate inter d subsequent text below the table. Drug Reactions to darunavir/rit reatment-Naïve HIV-1-Infected A ation Site Conditions ers isorders	// // to ritonavir prescribing information se reaction rates observed in the cl ed in clinical practice. trial TMC114-C211 comparing d maive HIV-infected adult subject (00/200 mg per day arm was 162.5 ent with darunavir/ritonavir 800/1 t than or equal to 5%) of at least m runavir/ritonavir arm discontinoavir 800/1 t darunavir/ritonavir arm discontinoavir 800/1 dult Subjects (Trial TMC114-C; N=343 6% 9% 4% 2%	n for ritonavir-associated adverse reactions. inical trials of a drug cannot be directly compared to farunavir/ritonavir 800/100 mg once daily versus sts. The total mean exposure for subjects in the 5 and 153.5 weeks, respectively. 100 mg once daily were mild in severity. The most noderate intensity (greater than or equal to Grade 2) treatment due to ADRs. le 2) in antiretroviral treatment-naïve HIV-1-infected p [*] of at Least Moderate Intensity (≥Grade 2) 211) lopinavir/ritonavir 800/200 mg per day + TDF/FTC N=346 6% 16% 16%	Clinical ADRs to darunavir/ritonavir (all gra decreased appetite (8.3%), pruritus (8.3%), There were no Grade 3 or 4 laboratory abnor 6.2 Postmarketing Experience The following adverse reactions have been i uncertain size, it is not always possible to rel Metabolism and Nutrition Disorders: Redistri Musculoskeletal and Connective Tissue Disor. Skin and Subcutaneous Tissue Disorders: Symptoms (see Warnings and Precautions (5. Renal and Urinary Disorders: Crystal nephrop 7 DRUG INTERACTIONS 7.1 Potential for darunavir/ritonavir to Darunavir co-administered with ritonavir is metabolized by CYP3A and CYP2D6 or are to therapeutic effect and adverse events. Daru plasma concentrations of these active metal 7.2 Potential for Other Drugs to Affece Darunavir and ritonavir (see Table 10). 7.3 Established and Other Potentially Table 10 provides dosing recommendations studies or predicted interactions due to the examples of potentially significant interactic drug that is co-administered with draunavir/ and specific actions to be taken with regard Table 10: Established and Other Potentially	nd rash (8.3%). Halties considered as ADRs in this tr entified during post-approval use of baby estimate their frequency or esta- ution of body fat rx: Rhabdomyolysis (associated with oxic epidermal necrolysis, acute gr W// Affect Other Drugs in inhibitor of CYP3A, CYP2D6, and ansported by P-gp may result in incr avir co-administered with ritonavir Difue(s), potentially leading to loss of Darunavir YP3A. <i>In vitro</i> data indicate that tai and ritonavir, resulting in lowerer 3A, or P-gp may decrease the clear Significant Drug Interactions is a result of drug interactions with	rial. f darunavir. Because these reactions are reported voluntarily from a population of ablish a causal relationship to drug exposure. h co-administration with HMG-CoA reductase inhibitors and darunavir/ritonavir) eneralized exanthematous pustulosis, drug rash with eosinophilia and systemic d P-gp. Co-administration of darunavir and ritonavir with drugs that are primarily reased plasma concentrations of such drugs, which could increase or prolong their with drugs that have active metabolite(s) formed by CYP3A may result in reduced t their therapeutic effect (see Table 10). darunavir may be a P-gp substrate. Drugs that induce CYP3A activity would be d plasma concentrations of darunavir and ritonavir. Co-administration of darunavir	ethinyl estradiol, norethindrone, drospirenone Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus Immunosuppressant/neoplastic: everolimus irinotecan Inhaled beta agonist:	↓ norethindrone drospirenone: effects unknown	For co-administration with drospirenone, clinical moni recommended due to the potential for hyperkalemia. No data are available to make recommendations on co with other hormonal contraceptives. Therapeutic concentration monitoring of the immunos agent is recommended when co-administered with ritonavir. Co-administration of everolimus and darunavir/ritonavi
	Solution (80 mg/mL) darunavir tablets with one 100 mg ritonavir , taken once daily with food 8 mL ¹ darunavir oral suspension with 1.25 mL ritonavir oral solution, taken once daily with food arunavir tablet with one 100 mg ritonavir , taken twice daily with food 6 mL darunavir oral suspension with 1.25 mL ritonavir oral solution, taken twice daily with food 89V 8 8 800 mg taken with ritonavir 100 mg twice daily with food. 8 should only be considered in certain pregnant patients who are already on a stable darunavir pregnancy, are virologically suppressed (HIV-1 RNA less than 50 copies per mL), and in whom a mg may compromise tolerability or compliance. sst than 18 years) 10 tose selection of darunavir tablets, transcription of the medication order, dispensing information see, and underdose. ets/ritonavir for each individual child based on body weight (kg) and should not exceed the dase. Darunavir tablets should be tassessed for the ability to swallow tablets. If a child is unable to id be considered. patients (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see dose). Darunavir tablets should be taken with ritonavir and with food. spinent were based on pediatric clinical trial data and population pharmacokinetic modeling and <i>ricology (12.3)</i> . ts or Antiretroviral Treatment-Experienced Pediatric patients with No Darunavir resistance avair 7 mg/kg once daily using the following table: 10 kg to Less Than 15 kg Who are Treatment-Naïve or Treatment-Experienced with No	 Hepatotxicity / See Warnings and Severe Skin Reactions / See Warning Diabets Mellitus/Hyperglycemia Fat Redistribution / See Warnings a Immune Reconstitution Syndrome Hemophilia / See Warnings and Prevention of the constitution Syndrome Hemophilia / See Warnings and Prevention of the constitution Syndrome International trials are conducted und rates in the clinical trials are conducted und rates in the clinical trials are conducted und rates in the clinical trials of a nother drug: Treatment Naïve-Adults: TMC114-C211 The safety assessment is based on al lopinavir/ritonavir 800/100 mg once dail The majority of the adverse drug reactic common clinical ADRs to darunavir/riton were diarrhea, headache, abdominal pain ADRs to darunavir/ritonavir 800/100 mg adult subjects are presented in Table 6 : Selected Clinical Adverse I Occurring in ≥ 2% of Antiretroviral T System organ class, preferred term, % Gastrointestinal Disorders Abdominal pain Diarrhea Nausea Vomiting General Disorders and Administration Fatigue Metabolism and Nutrition Disorders Headache Skin and Subcutaneous Tissue Di Rash N – total number of subjects per treatmer Excluding laboratory abnormalities repolates common Adverse Reactions 	Precautions (5.2)/ Ings and Precautions (5.3)/ Issee Warnings and Precautions (5.6), and Precautions (5.7)/ Issee Warnings and Precautions (5.6), and Precautions (5.7)/ Issee Warnings and Precautions (5.8)/ Iarunavir with ritonavir, please refer er widely varying conditions, advers and may not reflect the rates observ Il safety data from the Phase 3 i y in 689 antiretroviral treatment- ity arm and in the lopinavir/itonavir 8 ons (ADRs) reported during treatment if 8001100 mg once daily (greate and rash. 2.3% of subjects in the da once daily of at least moderate inter d subsequent text below the table. 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Drugs that induce CYP3A activity would be d plasma concentrations of darunavir and ritonavir. Co-administration of darunavir	sirolimus Immunosuppressant/neoplastic: everolimus irinotecan Inhaled beta agonist:	↑ immunosuppressants	agent is recommended when co-administered with ritonavir. Co-administration of everolimus and darunavir/ritonavi recommended. Discontinue darunavir/ritonavir at least 1 week prior irinotecan therapy. Do not administer darunavir/rito
	600 mg taken with ritonavir 100 mg twice daily with food. should only be considered in certain pregnant patients who are already on a stable darunavir pregnancy, are virologically suppressed (HIV-1 RNA less than 50 copies per mL), and in whom a mg may compromise tolerability or compliance. sstan 18 years) Jose selection of darunavir tablets, transcription of the medication order, dispensing information see, and underdose. test/irtonavir for each individual child based on body weight (kg) and should not exceed the an or equal to 15 kg should be assessed for the ability to swallow tablets. If a child is unable to id be considered. an or equal to 15 kg should be assessed for the ability to swallow tablets. If a child is unable to id be considered. griments (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see id ose. Darunavir tablets should be taken with ritonavir and with food. griments (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see id coolgy (<i>12.3</i>)). is to antiretroviral Treatment-Experienced Pediatric Patients with No Darunavir resistance havir 7 mg/kg once daily using the following table: 10 kg to Less Than 15 kg Who are Treatment-Naïve or Treatment-Experienced with No 10 muravir 3.6 mL (420 mg) with ritonavir 0.8 mL (64 mg) 10 arunavir 3.6 mL (420 mg) with ritonavir 0.8 mL (64 mg) 10 arunavir 4.6 mL ¹ (455 mg) with ritonavir 1.2 mL (80 mg) 11 Darunavir 4.6 mL ¹ (450 mg) with ritonavir 1.2 mL (86 mg) 12 arunavir 5 mL ¹ (490 mg) wit	The safety assessment is based on al lopinavi/ritonavir 800/200 mg per day darunavi/ritonavir 800/200 mg once dai The majority of the adverse drug reacti- common clinical ADRs to darunavir/riton were diarrhea, headache, abdominal pain ADRs to darunavir/ritonavir 800/100 mg adult subjects are presented in Table 6 ar Table 6: Selected Clinical Adverse I Occurring in ≥ 2% of Antiretroviral T System organ class, preferred term, % Gastrointestinal Disorders Abdominal pain Diarrhea Nausea Vomiting General Disorders and Administra Fatigue Metabolism and Nutrition Disord Anorexia Nervous System Disorders Headache Skin and Subcutaneous Tissue Di Rash N – total number of subjects per treatmer ¹ Excluding laboratory abnormalities repo	I safety data from the Phase 3 i in 689 antiretroviral treatment- ly arm and in the lopinavir/itonavir 8 ons (ADRs) reported during treatm avir 800/100 mg once daily (greate and rash. 2.3% of subjects in the da once daily of at least moderate inte dusbageunt text below the table. Drug Reactions to darunavir/irit reatment-Naïve HIV-1-Infected A Daru ation Site Conditions ers	naive HIV-1-infected adult subjec 00/200 mg per day arm was 162.5 ent with darunavir/itionavir 800/1 than or equal to 5%) of at least m runavir/itionavir arm discontinued onavir 800/100 mg Once Daily ddult Subjects (Trial TMC114-C: navir/ritonavir 800/100 mg once daily + TDF/FTC N=343 6% 9% 4% 2%	tts. The total mean exposure for subjects in the and 153.5 weeks, respectively. 100 mg once daily were mild in severity. The most noderate intensity (greater than or equal to Grade 2) treatment due to ADRs. le 2) in antiretroviral treatment-naïve HIV-1-infected of at Least Moderate Intensity (≥ Grade 2) 211) lopinavir/ritonavir 800/200 mg per day + TDF/FTC N=346 6% 16% 4%	7.1 Potential for darunavir/ritonavir is Darunavir co-administered with ritonavir is metabolized by CYP3A and CYP2D6 or are t therapeutic effect and adverse events. Daru plasma concentrations of these active metal 7.2 Potential for Other Drugs to Affec Darunavir and ritonavir are metabolized by expected to increase the clearance of daruna and ritonavir and other drugs that inhibit CY of darunavir and ritonavir (see Table 10). 7.3 Established and Other Potentially Table 10 provides dosing recommendations studies or predicted interactions due to the examples of potentially significant interacti drug that is co-administered with darunavir/ table 10: Established and Other Potent	n inhibitor of CYP3A, CYP2D6, and ansported by P.gp may result in incr avir co-administered with ritonavir júlets), potentially leading to loss of Darunavir CYP3A. <i>In vitro</i> data indicate that u vir and ritonavir, resulting in lowerer 3A, or P.gp may decrease the clear Significant Drug Interactions is a result of drug interactions with	reased plasma concentrations of such drugs, which could increase or prolong their with drugs that have active metabolite(s) formed by CYP3A may result in reduced their therapeutic effect (see Table 10). darunavir may be a P-gp substrate. Drugs that induce CYP3A activity would be d plasma concentrations of darunavir and ritonavir. Co-administration of darunavir	everolimus irinotecan Inhaled beta agonist:		Co-administration of everolimus and darunavir/ritonavi recommended. Discontinue darunavir/ritonavir at least 1 week prior irinotecan therapy. Do not administer darunavir/rito
	should only be considered in certain pregnant patients who are already on a stable darunavir pregnancy, are virologically suppressed (HIV-1 RNA less than 50 copies per mL), and in whom a ng may compromise tolerability or compliance. sss than 18 years) Jose selection of darunavir tablets, transcription of the medication order, dispensing information see, and underdose. tets/ritonavir for each individual child based on body weight (kg) and should not exceed the an or equal to 15 kg should be assessed for the ability to swallow tablets. If a child is unable to id be considered. patients (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see tdose. Darunavir tablets should be taken with ritonavir and with food. gimens were based on pediatric clinical trial data and population pharmacokinetic modeling and <i>acology (12.3)</i> . ts or Antiretroviral Treatment-Experienced Pediatric Patients with No Darunavir Resistance patients or antiretroviral treatment-experienced pediatric patients with no darunavir resistance avir 7 mg/kg once daily using the following table: 10 kg to Less Than 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/L) Darunavir 3.6 mL ¹ (355 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4.2 mL (420 mg) with ritonavir 1.2 mL (80 mg) Darunavir 4.6 mL ¹ (455 mg) with ritonavir 1.2 mL (96 mg) . 1 , ATV, I50V, I54M, I54L, T74P, L76V, I84V and L89V he specified weight groups were rounded up for suspension dosing convenience to 3.6 mL,	darunavir/ritonavir 800/100 mg once dai The majority of the adverse drug reacti common clinical ADRs to darunavir/riton were diarrhea, headache, abdominal pain ADRs to darunavir/ritonavir 800/100 mg adult subjects are presented in Table 6 ar Table 6: Selected Clinical Adverse I Occurring in ≥ 2% of Antiretroviral T System organ class, preferred term, % Gastrointestinal Disorders Abdominal pain Diarrhea Nausea Vomiting General Disorders and Administra Fatigue Metabolism and Nutrition Disorders Headache Skin and Subcutaneous Tissue Di Rash N – total number of subjects per treatmer * Excluding laboratory abnormalities repo Less Common Adverse Reactions	y arm and in the lopinavir/ritonavir 8 ons (ADRs) reported during treatme avir 800/100 mg once daily (greater and rash. 2.3% of subjects in the da once daily of at least moderate inten d subsequent text below the table. Drug Reactions to darunavir/rit reatment-Naïve HIV-1-Infected A Daru ation Site Conditions ers	100/200 mg per day arm was 162.5 ent with darunavir/intonavir 800/ r than or equal to 5%) of at least m unavir/intonavir arm discontinued nsity (greater than or equal to Grad onavir 800/100 mg Once Daily (dult Subjects (Trial TMC114-C: navir/ritonavir 800/100 mg once daily + DF/FTC N=343 6% 9% 4% 2% <1%	5 and 153.5 weeks, respectively. 100 mg once daily were mild in severity. The most noderate intensity (greater than or equal to Grade 2) treatment due to ADRs. le 2) in antiretroviral treatment-naïve HIV-1-infected of at Least Moderate Intensity (≥ Grade 2) 211) lopinavir/ritonavir 800/200 mg per day + TDF/FTC N = 346 6% 16% 4%	metabolized by CYP3A and CYP2D6 or are t therapeutic effect and adverse events. Daru plasma concentrations of these active metal 7.2 Potential for Other Drugs to Affec Darunavir and ritonavir are metabolized by expected to increase the clearance of daruna and ritonavir and other drugs that inhibit CY of darunavir and ritonavir (see Table 10). 7.3 Established and Other Potentially Table 10 provides dosing recommendations studies or predicted interactions due to the examples of potentially significant interactic drug that is co-administered with darunavir/ and specific actions to be taken with regard Table 10: Established and Other Potent	ansported by P-gp may result in incr awir co-administered with ritonawir olite(s), potentially leading to loss of Darunavir YP3A. <i>In witro</i> data indicate that vir and ritonavir, resulting in lowereu 3A, or P-gp may decrease the clear Significant Drug Interactions is a result of drug interactions with	reased plasma concentrations of such drugs, which could increase or prolong their with drugs that have active metabolite(s) formed by CYP3A may result in reduced their therapeutic effect (see Table 10). darunavir may be a P-gp substrate. Drugs that induce CYP3A activity would be d plasma concentrations of darunavir and ritonavir. Co-administration of darunavir	irinotecan		recommended. Discontinue darunavir/ritonavir at least 1 week prior irinotecan therapy. Do not administer darunavir/rito
	ng may compromise tolerability or compliance. ss than 18 years) does election of darunavir tablets, transcription of the medication order, dispensing information ses, and underdose. lets/ritonavir for each individual child based on body weight (kg) and should not exceed the an or equal to 15 kg should be assessed for the ability to swallow tablets. If a child is unable to due considered. patients (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see close. Darunavir tablets should be taken with ritonavir and with food. grimens were based on pediatric clinical trial data and population pharmacokinetic modeling and <i>actogy (12.3)</i> . It is or Antiretroviral Treatment-Experienced Pediatric Patients with no darunavir resistance patients or antiretroviral treatment-experienced pediatric patients with no darunavir resistance havir 7 mg/kg once daily using the following table: 10 kg to Less Than 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL) Darunavir 3.6 m ¹ (350 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4.2 mL (420 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4.6 mL ¹ (455 mg) with ritonavir 1.1 mL (80 mg) Darunavir 5 mL ² (490 mg) with ritonavir 1.2 mL (96 mg) , (47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V he specified weight groups were rounded up for suspension dosing convenience to 3.6 mL,	common clinical ADRs to darunavir/riton were diarrhea, headache, abdominal pain ADRs to darunavir/ritonavir 800/100 mg adult subjects are presented in Table 6 ar Table 6: Selected Clinical Adverse I Occurring in ≥ 2% of Antiretroviral T System organ class, preferred term, % Gastrointestinal Disorders Abdominal pain Diarrhea Nausea Vomiting General Disorders and Administra Fatigue Metabolism and Nutrition Disord Anorexia Nervous System Disorders Headache Skin and Subjects per treatmer * Excluding laboratory abnormalities repo Less Common Adverse Reactions	avir 800/100 mg once daily (greate and rash. 2.3% of subjects in the da once daily of at least moderate inte di subsequent text below the table. Drug Reactions to darunavir/rit reatment-Naïve HIV-1-Infected A Daru Daru ation Site Conditions ers isorders	r than or equal to 5%) of at least m runavir/ritonavir arm discontinued nsity (greater than or equal to Grad onavir 800/100 mg Once Daily kdult Subjects (Trial TMC114-C; navir/ritonavir 800/100 mg once daily + TDF/FTC N=343 6% 6% 9% 4% 2% 2%	noderate intensity (greater than or equal to Grade 2) treatment due to ADRs. le 2) in antiretroviral treatment-naïve HIV-1-infected y [*] of at Least Moderate Intensity (≥Grade 2) 211) lopinavir/ritonavir 800/200 mg per day + TDF/FTC N=346 6% 16% 4%	plasma concentrations of these active metal 7.2 Potential for Other Drugs to Affec Darunavir and ritonavir are metabolized by expected to increase the clearance of daruna and ritonavir and other drugs that inhibit CY of darunavir and ritonavir (see Table 10). 7.3 Established and Other Potentially Table 10 provides dosing recommendations studies or predicted interactions due to the examples of potentially significant interactid drug that is co-administered with darunavir/ and specific actions to be taken with regard Table 10: Established and Other Potenti	olite(s), potentially leading to loss of Darunavir 2YP3A. <i>In vitro</i> data indicate that (vir and ritonavir, resulting in lowerer 3A, or P-gp may decrease the clear: Significant Drug Interactions is a result of drug interactions with	f their therapeutic effect (see Table 10). darunavir may be a P-gp substrate. Drugs that induce CYP3A activity would be d plasma concentrations of darunavir and ritonavir. Co-administration of darunavir			irinotecan therapy. Do not administer darunavir/rito
	does eslection of darunavir tablets, transcription of the medication order, dispensing information see, and underdose. lets/ritonavir for each individual child based on body weight (kg) and should not exceed the an or equal to 15 kg should be assessed for the ability to swallow tablets. If a child is unable to id be considered. patients (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see (dose. Darunavir tablets should be taken with ritonavir and with food. gimens were based on pediatric clinical trial data and population pharmacokinetic modeling and <i>acology (12.3)</i> . ts or Antiretroviral Treatment-Experienced Pediatric Patients with No Darunavir Resistance havir 7 mg/kg once daily using the following table: 10 kg to Less Than 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL) Darunavir 3.6 mL ³ (350 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4.2 mL (420 mg) with ritonavir 1.2 mL (64 mg) Darunavir 4.2 mL ³ (490 mg) with ritonavir 1.2 mL (96 mg) Laruavir 5 mL ³ (490 mg) with ritonavir 1.2 mL (96 mg) Laruavir 5 mL ³ (490 mg) with ritonavir 1.2 mL (96 mg) Laruavir 5 mL ³ (490 mg) with ritonavir 1.2 mL (96 mg) Laruavir 5 mL ³ (490 mg) with ritonavir 1.2 mL (96 mg) Laruavir 5 mL ³ (490 mg) with ritonavir 1.2 mL (96 mg) Laruavir 5 mL ³ (490 mg) with ritonavir 1.2 mL (96 mg) Laruavir 5 mL ³ (490 mg) with rit	adult subjects are presented in Table 6 ar Table 6: Selected Clinical Adverse I Occurring in ≥ 2% of Antiretroviral T System organ class, preferred term, % Gastrointestinal Disorders Abdominal pain Diarrhea Nausea Vomiting General Disorders and Administra Fatigue Metabolism and Nutrition Disorder Anorexia Nervous System Disorders Headache Skin and Subcutaneous Tissue Di Rash N- total number of subjects per treatmer * Excluding laboratory abnormalities repo Less Common Adverse Reactions	In subsequent text below the table. Drug Reactions to darunavir/rit reatment-Naïve HIV-1-Infected A Daru ation Site Conditions ers isorders isorders	onavir 800/100 mg Once Daily Idult Subjects (Trial TMC114-C: navir/ritonavir 800/100 mg once daily + TDF/FTC N=343 6% 9% 4% 2% <1%	y* of at Least Moderate Intensity (≥Grade 2) 211) Iopinavir/ritonavir 800/200 mg per day + TDF/FTC N=346 6% 16% 4%	expected to increase the clearance of darum and ritonavir and other drugs that inhibit CY of darunavir and ritonavir (see Table 10). 7.3 Established and Other Potentially Table 10 provides dosing recommendations studies or predicted interactions due to the examples of potentially significant interacti- drug that is co-administered with darunavir/ and specific actions to be taken with regard Table 10: Established and Other Potent	vir and ritonavir, resulting in lowered 3A, or P-gp may decrease the clear Significant Drug Interactions Is a result of drug interactions with	d plasma concentrations of darunavir and ritonavir. Co-administration of darunavir			1
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	Id be considered. patients (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see close. Darunavir tablets should be taken with ritonavir and with food. gimens were based on pediatric clinical trial data and population pharmacokinetic modeling and acology (12.3). Is or Antiretroviral Treatment-Experienced Pediatric Patients with No Darunavir Resistance patients or antiretroviral treatment-experienced pediatric patients with no darunavir resistance navir 7 mg/kg once daily using the following table: 10 kg to Less Than 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL) Darunavir 3.6 mL ¹ (335 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4.2 mL (420 mg) with ritonavir 1.2 mL (80 mg) Darunavir 4.5 mL ¹ (455 mg) with ritonavir 1.2 mL (96 mg) . LATV, I50V, I54M, I54L, T74P, L76V, I84V and L89V he specified weight groups were rounded up for suspension dosing convenience to 3.6 mL,	term, % Gastrointestinal Disorders Abdominal pain Diarrhea Nausea Vomiting General Disorders and Administra Fatigue Metabolism and Nutrition Disorders Headache Skin and Subcutaneous Tissue Di Rash N – total number of subjects per treatmer 'Excluding laboratory abnormalities repo Less Common Adverse Reactions	ation Site Conditions ers isorders i	once daily + TDF/FTC N=343 6% 9% 4% 2% 2%	6% 16% 4%	studies or predicted interactions due to the examples of potentially significant interacti- drug that is co-administered with darunavir/ and specific actions to be taken with regard Table 10: Established and Other Potent		1 11 1 1 T			cardiovascular adverse events associated with s including QT prolongation, palpitations and sinus tachyo
	gimens were based on pediatric clinical trial data and population pharmacokinetic modeling and <i>acology (12.3)I.</i> Is or Antiretroviral Treatment-Experienced Pediatric Patients with No Darunavir Resistance patients or antiretroviral treatment-experienced pediatric patients with No Darunavir resistance navir 7 mg/kg once daily using the following table: 10 bg to Less Than 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL) Darunavir 3.6 mL ³ (350 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4.2 mL (420 mg) with ritonavir 1.8 mL (64 mg) Darunavir 4.2 mL (455 mg) with ritonavir 1.1 mL (80 mg) Darunavir 5 mL ³ (490 mg) with ritonavir 1.2 mL (96 mg) , I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V he specified weight groups were rounded up for suspension dosing convenience to 3.6 mL,	Abdominal pain Diarrhea Nausea Vomiting General Disorders and Administra Fatigue Metabolism and Nutrition Disorder Anorexia Nervous System Disorders Headache Skin and Subcutaneous Tissue Di Rash N- total number of subjects per treatmer 'Excluding laboratory abnormalities repo Less Common Adverse Reactions	ers	8% 9% 4% 2% <1%	6% 16% 4%	drug that is co-administered with darunavir/ and specific actions to be taken with regard Table 10: Established and Other Potent		and potential for serious adverse events or loss of efficacy. The table includes	HMG-CoA reductase inhibitors:		
	ts or Antiretroviral Treatment-Experienced Pediatric Patients with No Darunavir Resistance patients or antiretroviral treatment-experienced pediatric patients with no darunavir resistance havir 7 mg/kg once daily using the following table: 10 kg to Less Than 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL) Dose: once daily with food Darunavir 3.6 mL ³ (305 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4.6 mL ³ (455 mg) with ritonavir 1 mL (80 mg) Darunavir 4.6 mL ³ (455 mg) with ritonavir 1.2 mL (96 mg) Ramavir 5 mL ³ (490 mg) with ritonavir 1.2 mL (96 mg) , IA7V, I50V, I54M, I54L, T74P, L76V, I84V and L89V he specified weight groups were rounded up for suspension dosing convenience to 3.6 mL,	Diarrhea Nausea Vomiting General Disorders and Administra Fatigue Metabolism and Nutrition Disorder Anorexia Nervous System Disorders Headache Skin and Subcutaneous Tissue Di Rash N- total number of subjects per treatmer 'Excluding laboratory abnormalities repo Less Common Adverse Reactions	ers	9% 4% 2% <1%	16% 4%		tonavir should be consulted for infor o co-administration.	rmation related to the route of metabolism, interaction pathways, potential risks,	lovastatin, simvastatin	† simvastatin	Co-administration is contraindicated due to potential f reactions such as myopathy including rhabdomyolysis.
	avir 7 mg/kg once daily using the following table: 10 kg to Less Than 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL) Dose: once daily with food Darunavir 3.6 mL ⁸ (350 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4 mL ⁸ (385 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4.2 mL (420 mg) with ritonavir 1 mL (80 mg) Darunavir 5 mL ⁸ (490 mg) with ritonavir 1.2 mL (96 mg) , I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V he specified weight groups were rounded up for suspension dosing convenience to 3.6 mL,	Vomiting General Disorders and Administra Fatigue Metabolism and Nutrition Disorder Anorexia Nervous System Disorders Headache Skin and Subcutaneous Tissue Di Rash N - total number of subjects per treatmer *Ecuduling laboratory abnormalities repo Less Common Adverse Reactions	ers	2% <1%			on (<i>see Contraindications (4)</i> for				Co-administration of darunavir/ritonavir with H reductase inhibitors may lead to adverse events such as Titrate atorvastatin, pravastatin or rosuvastatin dos
<form></form>	10 kg to Less Than 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL) Dose: once daily with food Darunavir 3.6 mL ⁺ (350 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4 mL ⁺ (385 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4.2 mL (420 mg) with ritonavir 1 mL (80 mg) Darunavir 4.6 mL ⁺ (455 mg) with ritonavir 1 nmL (80 mg) Darunavir 5 mL ⁺ (490 mg) with ritonavir 1.2 mL (96 mg) , 147V, I50V, I54M, I54L, T74P, L76V, I84V and L89V he specified weight groups were rounded up for suspension dosing convenience to 3.6 mL,	Fatigue Metabolism and Nutrition Disorder Anorexia Nervous System Disorders Headache Skin and Subcutaneous Tissue Di Rash N- total number of subjects per treatmer *Excluding laboratory abnormalities repo Less Common Adverse Reactions	ers		1	Concomitant Drug Class	Effect on Concentration of				and use the lowest necessary dose while monitoring
<form>Image: marked by the problemImage: marked by the problem<td>ritonavir oral solution (80 mg/mL) Dose: once daily with food Darunavir 3.6 mL³ (350 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4.1 mL² (385 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4.2 mL (420 mg) with ritonavir 1 mL (80 mg) Darunavir 4.5 mL³ (455 mg) with ritonavir 1.2 mL (90 mg) Darunavir 5 mL³ (490 mg) with ritonavir 1.2 mL (96 mg) , 147V, 150V, 154M, 154L, T74P, L76V, 184V and L89V he specified weight groups were rounded up for suspension dosing convenience to 3.6 mL,</td><td>Nervous System Disorders Headache Skin and Subcutaneous Tissue Di Rash N- total number of subjects per treatmer *Excluding laboratory abnormalities repo Less Common Adverse Reactions</td><td></td><td>2%</td><td>3%</td><td></td><td></td><td></td><td></td><td>↑ lomitapide</td><td>Co-administration is contraindicated due to potential fo</td></form>	ritonavir oral solution (80 mg/mL) Dose: once daily with food Darunavir 3.6 mL ³ (350 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4.1 mL ² (385 mg) with ritonavir 0.8 mL (64 mg) Darunavir 4.2 mL (420 mg) with ritonavir 1 mL (80 mg) Darunavir 4.5 mL ³ (455 mg) with ritonavir 1.2 mL (90 mg) Darunavir 5 mL ³ (490 mg) with ritonavir 1.2 mL (96 mg) , 147V, 150V, 154M, 154L, T74P, L76V, 184V and L89V he specified weight groups were rounded up for suspension dosing convenience to 3.6 mL,	Nervous System Disorders Headache Skin and Subcutaneous Tissue Di Rash N- total number of subjects per treatmer *Excluding laboratory abnormalities repo Less Common Adverse Reactions		2%	3%					↑ lomitapide	Co-administration is contraindicated due to potential fo
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	Darunavir 5 mL ³ (490 mg) with ritonavir 1.2 mL (96 mg) , I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V he specified weight groups were rounded up for suspension dosing convenience to 3.6 mL,	Less Common Adverse Reactions			x /a	was indinavir/ritonavir 800/100 mg twice daily.)				↑ oxycodone	(including potentially fatal respiratory depression) is red
	he specified weight groups were rounded up for suspension dosing convenience to 3.6 mL,			equal to Grade 2) occurring in less	than 2% of antiretroviral treatment-naïve subjects	iopinavii /ritonavii	•	Hence, it is not recommended to co-administer lopinavir/ritonavir		↑ tramadol	A dose decrease may be needed for tramadol with conco
		Gastrointestinal Disorders: acute pancrea	atitis, dyspepsia, flatulence	system:		saquinavir	•	Hence, it is not recommended to co-administer saquinavir and	buprenorphine,		No dose adjustment for buprenorphine or buprenorphi
<form> All of the second of the s</form>		Hepatobiliary Disorders: acute hepatitis (e.g., acute hepatitis, cytolytic hepat					As co-administration with darunavir/ritonavir has not been studied,	ouprenorpnine/naioxone		is required with concurrent administration of darunav Clinical monitoring is recommended if darunavir/rit buprenorphine or buprenorphine/naloxone are co-admini
<form>control<t< td=""><td></td><td>Metabolism and Nutrition Disorders: diab</td><td>etes mellitus</td><td>31101</td><td></td><td>Interactions (7.4)]</td><td>ptor antagonists</td><td></td><td>methadone</td><td>\downarrow methadone</td><td>No adjustment of methadone dosage is required whe co-administration of darunavir/ritonavir. Howeve</td></t<></form>		Metabolism and Nutrition Disorders: diab	etes mellitus	31101		Interactions (7.4)]	ptor antagonists		methadone	\downarrow methadone	No adjustment of methadone dosage is required whe co-administration of darunavir/ritonavir. Howeve
	psules or tablets (100 mg) (100 mg/mL) and ritonavir oral solution (80 mg/mL)	Psychiatric Disorders: abnormal dreams	,	nson Syndrome, urticaria		maraviroc			0-1-11 •		monitoring is recommended as the dose of methad maintenance therapy may need to be adjusted in some p
	600 mg with ritonavir 100 mg Darunavir 6 mL (600 mg) with ritonavir 1.25 mL	<i>Laboratory Abnormalities</i> Selected Grade 2 to 4 laboratory abnorr	malities that represent a worsening		troviral treatment-naïve adult subjects treated with	Alpha 1-adrenoreceptor antagonist:	↑ alfuzosin	Co-administration is contraindicated due to notential for serious		↑ naloxegol	Co-administration of darunavir/ritonavir and naloxegol contraindicated due to notential for precipitating onioi
	675 mg with ritonavir 100 mg Darunavir 6.8 mL ^{tor} (675 mg) with ritonavir 1.25 mL	Table 7: Grade 2 to 4 Laboratory Abn	ormalities Observed in Antiretro			Antibacterial:		and/or life threatening reactions such as hypotension.			
	800 mg with ritonavir 100 mg Darunavir 8 mL° (800 mg) with ritonavir 1.25 mL		Limit					with normal renal function. For co-administration of clarithromycin	e.g. avanafil, sildenafil, tadalafil,	use of sildenafil at doses used	Co-administration with darunavir/ritonavir may res increase in PDE-5 inhibitor-associated adverse events
	rounded up to 6.8 mL for suspension dosing convenience.	Alanine Aminotransferase	> 25 to < 5.0 V 10 M	01/	01/			following dose adjustments should be considered: • For subjects with CLcr of 30 to 60 mL/min, the dose of		dysfunction has been studied	hypotension, syncope, visual disturbances and priapism
		Grade 3	$>$ 5.0 to \leq 10.0 X ULN	3%	3%			clarithromycin should be reduced by 50%. • For subjects with CLcr of <30 mL/min, the dose of			Use of PDE-5 inhibitors for pulmonary arterial hyperte (PAH): Co-administration with sildenafil used for PAH is cont
	llowing table:	Aspartate Aminotransferase	I					אמונוווטוווזעאו אווטווע עפ ופסעכפס by / לא.			due to potential for sildenafil associated adverse react include visual disturbances, hypotension, prolonged en
	· · · ·	Grade 3	$>$ 5.0 to \leq 10.0 X ULN	4%	2%		↑ apixaban	co-administration of apixaban with darunavir/ritonavir depend on the			The following dose adjustments are recommended for
	ritonavir oral solution (80 mg/mL)	Alkaline Phosphatase				rivarovaban	↑ rivarovahan	with P-gp and strong CYP3A inhibitors in apixaban prescribing information.			tadalafil with darunavir/ritonavir: • <u>Co-administration of tadalafil in patients on darun</u> In patients receiving darunavir/ritonavir for at leas
	Darunavir 2 mL (200 mg) with ritonavir 0.4 mL (32 mg)	Grade 3	$>\!5.0$ to $\leq\!10.0$ X ULN	0%	<1%			recommended because it may lead to an increased bleeding risk.			start tadalafil at 20 mg once daily. Increase to 4 daily based upon individual tolerability.
	Darunavir 2.4 mL (240 mg) with ritonavir 0.5 mL (40 mg)	Hyperbilirubinemia						for recommendations regarding co-administration. The specific recommendations are based on indication, renal function, and effect			
	Darunavir 2.8 mL (280 mg) with ritonavir 0.6 mL (48 mg)							dabigatran or edoxaban. Clinical monitoring is recommended when a DOAC not affected by CYP3A4 but transported by P·gp, including			ritonavir. Stop tadalafil at least 24 hours prior darunavir/ritonavir. After at least one week fo
		Grade 4				Dahar A-str	1 yuu	/ritonavir.			initiation of darunavir/ritonavir, resume tadalafi once daily. Increase to 40 mg once daily based upo tolerability.
	· · · ·			3%	10%		•	darunavir/ritonavir. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined			Sildenafil at a single dose not exceeding 25 mg in
	blets, capsules (100 mg/mL) and ritonavir oral solution		8.49 to 13.56 mmol/L 751 to 1200 mg/dL								vardenafil at a single dose not exceeding 2.5 mg dose i or tadalafil at a single dose not exceeding 10 mg dose can be used with increased monitoring for PDE-
	daily with food Dose: twice daily with food		> 13.56 mmol/L	1%	1%			need to be adjusted when initiating co-administration with darunavir/ ritonavir and carbamazepine. Clinical monitoring of carbamazepine			Co-administration of darunavir/ritonavir and avanafil i
				23%	27%	clonazepam	↑ clonazepam	desired clinical response. Clinical monitoring of anticonvulsants that are metabolized by		↑ ticagrelor	Co-administration of darunavir/ritonavir and ticagrelor
	600 mg with Darunavir 6 mL (600 mg) with ritonavir 1.25 mL (100 mg)		> 7.77 mmol/L > 300 mg/dL	1%	5%		↔ darunavir	CYP3A is recommended. Phenytoin and phenobarbital levels should be monitored when co-	clopidogrel		Co-administration of darunavir/ritonavir and clopidogre
	ht group is rounded up to 3.8 mL and 4.6 mL for suspension dosing convenience.	, , , ,	ol 4.13 to 4.90 mmol/L	14%	12%		↓ phenytoin		prasugrel		activity of clopidogrel. No dose adjustment is needed when prasugrel is co-ad
		Grade 3	≥4.91 mmol/L	9%	6%	Selective Serotonin Reuptake			Proton pump inhibitor:		
	hepatic impairment. No data are available regarding the use of darunavir tablets/ritonavir when		6.95 to 13.88 mmol/L	11%	10%			darunavir/ritonavir, dose titrating the SSRI based on a clinical			When omeprazole is co-administered with darunav monitor patients for decreased efficacy of omeprazol
	acology (12.3)].		126 to 250 mg/dL 13.89 to 27.75 mmol/L					for antidepressant response in patients on a stable dose of			increasing the omeprazole dose in patients whose syn not well controlled; avoid use of more than 40 mg omeprazole.
		Grade 4	251 to 500 mg/dL > 27.75 mmol/L	0%	0%					↑ midazolam	Co-administration is contraindicated due to potential
				3%	2%		↑ desipramine	due to potential increased adverse events such as nausea,			and/or life-threatening reactions such as prolonged or sedation or respiratory depression. Triazolam administered midazolam are extensively metabolized by
	Interactions (7.3)]. Due to the need for co-administration of darunavir tablets with ritonavir, please	Grade 3	$>$ 3.0 to \leq 5.0 X ULN	<1%	1%			чиссинезэ, нурисепзии али зупсоре.			administered midazolam are extensively metabolized by administration of triazolam or orally administered mid- darunavir may cause large increases in the concentration
	npairment	Pancreatic Amylase Grade 2	$>$ 1.5 to \leq 2.0 X ULN	5%	2%		↑ trazodone			↑ sedatives/hypnotics	Titration is recommended when co-administering
	warnonnuina				4%	itraconazole, isavuconazole,					lower dose of the sedatives/hypnotics should be consi monitoring for adverse events.
	ក្រមរដ្ឋបាល។៣២	^a Grade 4 data not applicable in Division of	f AIDS grading scale.	tenofovir disoproxil fumarate		אפרטרטוואבטופ, posaconazole	† isavuconazole	co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg with monitoring for			Co-administration of parenteral midazolam should be setting which ensures close clinical monitoring and a
	nary arterial hypertension	The safety assessment is based on al	I safety data from the Phase 3 t			voriconazole	↔ posaconazole				prolonged sedation. Dosage reduction for midazolam considered, especially if more than a single dose of mi
		darunavir/ritonavir 600/100 mg twice da The majority of the ADRs reported durir	 ily arm and in the lopinavir/ritonavir ng treatment with darunavir/ritonav	400/100 mg twice daily arm was 8 rir 600/100 mg twice daily were r	80.7 and 76.4 weeks, respectively. mild in severity. The most common clinical ADRs to			/ritonavir unless an assessment comparing predicted benefit to		↑ fesoterodine	
	ve the desired antiviral effect. Failure to administer darunavir with ritonavir and food may result	rash, abdominal pain and vomiting. 4.7%	of subjects in the darunavir/ritonavi	r arm discontinued treatment due to	o ADRs.	-	↑ colchicine				not exceed a fesoterodine dose of 4 mg once daily. When solifenacin is co-administered with darunavir/rite
margin	mation on precautionary measures.	infected adult subjects are presented in T Table 8: Selected Clinical Adverse I	able 8 and subsequent text below th Drug Reactions to darunavir/rite	ne table. onavir 600/100 mg Twice Dail	y' of at Least Moderate Intensity (\geq Grade 2)			life-threatening reactions.		ant Interactions with Darunavir	
multiplication distribution distributio distribution distribution distribution distribution distribut	therapy with darunavir/ritonavir. Patients with pre-existing liver dysfunction, including chronic		Darunavir/	ritonavir 600/100 mg	lopinavir/ritonavir 400/100 mg			• <u>Treatment of gout-flares -co-administration of colchicine in</u> <u>patients on darunavir/ritonavir :</u> 0.6 mg (1 tablet) × 1 dose,	No dosage adjustments are recommende etravirine, nevirapine, nucleoside reverse t	l when darunavir/ritonavir is co-admir anscriptase inhibitors (abacavir, emtri	
	e been reported. These have generally occurred in patients with advanced HIV-1 disease taking							to be repeated no earlier than 3 days.	8 USE IN SPECIFIC POPULATIONS	,, or represented.	
	ed. Ig therapy with darunavir/ritonavir and patients should be monitored during treatment. Increased	Abdominal distension Abdominal pain		6%	3%			patients on darunavir/ritonavir: If the original regimen was 0.6 mg twice a day, the regimen	<u>Pregnancy Exposure Registry</u> There is a pregnancy exposure registry that		
in contraction Sing Sing<	derlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of vir/ritonavir treatment.	Diarrhea Dyspepsia		2%	1%			If the original regimen was 0.6 mg once a day, the regimen	Risk Summary		
attrait attraitrait attrait attrait <td></td> <td>Vomiting General Disorders and Administra</td> <td>tion Site Conditions</td> <td>5%</td> <td>3%</td> <td></td> <td></td> <td>• Treatment of familial Mediterranean fever -co-administration</td> <td>Available limited data from the APR show n rate for major birth defects of 2.7% in a U.S</td> <td>statistically significant difference in th reference population of the Metropolita</td> <td>e overall risk of major birth defects for darunavir compared v n Atlanta Congenital Defects Program (MACDP/<i>[see Data]</i>.</td>		Vomiting General Disorders and Administra	tion Site Conditions	5%	3%			• Treatment of familial Mediterranean fever -co-administration	Available limited data from the APR show n rate for major birth defects of 2.7% in a U.S	statistically significant difference in th reference population of the Metropolita	e overall risk of major birth defects for darunavir compared v n Atlanta Congenital Defects Program (MACDP/ <i>[see Data]</i> .
tabe	rely (less than 0.1%) reported during the clinical development program. During post-marketing	Fatigue	ire						is 15 to 20%. The background risk of major	irth defects and miscarriage for the indi	cated population is unknown.
grades, regardles, regar	of severe skin reactions develop. These can include but are not limited to severe rash or rash ches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.	Metabolism and Nutrition Disorde Anorexia	11 J				•		were lower (less than 1-fold) than human ex		
Intrastruct draws community in statturet acceptioned subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir compared to subjects receiving reginenes containing darnawir/intoawir + relargavir without a history of subjects sectored and holenees of the containes and reginenes containes receiving reginenes containes dard bar reginenes accepter relations receiving reginenes containes receiving reginenes rec		Nervous System Disorders Headache					↑ lumefantrine	should be used with caution as increased lumefantrine exposure	The recommended dosage in pregnant patie Darunavir 800 mg taken with ritonavir 100	mg once daily should only be considered	in certain pregnant patients who are already on a stable dar
ps. Thesa rashes were mid to moderate in sever mid to moderate in severe mid to moderate in severe mid to moderate in sever mid to moderate in severe mid to moderate in sever mid to moderate	navir/ritonavir. However, rash that was considered drug related occurred at similar rates for all	Rash			3%				darunavir 600 mg with ritonavir 100 mg ma		
r contains a sulfonamide moiety. Darunavir should be used with caution in patients with a known sulfonamide allergy. In clinical studies with frakturn righteen subjects were enrolled in each BIG and DIG treatment-experienced duil, are issued patients. The inclinead studies with or without a history of sulfonamide allergy. In clinical studies with a clone cub BIG and DIG treatment-experienced duil, are issued patients. The inclinead studies with a known sulfonamide allergy. In clinical studies with a subject steree wing here studies with a known sulfonamide allergy. In clinical studies with a known sulfonamide allergy. In clinical studies with a known sulfonamide allergy. In clinical studies with a subject steree wing here studies with a subject steree wing	d not limit therapy; there were no discontinuations due to rash.	^a Excluding laboratory abnormalities repo Less Common Adverse Reactions	rted as ADRs.	-		rifabutin		Dose reduction of rifabutin by at least 75% of the usual dose	<i>Human Data</i> Darunavir/ritonavir (600/100 mg twice dail		
of darunavir/itonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A in initiation of m	n subjects with or without a history of sulfonamide allergy.	subjects receiving darunavir/ritonavir 60	0/100 mg twice daily are listed below		ss than $\angle\%$ of antiretroviral treatment-experienced			150 mg every other day). Increased monitoring for adverse events is warranted in patients receiving this combination and	completed the trial through the postpartum 2 subjects in the QD arm.	period (6 to 12 weeks after delivery) an	d 7 subjects discontinued before trial completion, 5 subjects
Autineouly (1) FURCH Skin and Subcutaneous fisue Disorders: puritus, uricaria of medications that inhibitor induct (YP3A. Skin and Subcutaneous fisue Disorders: puritus, uricaria of medications that inhibitor induct (YP3A. Skin and Subcutaneous fisue Disorders: puritus, uricaria rationeous fisue Disorders: puritus, uricaria Skin and Subcutaneous fisue Disorders: puritus, uricaria rationeous fisue Disorders: puritus, uricaria Skin and Subcutaneous fisue Disorders: puritus, uricaria rationeous fisue Disorders: puritus, uricaria A decrease in the dosage or an adjustement of the dosing interval A decrease in the dosage or an adjustement of the dosing interval Virilogic cutcomes during the third trimester visit, and 61% (11/18) rationeous fisue Disorders: puritus, uricaria Skin and Subcutaneous fisue Disorders: puritus, uricaria Virilogic response was preserved. In the BID arm, the proportion of subjects with HIV-1 RNA <50 copies/mL were 39% (7/18) at baseline, 6	eiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in	Musculoskeletal and Connective Tissue D	<i>Disorders:</i> myalgia			\$ 1.	↓ darunavir	Co-administration of darunavir/ritonavir with rifapentine is not	The pharmacokinetic data demonstrate the postpartum (6 to 12 weeks). Exposure red		
inically significant adverse reactions, potentially leading to severe, life threatening, or fatal events from greater exposures of concomitant medications. inically significant adverse reactions from greater exposures of darunavir/ritonavir. Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with darunavir/ritonavir. Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with darunavir/ritonavir. Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with darunavir/ritonavir. Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with darunavir/ritonavir. Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with darunavir/ritonavir. Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with darunavir/ritonavir. Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with darunavir/ritonavir. Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with darunavir/ritonavir. Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with darunavir/ritonavir. Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretrov	or decrease concentrations of darunavir/ritonavir, respectively.	Skin and Subcutaneous Tissue Disorders: Laboratory Abnormalities	pruritus, urticaria				↑ antineoplastics		Virologic response was preserved. In the Bl		
		Selected Grade 2 to 4 laboratory abnorn		from baseline observed in antiretro	oviral treatment-experienced adult subjects treated			of dasatinib and nilotinib may be necessary for patients. Please refer to the dasatinib and nilotinib prescribing information for	\geq 50 copies/mL for 11% (2/18) of subjec	s and were missing for 5 subjects (1) copies/mL were 61% (11/18) at baselin	subject discontinued prematurely due to virologic failure). .e, 83% (15/18) through the third trimester visit, and 78% (1
oss of therapeutic effect of the concomitant medications from	6 6 8 4 4 contained of the second sec	00 mg with ritesavir 100 mg 1 Darumvir 6 m (100 mg) with ritesavir 1.25 ml 100 mg 1 Darumvir 6.8 mt (175 mg) with ritesavir 1.25 mt 100 mg 1 Darumvir 6 mg 100 mg with ritesavir 1.25 mt 100 mg 1 Darumvir 6 mg 100 mg with ritesavir 1.25 mt 100 mg 1 Darumvir 6 mg 100 mg with ritesavir 1.25 mt 100 mg 1 Darumvir 6 mg 100 mg with ritesavir 1.25 mt 100 mg 1 Darumvir 6 mg 100 mg	te chily mit field min min mit field min min mit field min min min min min min min min min min	are in market from the income of a set of the set of	at may be may						

Baseline Resistance Darumavir tablets with ritonavir tablets (100 mg/mL) with ritonavir oral suspension With no darunavir resistance associated Two 400 mg darunavir tablets with one 100 mg ritonavir 8 mL ³ darunavir oral suspension with	The following adverse reactions are discussed in other sections of labeling: Hepatotoxicity <i>(see Warnings and Precautions (5.2))</i> Severe Skin Reactions <i>(see Warnings and Precautions (5.3))</i> 	There were no Grade 3 or 4 laboratory abnormalities considered as ADRs in 6.2 Postmarketing Experience		ethinyl estradiol, norethindrone,	↓ ethinyl estradiol ↓ norethindrone	Specific Populations (8.3)/. For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia.
substitutions" tablet/capsule, taken once daily with food 1.25 mL ritonavir ral subtin a substitutions" 1.25 mL ritonavir ral solution, taken once daily with food 0.125 mL ritonavir ral substitutions once daily with food	Diabetes Mellitus/Hyperglycemia <i>[see Warnings and Precautions [5.6]]</i> Fat Redistribution <i>[see Warnings and Precautions [5.7]]</i> Immune Reconstitution Syndrome <i>(see Warnings and Precautions (5.8)]</i> Hemophila <i>[see Warnings and Precautions (5.9)]</i>	uncertain size, it is not always possible to reliably estimate their frequency Metabolism and Nutrition Disorders: Redistribution of body fat		drospirenone	 drospirenone: effects unknown 	No data are available to make recommendations on co-administration with other hormonal contraceptives.
associated substitutions", or with no baseline resistance information	 Hemophilia (see warnings and Frecautions (a.SI) Due to the need for co-administration of darunavir with ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions. Clinical Trials Experience 		ed with co-administration with HMG-CoA reductase inhibitors and darunavir/ritonavir) cute generalized exanthematous pustulosis, drug rash with eosinophilia and systemic	Immunosuppressants: e.g. cyclosporine, tacrolimus,	↑ immunosuppressants	Therapeutic concentration monitoring of the immunosuppressive
*V111, V321, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V *An 8 mL darunavir dose should be taken as two 4 mL administrations with the included oral dosing syringe.	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	Renal and Urinary Disorders: Crystal nephropathy, crystalluria 7 DRUG INTERACTIONS		sirolimus		agent is recommended when co-administered with darunavir/ ritonavir.
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	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.		D6, and P-gp. Co-administration of darunavir and ritonavir with drugs that are primarily in increased plasma concentrations of such drugs, which could increase or prolong their	Immunosuppressant/neoplastic: everolimus		Co-administration of everolimus and darunavir/ritonavir is not recommended.
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.		therapeutic effect and adverse events. Darunavir co-administered with ritu plasma concentrations of these active metabolite(s), potentially leading to 7.2 Potential for Other Druos to Affect Darunavir	onavir with drugs that have active metabolite(s) formed by CYP3A may result in reduced loss of their therapeutic effect (see Table 10).	irinotecan		Discontinue darunavir/ritonavir at least 1 week prior to starting irinotecan therapy. Do not administer darunavir/ritonavir with irinotecan unless there are no therapeutic alternatives.
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.		Darunavir and ritonavir are metabolized by CYP3A. <i>In vitro</i> data indicate expected to increase the clearance of darunavir and ritonavir, resulting in lo	e that darunavir may be a P-gp substrate. Drugs that induce CYP3A activity would be owered plasma concentrations of darunavir and ritonavir. Co-administration of darunavir a classrance of darunavir and ritonavir and may result in increased plasma concentrations	Inhaled beta agonist: salmeterol	↑ salmeterol	Co-administration of salmeterol and darunavir/ritonavir is not
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	$\label{eq:constraint} Occurring in \geq 2\% of Antiretroviral Treatment \cdot Na \" vert HIV \cdot 1 \cdot Infected Adult Subjects (Trial TMC114 \cdot C211)$	 and ritonavir and other drugs that inhibit CTP3A, or P-gp may decrease the of darunavir and ritonavir (see Table 10). 7.3 Established and Other Potentially Significant Drug Interaction 	e clearance of darunavir and ritonavir and may result in increased plasma concentrations ns			recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
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.	System organ class, preferred Darunavir/ritonavir 800/100 mg lopinavir/ritonavir 800/200 mg	studies or predicted interactions due to the expected magnitude of inter examples of potentially significant interactions but is not all inclusive <i>(see</i>	s with darunavir/ritonavir. These recommendations are based on either drug interaction action and potential for serious adverse events or loss of efficacy. The table includes <i>Contraindications (4) and Clinical Pharmacology</i> (12.3)], and therefore the label of each	Lipid Modifying Agents: <u>HMG-CoA reductase inhibitors:</u> lovastatin, simvastatin	↑ lovastatin	
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)].	Abdominal pain 6% 6%	and specific actions to be taken with regard to co-administration.	r information related to the route of metabolism, interaction pathways, potential risks, ractions: Alterations in Dose or Regimen May be Recommended Based on Drug	atorvastatin, pravastatin,	↑ simvastatin ↑ simvastatin ↑ HMG-CoA reductase	Co-administration is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis. Co-administration of darunavir/ritonavir with HMG-Co A
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	Diarrhea 9% 16% Nausea 4% 4% Vomiting 2% 4%	Interaction Studies or Predicted Interaction (see Contraindications) for Magnitude of Interaction, Tables 15 and 16]	(4) for a list of examples of contraindicated drugs) [see Clinical Pharmacology (12.3)	rosuvastatin	inhibitors	reductase inhibitors may lead to adverse events such as myopathy. Titrate atorvastatin, pravastatin or rosuvastatin dose carefully and use the lowest necessary dose while monitoring for adverse
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	Fatigue <1% 3%	Concomitant Drug Class Effect on Concentrati Drug Name Examples Drug Name Examples	nt Drug Clinical Comment	Other lipid modifying agents:		events. Do not exceed atorvastatin 20 mg/day.
Darunavir Resistance Associated Substitutions" Formulation: Darunavir oral suspension (100 mg/mL) and	Metabolism and Nutrition Disorders Anorexia 2% <1%	HIV-1-Antiviral Agents: Nucleoside Reverse Transcriptase Inhii didanosine ↔ darunavir ↔ didanosine	bitors (NRTIs) Didanosine should be administered one hour before or two hours after darunavir/ritonavir (which are administered with food).	lomitapide Narcotic analgesics	↑ lomitapide	Co-administration is contraindicated due to potential for markedly increased transaminases.
Body weight (kg) 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 ¹ (350 mg) with ritonavir 0.8 mL (64 mg)	Headache 7% 6% Skin and Subcutaneous Tissue Disorders 6% 7%	HIV-1-Antiviral Agents: HIV-Protease Inhibitors (PIs)	The appropriate dose of indinavir in combination with darunavir/	metabolized by CYP3A: e.g. fentanyl, oxycodone	↑ fentanyl	Careful monitoring of therapeutic effects and adverse reactions
Greater than or equal to 11 kg to less than 12 kg Darunavir 4 mL ¹ (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 ¹ (455 mg) with ritonavir 1 mL (80 mg)	N=SII 078 778 N=total number of subjects per treatment group; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate *Excluding laboratory abnormalities reported as ADRs.	(i he reference regimmen for indinavir was indinavir/ritonavir 800/100 mg twice daily.) lopinavir/ritonavir ⊥ darunavir	ritonavir has not been established. Appropriate doses of the combination have not been established.		↑ oxycodone	associated with CYP3A- metabolized narcotic analgesics (including potentially fatal respiratory depression) is recommended with co-administration.
Greater than or equal to 14 kg to less than 15 kg Darunavir 5 mL [*] (490 mg) with ritonavir 1.2 mL (96 mg) ^a darunavir resistance associated substitutions: V1 11, V321, L33F, 147V, 150V, 154M, 154L, 174P, L76V, 184V and L89V	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:	saquinavir ↓ darunavir	Hence, it is not recommended to co-administer lopinavir/ritonavir and darunavir, with or without ritonavir. Appropriate doses of the combination have not been established.	tramadol Narcotic analgesics/treatment of opioid dependence:	↑ tramadol	A dose decrease may be needed for tramadol with concomitant use.
^a 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. <i>Pediatric Patients Weighing At Least 15 kg</i>	Gastrointestinal Disorders: acute pancreatitis, dyspepsia, flatulence General Disorders and Administration Site Conditions: asthenia	↔ saquinavir	Hence, it is not recommended to co-administer saquinavir and darunavir, with or without ritonavir.	buprenorphine, buprenorphine/naloxone	 ↔ buprenorphine, naloxone ↑ norbuprenorphine 	No dose adjustment for buprenorphine or buprenorphine/naloxone is required with concurrent administration of darunavir/ritonavir.
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'	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	Other HIV protease inhibitors, except atazanavir <i>[see Drug</i> Interactions (7.4)]	As co-administration with darunavir/ritonavir has not been studied, co-administration is not recommended.	methadone	(metabolite) ↓ methadone	Clinical monitoring is recommended if darunavir/ritonavir and buprenorphine or buprenorphine/naloxone are co-administered. No adjustment of methadone dosage is required when initiating
Body weight (kg) Formulation: Darunavir tablet(s) and ritonavir capsules or tablets (100 mg) Formulation: Darunavir oral suspension (80 mg/mL) (80 mg/mL) (80 mg/mL) (80 mg/mL) (100 mg/mL) <t< td=""><td>Musculoskeletal and Connective Tissue Disorders: myalgia, osteonecrosis Psychiatric Disorders: abnormal dreams</td><td>HIV-1-Antiviral Agents: CCR5 co-receptor antagonists maraviroc</td><td>When used in combination with darunavir/ritonavir, the dose of maraviroc should be 150 mg twice daily.</td><td></td><td></td><td>co-administration of darunavir/ritonavir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients.</td></t<>	Musculoskeletal and Connective Tissue Disorders: myalgia, osteonecrosis Psychiatric Disorders: abnormal dreams	HIV-1-Antiviral Agents: CCR5 co-receptor antagonists maraviroc	When used in combination with darunavir/ritonavir, the dose of maraviroc should be 150 mg twice daily.			co-administration of darunavir/ritonavir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients.
Dose: once daily with food Dose: once daily with food Greater than or equal to 15 kg to less Darunavir tablets 600 mg with ritonavir 100 mg Darunavir 6 mL (600 mg) with ritonavir 1.25 mL	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	Other Agents Alpha 1-adrenoreceptor antagonist: alfunction		Opioid Antagonist naloxegol	↑ naloxegol	Co-administration of darunavir/ritonavir and naloxegol is
than 30 kg (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 th (675 mg) with ritonavir 1.25 mL (100 mg)	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' (Trial TMC114-C211)	alfuzosin ↑ alfuzosin Antibacterial:	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as hypotension.	PDE-5 inhibitors:		contraindicated due to potential for precipitating opioid withdrawal symptoms.
Greater than or equal to 40 kg Darunavir tablets 800 mg with ritonavir 100 mg Darunavir 8 mL ² (800 mg) with ritonavir 1.25 mL (100 mg)	Laboratory parameter % Limit Darunavir/ritonavir 800/100 mg once daily + TDF/FTC Iopinavir/ritonavir 800/200 mg per day + TDF/FTC Biochemistry	clarithromycin ↔ darunavir ↑ clarithromycin	No dose adjustment of the combination is required for patients with normal renal function. For co-administration of clarithromycin and darunavir/ritonavir in patients with renal impairment, the	e.g. avanafil, sildenafil, tadalafil, vardenafil	↑ PDE-5 inhibitors (only the use of sildenafil at doses used for treatment of erectile	Co-administration with darunavir/ritonavir may result in an increase in PDE-5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances and priapism.
 ^a darunavir resistance associated substitutions: V111, V321, 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. 	Alanine Aminotransferase Grade 2 > 2.5 to ≤ 5.0 X ULN 9% 9%		following dose adjustments should be considered: • For subjects with CLcr of 30 to 60 mL/min, the dose of clarithromycin should be reduced by 50%.		dysfunction has been studied with darunavir/ritonavir)	Use of PDE-5 inhibitors for pulmonary arterial hypertension
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	Grade 3 > 5.0 to ≤ 10.0 X ULN 3% 3% Grade 4 > 10.0 X ULN <1%		 For subjects with CLcr of < 30 mL/min, the dose of clarithromycin should be reduced by 75%. 			(PAH): Co-administration with sildenafil used for PAH is contraindicated due to potential for sildenafil associated adverse reactions (which
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"	Grade 2 > 2.5 to ≤ 5.0 X ULN 7% 10%	Anticoagulants: <u>Direct Oral Anticoagulants (DOACs)</u> apixaban ↑ apixaban	Due to potentially increased bleeding risk, dosing recommendations for co-administration of anixaban with darunavir/iritonavir depend on the			include visual disturbances, hypotension, prolonged erection, and syncope). The following dose adjustments are recommended for use of
Formulation: Darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL)	Grade 4 > 10.0 X ULN 1% 3% Alkaline Phosphatase		co-administration of apixaban with darunavir/intonavir depend on the apixaban dose. Refer to apixaban dosing instructions for co-administration with P-gp and strong CYP3A inhibitors in apixaban prescribing information.			tadalafil with darunavir/ritonavir: • <u>Co-administration of tadalafil in patients on darunavir/ritonavir:</u>
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)	Grade 2 > 2.5 to ≤ 5.0 X ULN 1% 1% Grade 3 > 5.0 to ≤ 10.0 X ULN 0% <1%	rivaroxaban ↑ rivaroxaban dabigatran etexilate ↑ dabigatran	Co-administration of darunavir/ritonavir and rivaroxaban is not recommended because it may lead to an increased bleeding risk. Refer to the dabigatran etexilate or edoxaban prescribing information			In patients receiving darunavir/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 darunavir/ritonavir in patients on
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)	Grade 4 > 10.0 X ULN 0% 0% Hyperbilirubinemia Grade 2 > 1.5 to ≤ 2.5 X ULN < 1%	dabigatran etexilate ↑ dabigatran edoxaban ↑ edoxaban	for recommendations regarding co-administration. The specific recommendations are based on indication, renal function, and effect of the co-administered P-gp inhibitors on the concentration of			Co-administration of darunavir/ritonavir in patients on tadalafil: Avoid use of tadalafil during the initiation of darunavir/ riterative Star tadalafil during the initiation of darunavir/
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 Weinhing At Least 15 kg	Grade 3 >2.5 to ≤5.0 X ULN <1%		dabigatran or edoxaban. Člinical monitoring is recommended when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate and edoxaban, is co-administered with darunavir			ritonavir. Stop tadalafil at least 24 hours prior to starting darunavir/ritonavir. After at least one week following the initiation of darunavir/ritonavir, resume tadalafil at 20 mg
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	Grade 4 > 5.0 X ULN 0% 0% Triglycerides 0 <t< td=""><td><u>Other Anticoagulants</u> ↓ warfarin warfarin ↔ darunavir</td><td>/ritonavir. Warfarin concentrations are decreased when co-administered with darunavir/ritonavir. It is recommended that the international</td><td></td><td></td><td>once daily. Increase to 40 mg once daily based upon individual tolerability. Use of PDE-5 inhibitors for erectile dysfunction:</td></t<>	<u>Other Anticoagulants</u> ↓ warfarin warfarin ↔ darunavir	/ritonavir. Warfarin concentrations are decreased when co-administered with darunavir/ritonavir. It is recommended that the international			once daily. Increase to 40 mg once daily based upon individual tolerability. Use of PDE-5 inhibitors for erectile dysfunction:
Besistance Associated Substitution* Formulation: Darunavir tablet(s) and ritonavir tablets, capsules Formulation: Darunavir oral suspension Body weight (kg) ritonavir tablets, capsules (100 mg/mL) and ritonavir oral solution	Grade 2 5.65 to 8.48 mmol/L 3% 10% 500 to 750 mg/dL 5% 5%	Anticonvulsants:	oarunavir/intonavir. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with darunavir/intonavir.			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
(100 mg) or oral solution (80 mg/mL) (80 mg/mL) Dose: twice daily with food Dose: twice daily with food	Grade 4 > 13.56 mm//L 1% > 1200 mg/dL 1%	anticonvursants: 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			can be used with increased monitoring for PDE-5 inhibitor- associated adverse events. Co-administration of darunavir/ritonavir and avanafil is not
Greater than or equal to 15 kg to less Darunavir tablets 375 mg with ritonavir Darunavir 3.8 mL (375 mg) ^b with ritonavir 0.6 mL (48 mg) than 30 kg 0.6 mL (48 mg) Darunavir 4.6 mL (450 mg) ^b with ritonavir 0.75 mL (60 mg)	Total Cholesterol Grade 2 6.20 to 7.77 mmol/L 23% 27%		concentrations and its dose titration is recommended to achieve the desired clinical response.	Platelet aggregation inhibitor: ticagrelor	↑ ticagrelor	recommended. Co-administration of darunavir/ritonavir and ticagrelor is not
than 40 kg 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)	240 to 300 mg/dL Grade 3 > 7.77 mmol/L 1% 5% > 300 mg/dL 5% 5% 5%	clonazepam ↑ clonazepam phenobarbital, phenytoin ↔ darunavir	Clinical monitoring of anticonvulsants that are metabolized by CYP3A is recommended. Phenytoin and phenobarbital levels should be monitored when co-	clopidogrel	↓ clopidogrel active metabolite	recommended. Co-administration of darunavir/ritonavir and clopidogrel is not recommended due to potential reduction of the antiplatelet
^a darunavir resistance associated substitutions: V111, V321, L33F, I47V, I50V, I54M, I54L, T74P, L76V, 184V 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.	Low-Density Lipoprotein Cholesterol Grade 2 4.13 to 4.90 mmol/L 14% 12% 160 to 190 mol/L 14% 12%	↓ phenytoin ↓ phenobarbital	administering with darunavir/ritonavir.	prasugrel	\leftrightarrow prasugrel active	activity of clopidogrel. No dose adjustment is needed when prasugrel is co-administered
The use of darunavir tablets/ritonavir in pediatric patients below 3 years of age is not recommended <i>[see Warnings and Precautions (5.10] and Use in Specific Populations (6.4)].</i> 2.6 Not Recommended in Patients with Severe Hepatic Impairment	Grade 3 ≥ 4.91 mmol/L 9% 6% ≥ 191 mg/dL 1 6% 1	Selective Serotonin Reuptake Inhibitors (SSRIs):		Proton pump inhibitor: omeprazole	metabolite	with darunavir/ritonavir.
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 <i>/see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)</i> .		paroxetine, sertraline ↓ paroxetine ↓ sertraline	If either sertraline or paroxetine is initiated in patients receiving darunavir/ritonavir, dose titrating the SSRI based on a clinical assessment of antidepressant response is recommended. Monitor	uneprazue	↓ umenazue ↔ darunavir	When omeprazole is co-administered with darunavir/ritonavir, monitor patients for decreased efficacy of omeprazole. Consider increasing the omeprazole dose in patients whose symptoms are
3 DOSAGE FORMS AND STRENGTHS 400 mg: orange, oval shaped, bevel edged, biconvex, film-coated tablets de-bossed with "H" on one side and "189" on the other side.	Grade 3 13.89 to 27.75 mmol/L 1% <1% 251 to 500 mg/dL 0% 0%		for antidepressant response in patients on a stable dose of sertraline or paroxetine who start treatment with darunavir/ ritonavir.	Sedatives/hypnotics:		not well controlled; avoid use of more than 40 mg per day of omeprazole.
600 mg: orange, oval shaped, biconvex, film-coated tablets de-bossed with "J" on one side and "7" on the other side. CONTRAINDICATIONS Co-administration of darunavir tablets/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma	> 500 mg/dL Pancreatic Lipase	Tricyclic Antidepressants (TCAs): amitriptyline, desipramine, î amitriptyline imipramine, nortriptyline î desipramine	Use a lower dose of the tricyclic antidepressants and trazodone due to potential increased adverse events such as nausea,	orally administered midazolam, triazolam	↑ midazolam ↑ triazolam	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. Triazolam and orally
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.	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	↑ imipramine ↑ nortriptyline	dizziness, hypotension and syncope.			administered midazolam are extensively metabolized by CYP3A. Co- administration of triazolam or orally administered midazolam with darunavir may cause large increases in the concentrations of these
Alpha 1-adrenoreceptor antagonist: alfuzosin Anti-gout: colchicine, in patients with renal and/or hepatic impairment Antimycobacterial: rifampin	Pancreatic Amylase Grade 2 > 1.5 to ≤ 2.0 X ULN 5% 2%	<u>Other:</u> trazodone ↑ trazodone		metabolized by CYP3A e.g. buspirone, diazepam,	↑ sedatives/hypnotics	benzodiazepines. Titration is recommended when co-administering darunavir/ ritonavir with sedatives/hypnotics metabolized by CYP3A and a
 Antipsychotics: lurasidone, pimozide Cardiac Disorders: dronedarone, ivabradine, ranolazine Ergot derivatives, e.g. dihydroergotamine, ergotamine, methylergonovine 	Grade 3 > 2.0 to ≤ 5.0 X ULN 5% 4% Grade 4 > 5.0 X ULN 0% <1%	Antifungals: itraconazole, isavuconazole, ↑ darunavir ketoconazole, posaconazole ↑ itraconazole	Monitor for increased darunavir/ritonavir and/or antifungal adverse events with concomitant use of these antifungals. When	estazolam, zolpidem		lower dose of the sedatives/hypnotics should be considered with monitoring for adverse events.
 Herbal product: St. John's wort (<i>Hypericum perforatum</i>) Hepatitis C direct acting antiviral: elbasvir/grazoprevir Lipid modifying agents: Iomitapide, Iovastatin, simvastatin 	N = total number of subjects per treatment group; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate * Grade 4 data not applicable in Division of AIDS grading scale. <u>Treatment-Experienced Adults: TMC114-C214</u>	↑ isavuconazole ↑ ketoconazole ↔ posaconazole	co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg with monitoring for increased antifungal adverse events.	parenterally administered midazolam		Co-administration of parenteral midazolam should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or reclement endation. Decease activation for priorazoleme chould be
Opioid Antagonist: naloxegol PDE-5 inhibitor: sildenafil when used for treatment of pulmonary arterial hypertension Sedatives/hypnotics: orally administered midazolam, triazolam	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.	voriconazole U voriconazole	Voriconazole is not recommended for patients receiving darunavir /ritonavir unless an assessment comparing predicted benefit to			prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.
5 WARNINGS AND PRECAUTIONS 5.1 Importance of Co-administration with Ritonavir	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.	Anti-gout: colchicine ↑ colchicine	risk ratio justifies the use of voriconazole. Co-administration is contraindicated in patients with renal and/or	Urinary antispasmodics fesoterodine	↑ fesoterodine	When fesoterodine is co-administered with darunavir/ritonavir, do not exceed a fesoterodine dose of 4 mg once daily.
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.	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' of at Least Moderate Intensity (>Grade 2)		hepatic impairment due to potential for serious and/or life-threatening reactions.	solifenacin	↑ solifenacin	When solifenacin is co-administered with darunavir/ritonavir, do not exceed a solifenacin dose of 5 mg once daily.
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	Occurring in ≥ 2% of Antiretroviral Treatment-Experienced HIV-1-Infected Adult Subjects (Trial TMC114-C214) Darunavir/ritonavir 600/100 mg Iopinavir/ritonavir 400/100 mg		For patients without renal or hepatic impairment: Treatment of gout-flares -co-administration of colchicine in patients on darunavir/ritonavir : 0.6 mg (1 tablet) × 1 dose,		ed when darunavir/ritonavir is co-admir transcriptase inhibitors (abacavir, emtri	nistered with the following medications: atazanavir, dolutegravir, efavirenz, icitabine, emtricitabine/tenofovir alafenamide, lamivudine, stavudine, tenofovir
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			 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 	8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy		
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	Abdominal distension 2% <1% Abdominal pain 6% 3%		patients on darunavir/ritonavir: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day.	Pregnancy Exposure Registry		en exposed to darunavir during pregnancy. Healthcare providers are encouraged 58-4263.
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.	Dyspepsia 2% 1%		If the original regimen was $0.6\ \text{mg}$ once a day, the regimen should be adjusted to $0.3\ \text{mg}$ once every other day.	<u>Risk Summary</u> Prospective pregnancy data from the APR a Available limited data from the APR show n		he risk of birth defects or miscarriage. he overall risk of major birth defects for darunavir compared with the background
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	General Disorders and Administration Site Conditions Asthenia 3%		 Treatment of familial Mediterranean fever -co-administration of colchicine in patients on darunavir/ritonavir: maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day). 	rate for major birth defects of 2.7% in a U.S The rate of miscarriage is not reported in th	S. reference population of the Metropolita he APR. The estimated background rate of	an Atlanta Congenital Defects Program (MACDP) <i>(see Data).</i> of miscarriage in clinically recognized pregnancies in the U.S. general population
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	Fatigue 2% 1% Metabolism and Nutrition Disorders 2% 2%	Antimalarial:	The combination of darunavir/ritonavir and artemether/lumefantrine	is 15 to 20%. The background risk of major Studies in animals did not show evidence o were lower (less than 1-fold) than human ex	of developmental toxicity. Exposures (ba	ased on AUC) in rats were 3-fold higher, whereas in mice and rabbits, exposures
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 <i>(see Adverse Reactions (6)</i>). 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	Diabetes mellitus 2% <1% Nervous System Disorders 2% <1%	↓ dihydroartemisinin ↑ lumefantrine	The combination of darinaswirintonavir and artemether/lumetantrine can be used without dose adjustments. However, the combination should be used with caution as increased lumetantrine exposure may increase the risk of QT prolongation.	<u>Clinical Considerations</u> The recommended dosage in pregnant patie Darunavir 800 mg taken with ritonavir 100	÷	navir 100 mg twice daily with food. d in certain pregnant patients who are already on a stable darunavir 800 mg with
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	Skin and Subcutaneous Tissue Disorders 0% Rash 7% 3%	← darunavir Antimycobacterials: rifampin ↓ darunavir	Co-administration is contraindicated due to potential for loss of	ritonavir 100 mg once daily regimen prior to darunavir 600 mg with ritonavir 100 mg ma	o pregnancy, are virologically suppresse	un certain pregnant patients who are aiready on a stable darundavir 300 mg with ed (HIV-1 RNA less than 50 copies per mL), and in whom a change to twice daily <i>[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].</i>
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	w = totan number of subjects per treatment group; usn = optimized background regimen * Excluding laboratory abnormalities reported as ADRs. Less Common Adverse Reactions	rifabutin ↑ darunavir ↑ rifabutin	therapeutic effect and development of resistance. Dose reduction of rifabutin by at least 75% of the usual dose (300 mg once daily) is recommended (i.e., a maximum dose of			ation with a background regimen was evaluated in a clinical trial of 36 pregnant ets were enrolled in each BID and OD treatment arms. Twenty nine subjects
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	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: <i>Gastrointestinal Disorders</i> : acute pancreatitis, flatulence	(The reference regimen for rifabutin was 300 mg once daily.)		completed the trial through the postpartum 2 subjects in the QD arm.	n period (6 to 12 weeks after delivery) an	cts were enrolled in each BID and QD treatment arms. Twenty-nine subjects nd 7 subjects discontinued before trial completion, 5 subjects in the BID arm and
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.	Musculoskeletal and Connective Tissue Disorders: myalgia Psychiatric Disorders: abnormal dreams	rifapentine ↓ darunavir	Turther dose reduction of ritabutin may be necessary. Co-administration of darunavir/ritonavir with rifapentine is not recommended.	postpartum (6 to 12 weeks). Exposure red Pharmacology (12.3)].	luctions during pregnancy were greater	is part of an antiretroviral regimen was lower during pregnancy compared with for the once daily regimen as compared to the twice daily regimen <i>/see Clinical</i>
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.	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	Antineoplastics: dasatinib, nilotinib \uparrow antineoplastics	A decrease in the dosage or an adjustment of the dosing interval of dasatinib and nilotinib may be necessary for patients. Please	the third trimester visit, and 61% (11/18) \geq 50 copies/mL for 11% (2/18) of subjec) through the 6 to 12 week postpartum cts and were missing for 5 subjects (1	HIV-1 RNA $<$ 50 copies/mL were 39% (7/18) at baseline, 61% (11/18) through m visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA subject discontinued prematurely due to virologic failure). In the QD arm, the
Clinically significant adverse reactions, proteinant learning to server, me timearening, or read events from greater exposures of concommant medications. Clinically significant adverse reactions from greater exposures of darunavir/ittonavir. Loss of therapeutic effect of darunavir/irtionavir and possible development of resistance from lower exposures of darunavir/ritonavir.	with darunavir/ritonavir 600/100 mg twice daily are presented in Table 9.		refer to the dasatinib and nilotinib prescribing information for dosing instructions.	proportion of subjects with HIV-1 RNA $<$ 5	50 copies/mL were 61% (11/18) at baselin comes during the third trimester visit sho	Res 83% (15/18) through the third trimester visit, and 78% (14/18) through the 6 wed HIV-1 RNA \geq 50 copies/mL for none of the subjects and were missing for 3
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Darunavir/ritonavir was well tolerated during pregnancy and postpartum. There were no new clinically relevant safety findings compared with the known safety profile of daruna onavir 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 to 15 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 r

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) erious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving darunavir /see Use in Specific Populations (8.4)].

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 subscription and 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 ontraception

Use of darunavir may reduce the efficacy of combined hormonal contraceptives and the progestin only pill. Advise patients to use an effective alternative (nonhormonal) 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

avir is not recommended in nediatric nationts below 3 years of ane 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

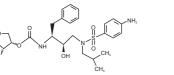
Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-infected subjects with moderate renal impairment (CrCL between 30 to 60 mL/min, n – 20). No pharmacokinetic data are available in HIV-1-infected patients with severe renal impairment 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 $Darunavir, has the following chemical name: \cite{15,2R-3-[[(4-Amino-phenyl)sulfonyl](2-methylpropylamino]-2-hydroxy-1-(phenylmethyl)propyl]}{Control of the second seco$ carbamicacid(3R,3aS,6aR)hexahydrofuro[2,3-b]-furan-3-yl ester. Its molecular formula is C₂₂H₂₂N₂₀S and its molecular weight is 547.66. Darunavir has the following structural formula:



Darunavir is an off-white to pale brow

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

MR (90% CI) AUC, To 0.69 (0.61: 0.7 0.68 (0.59: 0.78) 0.70 (0.57: 0.85) Cmin, Tot **⊢**₽**−**−i 0.50 (0.35: 0.72) 0.79 (0.70: 0.90) H÷-E AUC, Unb Hè-D 0.82 (0.73: 0.91) 0.88 (0.70: 1.11) H-+++ Cmin, Unbo

Legend: 90% CI: 90% confidence interval; GMR: geometric mean ratio. Solid vertical line: ratio of 1.0; dotted vertical lines: reference lines of 0.8 and 1.25.

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, CYP2D6, and P-gp. Co-administration of darunavir and ritonavir with drugs primarily metabolized by CYP3A and CYP2D6, or are transported by P-gp, may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events

expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma conjent rations of darunavir and ritonavir. Co-administration of darunavi and ritonavir and other drugs that inhibit CYP3A or P-gp 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 pharmacokineti interactions. The effects of co-administration of darunavir on the AUC, C_{ema} and C_{em} values are summarized in Table 15 (effect of other drugs on darunavir) and Table 16 (effect of drunavir on other drugs). For information regarding clinical recommendations, *see Drug Interactions (7)*.

Table 15: Drug Interactions: Pl

Co-administered		chedule		РК		CI) of <u>darunavir</u> Pharma co-administered drug n	
drug	Co-administered Drug	Darunavir/ ritonavir	N	РК	Cmax	AUC	Cmin
Co to administration	with other HIV proteas	e inhibitors			LI		
Atazanavir	300 mg q.d.°	400/100 mg b.i.d. ^b	13	\leftrightarrow	1.02 (0.96 to 1.09)	1.03 (0.94 to 1.12)	1.01 (0.88 to 1.16
Indinavir	800 mg b.i.d.	400/100 mg b.i.d.	9	Î	1.11 (0.98 to1.26)	1.24 (1.09 to 1.42)	1.44 (1.13 to 1.82
Lopinavir/ritonavir	400/100 mg b.i.d.	1200/100 mg b.i.d. ^c	14	Ļ	0.79 (0.67 to 0.92)	0.62 (0.53 to 0.73)	0.49 (0.39 to 0.63
	533/133.3 mg b.i.d.	1200 mg b.i.d. ^c	15	Ļ	0.79 (0.64 to 0.97)	0.59 (0.50 to 0.70)	0.45 (0.38 to 0.52
Saquinavir hard gel capsule	1000 mg b.i.d.	400/100 mg b.i.d.	14	Ļ	0.83 (0.75 to 0.92)	0.74 (0.63 to 0.86)	0.58 (0.47 to 0.72
Co to administration	with other HIV antiret						
Didanosine	400 mg q.d.	600/100 mg b.i.d.	17	\leftrightarrow	0.93 (0.86 to 1.00)	1.01 (0.95 to 1.07)	1.07 (0.95 to 1.21
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	\downarrow	0.85 (0.72 to 1.00)	0.87 (0.75 to 1.01)	0.69 (0.54 to 0.8)
Etravirine	200 mg b.i.d.	600/100 mg b.i.d.	15	\leftrightarrow	1.11 (1.01 to 1.22)	1.15 (1.05 to 1.26)	1.02 (0.90 to 1.17
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	î	1.40 ^d (1.14 to 1.73)	1.24 ^d (0.97 to 1.57)	1.02 ^d (0.79 to 1.32
Rilpivirine	150 mg q.d.	800/100 mg q.d.	15	\leftrightarrow	0.90 (0.81 to 1.00)	0.89 (0.81 to 0.99)	0.89 (0.68 to 1.16
Tenofovir disoproxil fumarate	300 mg q.d.	300/100 mg b.i.d.	12	î	1.16 (0.94 to 1.42)	1.21 (0.95 to 1.54)	1.24 (0.90 to 1.69
Co to administration	with other drugs						
Artemether/ lumefantrine	80/480 mg (6 doses at 0, 8, 24, 36, 48, and 60 hours)	600/100 mg b.i.d.	14	¢	1.00 (0.93 to 1.07)	0.96 (0.90 to 1.03)	0.87 (0.77 to 0.98
Carbamazepine	200 mg b.i.d.	600/100 mg b.i.d.	16	\leftrightarrow	1.04 (0.93 to 1.16)	0.99 (0.90 to 1.08)	0.85 (0.73 to 1.00
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	\leftrightarrow	0.83 (0.72 to 0.96)	0.87 (0.75 to 1.01)	1.01 (0.81 to 1.26
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	14	î	1.21 (1.04 to 1.40)	1.42 (1.23 to 1.65)	1.73 (1.39 to 2.14
Omeprazole	20 mg q.d.	400/100 mg b.i.d.	16	\leftrightarrow	1.02 (0.95 to 1.09)	1.04 (0.96 to 1.13)	1.08 (0.93 to 1.25
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	\leftrightarrow	0.97 (0.92 to 1.02)	1.02 (0.95 to 1.10)	1.07 (0.96 to 1.19
Pitavastatin	4 mg q.d.	800/100 mg q.d.	27	\leftrightarrow	1.06 (1.00 to 1.12)	1.03 (0.95 to 1.12)	NA
Ranitidine	150 mg b.i.d.	400/100 mg b.i.d.	16	\leftrightarrow	0.96 (0.89 to 1.05)	0.95 (0.90 to 1.01)	0.94 (0.90 to 0.99
Rifabutin	150 mg q.o.d.°	600/100 mg b.i.d.	11	î	1.42 (1.21 to 1.67)	1.57 (1.28 to 1.93)	1.75 (1.28 to 2.3)
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	\leftrightarrow	1.01 (0.89 to 1.14)	0.98 (0.84 to 1.14)	0.94 (0.76 to 1.16

The pharmacokinetic parameters of darunavir in this study were compared with the pharmacokinetic parameters following administration of dar 600/100 mg twice daily.

°q.o.d. = every other day

Table 16: Drug Interact	ions: Pharmacokinetic P	arameters for <u>Co-Adn</u>	ninistered Dr	u <u>gs</u> in the	Presence of Darunav	ir/ritonavir	
	Dose/S	chedule			pharmacokinetic p	o (90% CI) of <u>co-adı</u> arameters with/wi no effect =1.00	
Co-administered drug	Co-administered drug	Darunavir/ ritonavir	N	РК	Cmax	AUC	Cim
Co-administration wit	h other HIV protease inhib	nitors					
Atazanavir	300 mg q.d.ª /100 mg ritonavir q.d. when administered alone	400/100 mg b.i.d. ⁵	13	↔	0.89 (0.78 to 1.01)	1.08 (0.94 to 1.24)	1.52 (0.99 to 2.34)
	300 mg q.d. when administered with						

9

14

15

17

12

15

15

15

15

17

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 Genetypic and/or phenotypic analysis of baseline virus may aid in determining darunavir susceptibility before initiation of darunavir/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 trials (Trials TMC114-C213, TMC114-C202, and TMC114-C215) (n = 439). The findings were confirmed with additional genotypic and phenotypic data control arms of etravirine trials TMC125-C206 and TMC125-C216 at Week 24 (n = 591).

Diminished virolonic resonness were observed in subjects with 5 or more baseline IAS-defined orimary 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 17).

substitution and/or resistance to emtricitabine, which was included in the fixed background regimen, was identified in 4 virologic failures from the

Cross-resistance among PIs has been observed. Darunavir has a less than 10-fold decreased susceptibility in cell culture against 90% of 3309 clinical isolates

resistant to amorenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to these PIs remain

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 EC₁₀₀ values less than 3 for tipranavir, indicative of limited cross-

resistance between darunavir and tipranavir. In trials TMC 114-C213, TMC 114-C202, and TMC 114-C215, 34% (64/187) of subjects in the darunavir/ritonavir arm

whose baseline isolates had decreased susceptibility to tipranavir (tipranavir fold change greater than 3) achieved tes than 50 copies/mL serum HL-1RNA levels at Week 96. Of the viruses isolated from subjects experiencing virologic failure on darunavir/ritonavir 600/100 mg twice daily (greater than 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,

In trial 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

Table 17: Response to darunavir/ritonavir 600/100 mg Twice Daily by Baseline Number of IAS-Defined Primary PI Resistance-Associated Substitutions: As-treated Analysis of Trials TMC114-C213, TMC114-C202, and TMC114-C215

IAS-defined primary PI substitutions Proportion of subjects with < 50 copies/mL at Week 96

		N=439			
	Overall	de novo ENF	Re-used/No ENF		
All	44% (192/439)	54% (61/112)	40% (131/327)		
0 to 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)		

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

seline of two or more of the substitutions V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V was associated with a decr onavir. In subjects not taking enfuvirtide de novo, the proportion of subjects achieving viral load less than 50 plasma HIV-1 RNA eks was 59%, 29%, and 12% when the baseline genotype had 0 to 1, 2 and greater than or equal to 3 of these substitutions, respectively. phenotype (shift in susceptibility relative to reference) was shown to be a predictive factor of virologic outcome. Response rates assessed by henotype are shown in Table 18. These baseline phenotype groups are based on the select brinning outputations in the trials TMC114-C213, TMC114-C215, and are not meant to represent definitive clinical susceptibility breakpoints for darunavir/ritonavir. The data are provided to

nation on the likelihood of virologic success based on pre-treatment susceptibility to darunavir

se (HIV-1 RNA < 50 copies/mL at Week 96) to darunavir/ritonavir 600/100 mg Twice Daily by Baseline Darunavir Phenotype and by :: As-treated Analysis of Trials TMC114-C213, TMC114-C202, and TMC114-C215

Daseinie Driv pileliotype	Floportion of subjects with < 50 copies/inc at week 50							
	N=417							
	AII	<i>de novo</i> ENF	Re-used/No ENF					
Overall	175/417 (42%)	61/112 (54%)	131/327 (40%)					
0 to 7	148/270 (55%)	44/65 (68%)	104/205 (51%)					
>7 to 20	16/53 (30%)	7/17 (41%)	9/36 (25%)					
> 20	11/94 (12%)	6/23 (26%)	5/71 (7%)					

CAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

itonavir arm and 7 virologic failures in the lopinav

Cross-resistance

susceptible to darunavi

atazanavir, indinavir, lopinavir or nelfinavir)

Carcinogenesis and Mutagenesis

c potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1000 mg/kg were Darunavir was evaluated for carcine administered to mice and doses of 50, 150 and 500 mg/kg was 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 thryroid 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.

14 CLINICAL STUDIES

14.1 Description of Adult Clinical Trials

The evidence of efficacy of darunavir/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 2 trials, TMC114-C213 and TMC114-C202 in antiretroviral treatment-experienced HIV-1-infected adult subjects

14.2 Treatment-Naïve Adult Subjects TMC114-C211

TMC114-C211 is a randomized controlled open-label Phase 3 trial comparing darupavir/ritopavir/R00/100 mg opce daily versus lopinavir/ritopavir/R00/200 mg opc Any (given as a twice daily or as a once daily regimen) in antiretroviral treatment-nive 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 greater than or equal to 5000 copies/mL. Randomization was stratified by screening plasma viral load (HIV-1 RNA less than 100,000 copies/mL or greater than or equal to 100,000 copies/mL) and screening CD4+ cell count (less than 200 cells/mn or greater than or equal to 200 cells/mm³). Virologic response was defined as a confirmed plasma HIV-1 RNA viral load less than 50 copies/mL. Analyses included 689 subjects in trial TMC114-C211 who had completed 192 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the darunavir/ritonavir arm and the lopinavi navir arm (see Table 19). Table 19 compares the demographic and baseline characteristics between subjects in the darunavir/ritonavir 800/100 mg once daily arm and subjects in the lopinavir/ritonavir 800/200 mg per day arm in trial TMC114-C211.

load of at least 1 log₁₀ versus bas In the pooled analysis for TMC114-C213 and TMC114-C202, demographics and baseline characteristics were balanced between the darunavir/ritonavir arm and the comparator PI arm (see Table 25). Table 25 compares the demographic and baseline characteristics between subjects in the darunavir/ritonavir 600/100 mg twice daily arm and subjects in the comparator PI arm in the pooled analysis of trials TMC114-C213 and TMC114-C202. Table 25: Demographic and Baseline Characteristics of Subjects in the Trials TMC114-C213 and TMC114-C202 (Pooled Analysis 600/100 mg twice daily + OBR N=124 + 0BFN = 131Demographic characteristics 43 (27 to 73) 44 (25 to 65) Median age (years) (range, years) 88% 89% 11% 12% 81% Baseline characteristic Mean baseline plasma HIV-1 RNA (log10 copies/mL 4.49 fedian baseline CD4+ cell count (cells/mm³) (range, cells/mn 53 (3 to 77 63 (3 to 1274) Percentage of patients with baseline viral load > 100,000 copies/mL rcentage of patients with baseline CD4+ cell count < 200 cells/mn Median darunavir fold change ledian number of resistance-associa PI mutations NNRTI mutations NRTI mutations entage of subjects with number of baseline primary proteas hibitor mutations*: 22% 21% Median number of ARVs previously used^b: Pls (excluding low-dose ritonavi Percentage of subjects resistant[®] to all available[®] PIs at baseline, excluding tipranavir and darunavir 61% centage of subjects with prior use of enfu OBR = optimized background regimen * 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 to 130 ^b Based on phenotype (Antivirogram[®]). ^c Commercially available PIs at the time of trial enrollment

^dCommercially available PIs at the time of trial enrollment.

/irologic success HIV·1 RNA <50 copies/mL

ued trial due to adverse event or death

N = total number of subjects with data; OBR = optimized background regime

ce daily arm and 93 cells/mm³ in the lopinavir/ritonavir 400/100 mg twice daily arr

No virologic data at Week 96 window^b

Discontinued trial for other reasons^d

Missing data during window^b but on trial

change in their OBR that was not permitted by the protocol.

Virologic failure

Reasons

Window 90 to 102 Weeks.

600/100 mg twice daily.

Male

Female

White

Black

NRTIs

NNRTIs

treatment during the specified window.

TMC114-C213 and TMC114-C202

Week 96 outcomes for subjects on darunavir/ritonavir 600/100 mg twice daily from trial TMC114-C214 are shown in Table 24

 $^{\circ}$ Other includes; withdrew consent. loss to follow-up, etc., if the viral load at the time of discontinuation was < 50 copies/mL

Table 24: Virologic Outcome of Randomized Treatment of Trial TMC114-C214 at 96 Weeks

Week 96 outcomes for subjects on the recommended dose darunavir/ritonavir 600/100 mg twice daily from the pooled trials TMC114-C213 and TMC114-C202 are shown in Table 26.

Table 26: Outcomes of Randomized Treatment Through Week 96 of the Trials TMC114-C213 and TMC114-C202 (Pooled Analysis)

TMC114-C213 and TMC114-C202 Comparator PI(s 600/100 mg twice daily +OBR N = 124

r/ritonavir 600/100 mg

twice daily + OBR

N=298

26%

8%

Includes patients who discontinued prior to Week 96 for lack or loss of efficacy and patients who are \geq 50 copies in the 96 week window and patients who had a

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

In trial TMC114-C214 at 96 weeks of treatment, the median increase from baseline in CD4 + cell counts was 81 cells/mm³ in the darunavir/ritonavir 600/100 mg

partially-blinded, dose-finding part and a second long-term part in which all subjects randomized to darunavir/ritonavir received the recommended dose of

HIV-1-infected subjects who were elinible for these trials had plasma HIV-1 RNA preater than 1000 conjes/ml had prior treatment with PI(s) NNRTI(s) and NRT1(s), had teast one primary Pl mutation (030), M4B(L, 648V, 160U/V, W82A(F)C), 148V, 190M) at screening, and were on a stable Pl-containing regimen at screening for at least 8 weeks. Randomization was stratified by the number of Pl mutations, screening viral load, and the use of enfuvirtide.

The virologic response rate was evaluated in subjects receiving darunavir/ritonavir plus an OBR versus a control group receiving an investigator-selected Pl(s)

regimen plus an OBR. Prior to randomization, P(Is) 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

14-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

opinavir/ritonavir 400/100 mg

twice daily + OBR

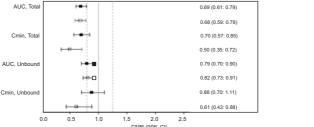
N = 297

52%

33%

7%

< 1%



Darunavir and ritonavir are metabolized by CYP3A. In vitro data indicate that darunavir may be a P-op substrate. Druos that induce CYP3A activity would be

Several interaction studies have l

applicable to the recommended do

frugs). For informa	tion regarding clinical rea	comm	endat	ions, <i>see Drug Interacti</i>	ons (7).		
	vith a dose other than th inistered drug and/or dar			nded dose of the co-adn	ninistered drug or darunav	ir; however, the results are	
harmacokinetic	Parameters for <u>Darun</u> a	<u>avir</u> iı	n the l	Presence of Co-Admir	nistered Drugs		
	Schedule				acokinetic parameters 10 effect =1.00		
dministered Drug	Darunavir/ ritonavir	N	PK	Cmax	AUC	Ci	ENF = enfuvirtide IAS Primary PI Substi
other HIV protea	se inhibitors						The presence at base
300 mg q.d.°	400/100 mg b.i.d. ^b	13	\leftrightarrow	1.02 (0.96 to 1.09)	1.03 (0.94 to 1.12)	1.01 (0.88 to 1.16)	virologic response to
800 mg b.i.d.	400/100 mg b.i.d.	9	î	1.11 (0.98 to1.26)	1.24 (1.09 to 1.42)	1.44 (1.13 to 1.82)	copies/mL at 96 week Baseline darunavir ph
10/100 mg b.i.d.	1200/100 mg b.i.d. ^c	14	Ļ	0.79 (0.67 to 0.92)	0.62 (0.53 to 0.73)	0.49 (0.39 to 0.63)	baseline darunavir ph
/133.3 mg b.i.d.	1200 mg b.i.d. ^c	15	Ļ	0.79 (0.64 to 0.97)	0.59 (0.50 to 0.70)	0.45 (0.38 to 0.52)	TMC114-C202, and give clinicians informa
1000 mg b.i.d.	400/100 mg b.i.d.	14	Ļ	0.83 (0.75 to 0.92)	0.74 (0.63 to 0.86)	0.58 (0.47 to 0.72)	Table 18: Response Use of Enfuvirtide: /
other HIV antiret							Baseline DRV ph
400 mg q.d.	600/100 mg b.i.d.	17	\leftrightarrow	0.93 (0.86 to 1.00)	1.01 (0.95 to 1.07)	1.07 (0.95 to 1.21)	Baseline DKV ph
600 mg q.d.	300/100 mg b.i.d.	12	Ļ	0.85 (0.72 to 1.00)	0.87 (0.75 to 1.01)	0.69 (0.54 to 0.87)	
200 mg b.i.d.	600/100 mg b.i.d.	15	\leftrightarrow	1.11 (1.01 to 1.22)	1.15 (1.05 to 1.26)	1.02 (0.90 to 1.17)	Overall
200 mg b.i.d.	400/100 mg b.i.d.	8	Î	1.40 ^d (1.14 to 1.73)	1.24 ^d (0.97 to 1.57)	1.02 ^d (0.79 to 1.32)	0 to 7
150 mg q.d.	800/100 mg q.d.	15	\leftrightarrow	0.90 (0.81 to 1.00)	0.89 (0.81 to 0.99)	0.89 (0.68 to 1.16)	>7 to 20
300 mg q.d.	300/100 mg b.i.d.	12	î	1.16 (0.94 to 1.42)	1.21 (0.95 to 1.54)	1.24 (0.90 to 1.69)	>20
other druas	I	L	I				ENF = enfuvirtide
80/480 mg	600/100 mg b.i.d.	14	\leftrightarrow	1.00 (0.93 to 1.07)	0.96 (0.90 to 1.03)	0.87 (0.77 to 0.98)	13 NONCLINICA
loses at 0, 8, 24,	ľ						13.1 Carcinogenes

1.23

(1.06 to 1.42)

(0.86 to 1.37)

1 09

0.96 to 1.24)

0.94 (0.76 to 1.17)

0.91

0.75 to 1.10

0.78 (0.72 to 0.85)

(0.69 to 0.81)

1.21

0.63

1.08 to 1.36)

1.27 (1.12 to 1.44)

2.30 (1.98 to 2.67)

1.10 to 1.35)

(2.57 to 3.74)

(0.76 to 0.97)

0.91 (0.78 to 1.06)

(0.96 to 1.30)

(0.69 to 1.02)

(0.74 to 0.91)

2.46 to 3.08)

2.75

0.89°

(0.78 to 1.02)

1 22

1.08 (0.95 to 1.22)

0.98 (0.78 to 1.22)

1 1 1

(0.96 to 1.30)

0.94 (0.78 to 1.13)

0.84

(0.59 to 1.20)

0.89 (0.83 to 0.97)

0.88

(0.78 to 1.00)

1.15

(0.97 to 1.35)

0.68

(0.57 to 0.82)

1.18 (1.02 to 1.37)

(1.56 to 2.06)

(1.08 to 1.42)

(1.46 to 3.59)

(1.20 to 2.60)

(0.48 to 0.67)

(0.68 to 1.05)

1.06 (0.82 to 1.39)

(0.61 to 1.11)

(0.66 to 1.01)

(1.49 to 1.83)

(0.79 to 1.08)

1.36

0.92°

1 24

2.25

(1.63 to 3.10)

1.23

(0.90 to 1.69)

1 13

(0.90 to 1.42)

0.82 (0.52 to 1.30)

0.62⁴

(0.56 to 0.69)

(0.52 to 0.76)

1.17

0.51

(0.54 to 0.73) (0.44 to 0.61)

(2.94 to 5.59) (6.35 to 10.1)

(1.01 to 1.36)

(1.20 to 1.82)

(2.39 to 3.24)

1.37

(1.19 to 1.57)

(4.51 to 6.15)

(1.37 to 2.40)

(0.90 to 1.05)

(0.82 to 1.22)

2.26

(1.92 to 2.67)

0.98°

(0.82 to 1.16)

1.71

All dosages for darunavir 12 CLINICAL PHARI 12.1 Mechanism of Ac Darunavir is an HIV-1 anti 12.2 Pharmacodynam	are expressed in terms of		vir	dioxide.				300 mg q.d. when administered with		L
)arunavir is an HIV-1 anti	MACOLOGY		vii.				Indinavir	darunavir/ritonavir 800 mg b.i.d. /100 mg	400/100 mg b.i.d.	╀
2.2 Pharmacodynam		gy (12.4)].						ritonavir b.i.d. when administered alone		
Cardiac Electrophysiology		-						800 mg b.i.d. when administered with		
	dy in 40 healthy subjects,	darunavir/ritonavir dos	es of 1.33 times the	e maximum recommer	nded dose did	not affect the QT/QTc interval.	Lopinavir/ritonavir	darunavir/ritonavir 400/100 mg b.i.d.°	1200/100 mg b.i.d.	╞
Pharmacokinetics in Adul General								533/133.3 mg b.i.d.°	1200 mg b.i.d.	
300 mg was given orally	in combination with 10	0 mg ritonavir twice da	aily, there was an a	approximate 14-fold	increase in th	vir. When a single dose of darunavir le systemic exposure of darunavir.	Saquinavir hard gel capsule	1000 mg b.i.d. /100 mg ritonavir b.i.d. when	400/100 mg b.i.d.	Ī
	ıld only be used in combin f darunavir, co-administe	-				t volunteers and in HIV-1-infected		administered alone		
subjects. Table 11 displa	ys the population pharma	cokinetic estimates of	darunavir after oral	administration of da	runavir/ritona	wir 600/100 mg twice daily (based ata) from trials TMC114-C202 and		1000 mg b.i.d. when administered with darunavir/ritonavir		
	navir/ritonavir 800/100 r					and 280 patients in trial TMC114-		ith other HIV antiretrovirals		L T
Table 11: Population	Pharmacokinetic Estin					(Trial TMC114·C211, 48·Week 4·C214, 48·Week Analysis, Trial	Didanosine	400 mg q.d.	600/100 mg b.i.d.	
TMC114-C229, 48-Wee	ek Analysis and Integra	ted Data from Trials 1	ek Analysis)	Dolutegravir Dolutegravir	30 mg q.d	600/100 mg b.i.d.				
	Darunavir/ritonavir 800/100 mg once daily 600/100 mg twice daily							50 mg q.d.	600/100 mg b.i.d. with 200 mg b.i.d. etravirine	
Parameter	TMC114-C211 N=335	TMC114-C229 N=280	TMC114-C2 N=285		14-C229 =278	TMC114-C213 + TMC114-C202 (integrated data) N=119	Efavirenz	600 mg q.d.	300/100 mg b.i.d.	t
AUC24h (ng.h/mL) ^a	00000 07050	00004 00000	440300 000	504 444000	00001	data) N=119	Etravirine	100 mg b.i.d.	600/100 mg b.i.d.	ł
Mean ± Standard Deviation	93026 ± 27050	93334 ± 28626	116796 ± 33		± 32681	124698 ± 32286	Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	ł
Median (Range)	87854 (45000 to 219240)	87788 (45456 to 236920)	111632 (64874 to 359		9401 to 323820)	123336 (67714 to 212980)	Rilpivirine	150 mg q.d.	800/100 mg q.d.	ł
Coh (ng/mL) Mean ± Standard	2282 ± 1168	2160 ± 1201	3490 ± 140	3386	± 1372	3578 ± 1151	Tenofovir disoproxil	300 mg q.d.	300/100 mg b.i.d.	ł
Deviation Median	2041	1896	3307		197	3539	fumarate Maraviroc	150 mg b.i.d.	600/100 mg b.i.d.	t
(Range) V = number of subjects wi	(368 to 7242) ith data	(184 to 7881)	(1517 to 13	198) (250	to 11865)	(1255 to 7368)			600/100 mg b.i.d.	ł
AUC _{24h} is calculated as A	UC _{12h} *2.								with 200 mg b.i.d. etravirine	
	ed with 100 mg ritonavir i					nately 2.5 to 4 hours. The absolute	Co-administration wi Atorvastatin	ith other drugs 40 mg q.d. when	300/100 mg b.i.d.	Т
	igle 600 mg dose of darui vir/ritonavir is an inhibitor			n 100 mg ritonavir tw	ice daily was	37% and 82%, respectively. <i>In vivo</i>		administered alone 10 mg q.d. when		
<u>Effects of Food on Oral Ab</u> When darunavir tablets v		ood, the C _{ma} and AUC o	of darunavir, co-adm	ninistered with ritona	avir, is approx	imately 40% higher relative to the		administered with darunavir/ritonavir		
	range of meals studied,					s evaluated ranged from 240 Kcal	Artemether	80 mg single dose	600/100 mg b.i.d.	t
Distribution	ly 95% bound to plasma p	rotaine Darunavir hind	e primarily to places	alpha 1 acid diveon	rotoin (AAC)		Dihydroartemisinin	single uuse		ŀ
Metabolism							Artemether	artemether/lumefantrin	600/100 mg b.i.d.	ł
CYP enzymes, primarily l	by CYP3A. A mass bala	nce study in healthy v	olunteers showed t	hat after a single do	ose administra	inavir is extensively metabolized by ation of 400 mg ¹⁴ C-darunavir, co-	Dihydroartemisinin	e 80/480 mg (6 doses at 0, 8, 24,		┝
	g ritonavir, the majority (howed activity that was a					netabolites of darunavir have been	Lumefantrine	36, 48, and 60 hours)		ŀ
<i>Elimination</i> A mass balance study in	n healthy volunteers sho	wed that after single	dose administration	n of 400 mg ¹⁴ C-dar	unavir, co•ad	ministered with 100 mg ritonavir,	Buprenorphine/	8/2 mg to 16/4 mg q.d.	600/100 mg b.i.d.	Ļ
approximately 79.5% and	d 13.9% of the administe	red dose of ¹⁴ C-darunav	ir was recovered in t	the feces and urine, r	espectively. l	Inchanged darunavir accounted for unavir was approximately 15 hours	Naloxone	6/2 mg tu 16/4 mg q.u.	000/100 mg b.i.a.	
	th ritonavir. After intrave					ministered with 100 mg twice daily	Norbuprenorphine			
Special Populations Hepatic Impairment	,,-						Carbamazepine	200 mg b.i.d.	600/100 mg b.i.d.	L
Jarunavir is primarily me						multiple dose co-administration of	Carbamazepine			L
Darunavir is primarily metabolized by the liver. The steady-state pharmacokinetic parameters of darunavir ser 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 B, n – 8). The effect of severe hepatic impairment normal hepatric mayairment (Child-Pugh Class B, n – 8). The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been evaluated/ <i>see Dosage</i>							ehoxine			
nepatic impairment (Child	J Administration (2.6) and Use in Specific Populations (8.6)]. Dabigatran etexilate 150 mg 800/100 mg							500 mg b.i.d.	400/100 mg b.i.d.	
nepatic impairment (Child and Administration (2.6) a Hepatitis B or Hepatitis C	and Use in Specific Popula Virus Co-infection	tions (8.6)].	tic impairment on th	e pharmacokinetics	of darunavir h	as not been evaluated <i>(see Dosage</i>	Clarithromycin		400/100 mg b.i.d. 800/100 mg single dose	
nepatic impairment (Child And Administration (2.6) a Supatitis B or Hepatitis C The 48-week analysis of 1	and Use in Specific Popula Virus Co-infection	<i>tions (8.6)]</i> . IC114-C211 and TMC1	tic impairment on th	e pharmacokinetics	of darunavir h		Clarithromycin		800/100 mg single	
nepatic impairment (Child and Administration (2.6) a Hepatitis B or Hepatitis C The 48-week analysis of 1 nfection status had no ap Renal Impairment	<i>and Use in Specific Popula</i> <i>Virus Co-infection</i> the data from Studies TM uparent effect on the expo	<i>tions (8.6)].</i> IC114-C211 and TMC1 Isure of darunavir.	tic impairment on th I 14-C214 in HIV-1-ir	e pharmacokinetics	of darunavir h cated that he	as not been evaluated <i>(see Dosage</i>	Clarithromycin		800/100 mg single dose	
hepatic impairment (Child and Administration (2.6) a Hepatitis B or Hepatitis C The 48-week analysis of 1 nfection status had no ap Renal Impairment Results from a mass bala unchanged drug. As daruu	and Üse in Specific Popula Virus Co-infection the data from Studies TM oparent effect on the expo nce study with ¹⁴ C-darun navir and ritonavir are hig	<i>tions (8.6)).</i> IC114-C211 and TMC1 Isure of darunavir. avir/ritonavir showed t Ihly bound to plasma pr	tic impairment on th 14-C214 in HIV-1-ir hat approximately 7 roteins, it is unlikely	e pharmacokinetics nfected subjects indi 7.7% of the administr that they will be sig	of darunavir h cated that he ered dose of c nificantly rem	as not been evaluated <i>(see Dosage</i> patitis B and/or hepatitis C virus co-	Clarithromycin Dabigatran etexilate	150 mg	800/100 mg single dose 800/100 mg q.d.'	
epatic impairment (Child and Administration (2.6) a Hepatitis B or Hepatitis C Che 48-week analysis of ti frection status had no ap Renal Impairment Results from a mass bala unchanged drug. As daruu liaolysis. Population pham onderate renal impairme	and Üse in Specific Popula Virus Co-infection the data from Studies TM parent effect on the expo nce study with ¹⁴ C-darun navir and ritonavir are hig macokinetic analysis sh nt (CrCL between 30 to	<i>tions (8.6)</i>]. IC114-C211 and TMC1 Isure of darunavir. avir/ritonavir showed th hhly bound to plasma pr wwed that the pharman 60 mL/min, n = 20). Th	tic impairment on th 14-C214 in HIV-1-ir hat approximately 7 roteins, it is unlikely cokinetics of daruna iere are no pharmac	e pharmacokinetics nfected subjects indir 7.7% of the administr that they will be sig avir were not signifi	of darunavir h cated that hep ered dose of c nificantly rem cantly affect	as not been evaluated <i>(see Dosage</i> patitis B and/or hepatitis C virus co- larunavir is excreted in the urine as oved by hemodialysis or peritoneal	Clarithromycin Dabigatran etexilate Dextromethorphan	150 mg	800/100 mg single dose 800/100 mg q.d.'	
epatic impairment (Child and Administration (2.6) à Hepatitis B or Hepatitis C The 43-week analysis of 1 nfection status had no ap <i>Benal Impairment</i> Results from a mass bala anchanged drug. As daru Ilialysis. Population phan moderate renal impairme mpairment or end stage ro Gender	nd Üse in Specific Popula Virus Co-infection the data from Studies TM parent effect on the expo nce study with ¹⁶ C-darun navir and ritonavir are hi macokinetic analysis sh nt (CrCL between 30 to enal disease <i>(see Use in S</i>)	tions (8.6)/. IC114-C211 and TMC1 Isure of darunavir. avir/ritonavir showed t hly bound to plasma pr owed that the pharma 60 mL/min, n = 20). Th oecific Populations (8.7	tic impairment on th 14-C214 in HIV-1-ir hat approximately 7 oteins, it is unlikely cokinetics of daruna rere are no pharmac 7//.	e pharmacokinetics nfected subjects indi 7.7% of the administ that they will be sig avir were not signifi cokinetic data availa	of darunavir h cated that hep ered dose of o nificantly rem cantly affect ble in HIV-1-i	as not been evaluated <i>(see Dosage</i> batitis B and/or hepatitis C virus co- larunavir is excreted in the urine as oved by hemodialysis or peritoneal ed in HIV-1-infected subjects with nfected patients with severe renal	Clarithromycin Dabigatran etexilate Dextromethorphan Dextrorphan	150 mg 30 mg 0.4 mg Ortho-Novum 1/35	800/100 mg single dose 800/100 mg q.d. ¹ 600/100 mg b.i.d.	
nepatic impairment (Child and Administration (2.6) & Hepatitis B or Hepatitis C The 48-week analysis of 1 nfection status had no ap <i>Benal Impairment</i> Results from a mass bala unchanged drug. As daruu ranchanged drug. As daruu dialysis. Population phar moderate renal impairme mpairment or end stage n <i>Sender</i> Opulation pharmacokine elevant.	nd Üse in Specific Popula Virus Co-infection the data from Studies TM parent effect on the expo nce study with ¹⁶ C-darun navir and ritonavir are hi macokinetic analysis sh nt (CrCL between 30 to enal disease <i>(see Use in S</i>)	tions (8.6)/. IC114-C211 and TMC1 Isure of darunavir. avir/ritonavir showed t hly bound to plasma pr owed that the pharma 60 mL/min, n = 20). Th oecific Populations (8.7	tic impairment on th 14-C214 in HIV-1-ir hat approximately 7 oteins, it is unlikely cokinetics of daruna rere are no pharmac 7//.	e pharmacokinetics nfected subjects indi 7.7% of the administ that they will be sig avir were not signifi cokinetic data availa	of darunavir h cated that hep ered dose of o nificantly rem cantly affect ble in HIV-1-i	as not been evaluated <i>(see Dosage</i> patitis B and/or hepatitis C virus co- larunavir is excreted in the urine as aved by hemodialysis or peritonaal ed in HIV-1-infected subjects with	Clarithromycin Dabigatran etexilate Dextromethorphan Dextrorphan Digoxin	150 mg 30 mg 0.4 mg	800/100 mg single dose 800/100 mg q.d.' 600/100 mg b.i.d. 600/100 mg b.i.d.	
epatic impairment (Child and Administration (2.0) à Hepatitis B or Hepatitis C The 48-week analysis of 1 Infection status had no ap Renal Impairment Results from a mass bala unchanged drug. As daruu Jialysis. Population phar moderate renal impairme mpairment or end stage n Gender Population pharmacokine levant. Race	nd Üse in Specific Popula Virus Co-infection the data from Studies TM parent effect on the expo nce study with ¹⁶ C-darun navir and ritonavir are hi macokinetic analysis sh nt (CrCL between 30 to enal disease <i>(see Use in S</i>)	tions (8.6)/. IC114-C211 and TMC1 isure of darunavir. avir/ritonavir showed t hly bound to plasma pr wed that the pharmar 60 mL/min, n = 20). Th pecific Populations (8.7 her mean darunavir ex	tic impairment on th 114-C214 in HIV-1-ir hat approximately 7 roteins, it is unlikely cokinetics of daruna rere are no pharmac 7/7. aposure in HIV-1-inf	e pharmacokinetics nfected subjects indii 7.7% of the administi that they will be sig avir were not signifi cokinetic data availa ected females comp	of darunavir h cated that hep ered dose of c nificantly rem cantly affect ble in HIV-1-i pared to male	as not been evaluated <i>(see Dosage</i> patitis B and/or hepatitis C virus co- larunavir is excreted in the urine as loved by hemodialysis or peritoneal ed in HIV-1-infected subjects with affected patients with severe renal s. This difference is not clinically	Clarithromycin Dabigatran etexilate Dextromethorphan Dextrorphan Digoxin Ethinyl estradiol (EE)	150 mg 30 mg 0.4 mg Ortho-Novum 1/35	800/100 mg single dose 800/100 mg q.d.' 600/100 mg b.i.d. 600/100 mg b.i.d.	
epatic impairment (Child and Administration (2.6) & Hepatitis B or Hepatitis C The 48-week analysis of 1 nfection status had no ap Renal Impairment Results from a mass bala unchanged drug. As daru noderate renal impairme mpairment or end stage n Gender Copulation pharmacokine elevant. Race Population pharmacokine Reiratire Patients Population pharmacokine	ind Üse in Specific Popula Virus Co-infection the data from Studies TM parent effect on the expc once study with ¹⁴ C-darum navir and ritonavir are hig macokinetic analysis sh nt (CrCL between 30 to enal disease <i>(see Use in S</i>) etic analysis showed hig tic analysis of darunavir i tic analysis of darunavir i	tions (8.6)/. IC114-C211 and TMC1 Isure of darunavir. avir/ritonavir showed t hyly bound to plasma pr wwed that the pharmar 60 mL/min, n = 20). Th <i>pecific Populations (8.7</i> her mean darunavir ex n HIV-1-infected subject worded subjects showed	tic impairment on th 114-C214 in HIV-1-ir hat approximately 7 toteins, it is unlikely cokinetics of darun ere are no pharmac 77. sposure in HIV-1-inf ts indicated that rac that darunavir phar	e pharmacokinetics nfected subjects indii 7.7% of the administi that they will be sig avir were not signifi cokinetic data availa iected females comp te had no apparent efi rmacokinetics are no	of darunavir h cated that hep ered dose of ci nificantly rem cantly affect ble in HIV-1-i pared to male fect on the ex tt considerabl	as not been evaluated <i>(see Dosage</i> patitis B and/or hepatitis C virus co- larunavir is excreted in the urine as loved by hemodialysis or peritoneal ed in HIV-1-infected subjects with affected patients with severe renal s. This difference is not clinically	Clarithromycin Dabigatran etexilate Dextromethorphan Dextrorphan Digoxin Ethinyl estradiol (EE) Norethindrone (NE)	150 mg 30 mg 0.4 mg 0rtho-Novum 1/35 (35 mcg EE /1 mg NE)	800/100 mg single dose 800/100 mg q.d. ¹ 600/100 mg b.i.d. 600/100 mg b.i.d. 600/100 mg b.i.d.	
eepatic impairment (Child and Administration (2.0) à Hepatitis B or Hepatitis C The 43-week analysis of 1 Infection status had no ap Renal Impairment Results from a mass bala unchanged drug. As daruu lialysis. Population pharm moderate renal impairme mpairment or end stager Render Population pharmacokine Geriatric Patients 75 years) evaluated in HIV	ind Üse in Specific Popula Virus Co-infection the data from Studies TM upparent effect on the expc once study with ¹⁴ C-darun navir and ritonavir are hig macokinetic analysis sh nt (CrCL between 30 to enal disease <i>[see Use in S]</i> etic analysis showed hig tic analysis of darunavir i	tions (8.6)/. IC114-C211 and TMC1 Isure of darunavir. avir/ritonavir showed t hyly bound to plasma pr wwed that the pharmar 60 mL/min, n = 20). Th <i>pecific Populations (8.7</i> her mean darunavir ex n HIV-1-infected subject worded subjects showed	tic impairment on th 114-C214 in HIV-1-ir hat approximately 7 toteins, it is unlikely cokinetics of darun ere are no pharmac 77. sposure in HIV-1-inf ts indicated that rac that darunavir phar	e pharmacokinetics nfected subjects indii 7.7% of the administi that they will be sig avir were not signifi cokinetic data availa iected females comp te had no apparent efi rmacokinetics are no	of darunavir h cated that hep ered dose of ci nificantly rem cantly affect ble in HIV-1-i pared to male fect on the ex tt considerabl	as not been evaluated <i>(see Dosage</i> patitis B and/or hepatitis C virus co- larunavir is excreted in the urine as loved by hemodialysis or peritoneal ed in HIV-1-infected subjects with affected patients with severe renal s. This difference is not clinically posure to darunavir.	Clarithromycin Dabigatran etexilate Dextromethorphan Dextrorphan Digoxin Ethinyl estradiol (EE) Norethindrone (NE) Ketoconazole	150 mg 30 mg 0.4 mg 0rthe-Novum 1/35 (35 mcg EE /1 mg NE) 200 mg b.i.d.	800/100 mg single dose 800/100 mg q.d. ¹ 600/100 mg b.i.d. 600/100 mg b.i.d. 400/100 mg b.i.d.	
Appatic impairment (Child and Administration (2.6) a Hepatitis B or Hepatitis C The 48-week analysis of 1 In fection status had no ap <i>Benal Impairment</i> Results from a mass bala anchanged drug. As daru dialysis. Population phan moderate renal impairme mpairment or end stage n <i>Bender</i> Population pharmacokine genet. <i>Pace</i> Population pharmacokine <i>Geriatric Patients</i> Population pharmacokine <i>Geliatric Patients</i> Population pharmacokine <i>Geliatric Patients</i>	ind Üse in Specific Popula Virus Co-infection the data from Studies TM upparent effect on the expc once study with ¹⁴ C-darun navir and ritonavir are hig macokinetic analysis sh nt (CrCL between 30 to enal disease <i>(see Use in S)</i> etic analysis of darunavir i tic analysis of darunavir i tic analysis in HIV-1-infe (-1-infected subjects (n– istered twice daily	tions (8.6)/. IC114-C211 and TMC11 sure of darunavir. avir/ritonavir showed th phy bound to plasma pr wwed that the pharmar 60 mL/min, n = 20). Th <i>pecific Populations (8.7</i> her mean darunavir ex n HIV-1-infected subject seted subjects showed 12, age greater than or	tic impairment on th 114-C214 in HIV-1-ir hat approximately 7 oteins, it is unlikely cokinetics of daruma rere are no pharmac 7/7. cposure in HIV-1-inf ts indicated that rac that darunavir phar equal to 65] /see Usa	e pharmacokinetics : nfected subjects indii 7.7% of the administi that they will be sig avir were not signifi- cokinetic data availa iected females comp iected females comp the had no apparent eff rmacokinetics are no <i>e in Specific Populatio</i>	of darunavir h cated that hep ered dose of c mificantly rem cantly affect ble in HIV-1-i hared to male fact on the ex t considerabl ons (8.5)/.	as not been evaluated <i>(see Dosage</i> patitis B and/or hepatitis C virus co- larunavir is excreted in the urine as oved by hemodialysis or peritoneal ed in HIV-1-infected subjects with nfected patients with severe renal s. This difference is not clinically posure to darunavir. y different in the age range (18 to	Clarithromycin Dabigatran etexilate Dextromethorphan Dextrorphan Digoxin Ethinyl estradiol (EE) Norethindrone (NE) Ketoconazole R-Methadone Omeprazole	150 mg 30 mg 0.4 mg 0.4 mg (35 mg EE /1 mg NE) 200 mg b.i.d. 55 to 150 mg q.d.	800/100 mg single dose 800/100 mg q.d. ¹ 600/100 mg b.i.d. 600/100 mg b.i.d. 600/100 mg b.i.d. 400/100 mg b.i.d.	
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(1.06 to 1.74) 1.15 to 1.85) (1.29 to 2.27) g b.i.d. 16 1.54 (1.41 to 1.68) 1.43 (1.34 to 1.53) 1.45 (1.35 to 1.57) 16 0.46 0.46 0.48 (0.45 to 0.51) (0.43 to 0.49) (0.44 to 0.49) n h.i.d. 1 26 2.74 (1.03 to 1.54) (1.35 to 1.84) (2.30 to 3.26) single 1 64 (1.21 to 2.23) (1.33 to 2.23) 13 ı q.d.' 1.22 1.18 (0.89 to 1.67) 0.90 to 1.53 g b.i.d. 12 2.27 2.70 (1.59 to 3.26) (1.80 to 4.05) 0.87 0.96 (0.77 to 0.98) (0.90 to 1.03) g b.i.d. (0.89 to 1.48) (0.81 to 2.27) a b.i.d (0.61 to 0.74) (0.50 to 0.63) (0.27 to 0.54) 11 0.90 0.86 0.70 (0.83 to 0.97) (0.75 to 0.98) (0.51 to 0.97) g b.i.d. 15 2.11 3.12 9.68 (1.81 to 2.44) (2.65 to 3.68) (6.44 to 14.55) q b.i.d. 0.85 (0.71 to 0.81) (0.78 to 0.91) (0.77 to 0.94) n b.i.d. (0.50 to 0.66) (0.48 to 0.90) 0.93 0.84 (0.71 to 1.21) (0.77 to 0.92) a b.i.d. 0.63 0.64 0.61 (0.59 to 0.71) (0.56 to 0.66) (0.55 to 0.73) ng q.d. (0.84 to 1.09) (0.69 to 0.80) g b.i.d. (0.95 to 2.82) (1.23 to 2.66) 1 h i d ^h 0.93 0.72 1 64 (0.55 to 0.93) (0.80 to 1.09) (1.48 to 1.81) 4.77 11 9.81 27.1 (8.09 to 11.9) (4.04 to 5.63) 22.2 to 33.2) q b.i.d. (0.49 to 0.63) (0.46 to 0.58) (0.45 to 0.57) n h.i.d. (0.55 to 0.70) (0.86 to 1.09) q b.i.d. 0.92 0.79 (0.86 to 0.97) (0.73 to 0.85) 1.42 1.23 (1.24 to 1.63) (0.97 to 1.57 compared with the pharmacokinetic parameters following administration of lopinavir/ri ere comparable when buprenorphine/naloxone was administered with or without an C_{max} and AUC₂₄ for darunavir/ritonavi ^f 800/100 mg q.d. for 14 days before co-administered with dabigatran etexilate. q.o.d. = every other day yproteins in infected cells, thereby preventing the ormation of mature virus particles Antiviral Activity arunavir 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_{s0} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demo antivital activity in cell culture against a broad panel of HIV-1 group M (A, B, C, D, E, F, G), and group D primary isolates with E C_{ss} values ranging that a transfer of the state combination with the PIs amprenavir, atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, or tipranavir, the N(t)RTIs abacavir, didanosine, emtricitabine, mivudine, 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-1 had 21- to 88-fold decreased susceptibility to darunavir and developed 2 to 4 of the following amino acid substitutions S37D, R41E/T, K55D, H69D, K70E, T74S, V77I, or 185V 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 1.10F, V111, 113, V15V, G16E, L23I, V32L, L33F, S37M, M4GI, I47V, I50V, F53L, L63P, A71V, G73S, L76V, V82L, I48V, T91AIS, and 092R, of which L10F, V32I, L33F, S37N, M4GI, I47V, I50V, L63P, A71V, and I84V were the most prevalent. These darunavir-resistant viruses had at least eight tease substitutions and exhibited 50- to 641-fold decreases in darunavir susceptibility with final EC_{so} values ranging from 125 nM to 3461 nM. Clinical trials of darunavir/ritonavir in treatment-experienced subjects: In a pooled analysis of the 600/100 mg darunavir/ritonavir twice daily arms of trials TMC114-C213, TMC114-C202, TMC114-C215, and the control arms of etravirine trials TMC125-C206 and TMC125-C216, the amino acid substitutions V321 and I54L or M developed most frequently on darunavir/irtonavir in 41% and 25%, respectively, of the treatment-experienced subjects who experienced virologic failure, either by rehound or by never being suppressed (less than 50 conjes/ml.). Other substitutions that developed frequently in darunavir/ritonavir virologic failure isolates occurred a tamino acid josticinos VII, IISV, L3S, IA7V, ISOV, and L89V. These amino acid substitutions were associated with decreased susceptibility to darunavir; 90% of the virologic failure isolates had a greater than 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 proteas cleavage sites in the Gag polyprotein of some darunavir/ritonavir virologic failure isolates. In trial TMC114-C212 of treatment-experienced pediatric subjects, the amino acid substitutions V32I, I54L and L89M developed most frequently in virologic failures on darunavir/ritonavir In the 96-week as-treated analysis of the Phase 3 trial TMC114-C214, the percent of virologic failures (never suppressed, rebounders and disco achieving suppression) was 21% (62/298) in the group of subjects receiving darunavir/ritonavir 600/100 mg twice daily compared to 32% (96/297) of subjects receiving suppression was 2 to (102200) in the group of subjects receiving daman minimum tool on growed any compared to 2, a (50/27) of subjects receiving lopinavir/ritonavir 400/100 mg twice daily. Examination of subjects who failed on darunavir/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 obenotypes greater than 7. The most common emerging P substitutions in these virologic failures were V321, L33F, M461 or L, 147V, 154L, 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 (greater than 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 (greater than 10-fold) to lopinavir at baseline. In the 48-week analysis of the Phase 3 trial 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 darunavir/ritonavir 800/100 mg once daily compared to 19% (56/296) of subjects receiving darunavir/rito 600/100 mg twice daily. Examination of isolates from subjects who failed on darunavir/ritonavir 800/100 mg once daily and had post-baseline genotypes sh 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 darunavir/intonavir 600/100 mg twice daily. Isolates from 2 subjects developed PI resistance associated substitutions associated with decreased susceptibility to darunavir/intonavir subject isolate in the darunavir/ritonavir 800/100 mg once daily arm, developed substitutions V32I, M46I, L76V and I84V associated with a 24-fold decreased suscentibility to darunavir, and 1 subject isolate in the darunavir/ritonavir 600/100 mo twice daily arm developed substitutions L33F and I50V sociated with 40-fold decreased susception, and reader to back an analytic to an 800 more daily and decreasing and analytic to an 800 more daily and decreased susception and the total decreased susception and the sociated with the total decreased susception of the social decreased susception and the treatment of the treatment of the social decreased susception of the treatment of the treatment of the social decreased susception of the treatment of the treatment of the treatment of the treatment of the social decreased susception of the treatment of the treatmen

[able 19: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C21]

	Darunavir/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 to 70)	33 (19 to 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 (log10 copies/mL)	4.86	4.84
Median baseline CD4 + cell count (cells/mm ³) (range, cells/mm ³)	228 (4 to 750)	218 (2 to 714)
Percentage of patients with baseline viral load \geq 100,000 copies/mL	34%	35%
Percentage of patients with baseline CD4+ cell count <200 cells/mm ³	41%	43%

FTC = emtricitabine: TDF = tenofovir disoproxil fumarate Week 192 outcomes for subjects on darunavir/ritonavir 800/100 mg once daily from trial TMC114-C211 are shown in Table 20.

Table 20: Virologic Outcome of Randomized Treatment of Trial TMC114-C211 at 192 Weeks

	Darunavir/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 ^b	12%	15%
No virologic data at Week 192 window ^c		
Reasons		
Discontinued trial due to adverse event or death ^d	5%	13%
Discontinued trial for other reasons ^e	13%	12%
Missing data during window ^c but on trial	<1%	0%

°95% CI: 1.9; 16.1

Includes patients who discontinued prior to Week 192 for lack or loss of efficacy and patients who are \geq 50 copies in the 192-week window and patients who had a change in their background regimen that was not permitted by the protocol. Window 186 to 198 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.

⁴ Other includes; withdrew consent, loss to follow-up, etc., if the viral load at the time of discontinuation was < 50 copies/mL

In trial TMC114-C211 at 192 weeks of treatment, the median increase from baseline in CD4 + cell counts was 258 cells/mm³ in the darunavir/ritonavir 800/100 mg once daily arm and 263 cells/mm³ in the lopinavir/ritonavir 800/200 mg per day arm. Of the darunavir/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 darunavir/ritonavir regimen over the lopinavir/ritonavir regimen was demonstrated for both ITT and OP populations.

14.3 Treatment-Experienced Adult Subjects

MC114-C229 TMC114-C229 is a randomized, open-label trial comparing darunavir/ritonavir 800/100 mg once daily to darunavir/ritonavir 600/100 mg twice daily in treatment experienced HIV-1 infected patients with screening genotype resistance test showing no darmavir resistance associated substitutions (i.e. V111, V321, L337, 147V, 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 lefined 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

Table 21 compares the demographic and baseline characteristics between subjects in the darunavir/ritonavir 800/100 mg once daily arm and subjects in the darunavir/ritonavir 600/100 mg twice daily arm in trial TMC114-C229. No imbalances between the 2 arms were noted.

Table 21: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C229

	Darunavir/ritonavir 800/100 mg once daily + OBR N=294	Darunavir/ritonavir 600/100 m twice daily + OBR N=296
Demographic characteristics		•
Median age (years) (range, years)	40 (18 to 70)	40 (18 to 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 (log10 copies/mL)	4.19	4.13
Median baseline CD4+ cell count (cells/mm ³) (range, cells/mm ³)	219 (24 to 1306)	236 (44 to 864)
Percentage of patients with baseline viral load \geq 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 to 1.8)	0.50 (0.1 to 1.9)
Median number of resistance-associated ^b :		
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 ^b :		
0	84%	84%
1	8%	9%
2	5%	4%
≥3	3%	2%
Median number of ARVs previously used ^c :		
NRTIs	3	3
NNRTIS	1	1
PIs (excluding low-dose ritonavir)	1	1

	Darunavir/ritonavir 800/100 mg once daily + OBR N=294	Darunavir/ritonavir 600/100 mg twice daily + OBR N=296
Virologic success HIV-1 RNA < 50 copies/mL	69%	69%
Virologic failure ^a	26%	23%
No virologic data at Week 48 window ^b		
Reasons		
Discontinued trial due to adverse event or death ^c	3%	4%
Discontinued trial for other reasons ⁴	2%	3%
Missing data during window [®] but on trial	0%	<1%

N = total number of subjects with data; OBR = optimized background regimer

'Includes patients who discontinued prior to Week 48 for lack or loss of efficacy, patients who are \geq 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 o trial medication) and patients who discontinued for reasons other than AEs/death and lack or loss of efficacy (provided their last available viral load was

N=131	
57% (39%)	10% (9%)
2011/	00%
	80%
	53% 19%
,.	8%
	3%
	7%

Subjects who did not achieve at least a confirmed 0.5 log, HIV-1 RNA drop from baseline at Week 12. Subjects who have to construct the boundary of the starting in the starting framework without a confirmed 1 log₁₀ drop in viral load), but without a confirmed 1 log₁₀ drop in viral load at Week 96. ⁵ Subjects who never reached a confirmed 1 log₁₀ drop in viral load before Week 96.

In the pooled trials TMC114-C213 and TMC114-C202 through 48 weeks of treatment, the proportion of subjects with HIV-1 RNA less than 400 copies/mL in the arm receiving darunavir/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, copies/mL in the arm receiving darunavir/ritonavir 600/100 mg twice daily and - 0.37 log, copies/mL for the comparator PI arm. The mean increase from baseline in CD4 + cell counts was higher in the arm receiving darunavir/ritonavir 600/100 mg twice daily 103 cells/mm³) than in the comparator PI arm (17 cells/mm³).

14.4 Pediatric Patients

The pharmacokinetic profile, safety and antiviral activity of darunavir/ritonavir were evaluated in 3 randomized, open-label, multicenter studies TMC114-C212

reatment 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 lo less than 30 kg, greater than or equal to 30 kg to less than 40 kg, greater than or equal to 20 kg and ess than 10 kg, and received darunavir 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 darunavir/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 introvir 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 log₁₀ copies/mL, and the median baseline CD4 + cell count was 330 cells/mm³ (range: 6 to 1505 cells/mm³). Overall, 38% of pediatric subjects had baseline plasma HV-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 increase in CD4 + cell count from baseline was 117 cells/mm³

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 darunavir oral suspension with ritonavir oral solution plus background therapy consisting of at least two active non-protease inhibitor antiretroviral drugs. Twentyone subjects received at least one dose of darunavir/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 log₁₀ copies/mL, the median baseline CD4+ cell count was 927 × 10⁶ cells/L (range: 209 to 2,429 × 10⁶ 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 48 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 at Week 48 was 71%. The mean increase in CD4 + percentage from baseline was 4%. The mean

change in CD4 + cell count from baseline was 187 × 10⁶ cells/L. TMC114-C230

Treatment-naïve pediatric subjects between the ages of 12 and less than 18 years and weighing at least 40 kg received the adult recommended dose of itonavir 800/100 mg once daily plus background therapy consisting of at least two non-prote

The 12 randomized pediatric subjects had a median age of 14.4 years (range 12.6 to 17.3 years), and were 33.3% male, 58.3% Caucasian and 41.7% Black. The baseline plasma HIV-1 RNA was 4.72 log₁₀ copies/mL, and the median baseline CD4+ cell count was 282 cells/mm³ (range: 204 to 515 cells/mm³). Overall, 41.7% of pediatric subjects had baseline plasma HIV-1 RNA \geq 100,000 copies/mL.

All subjects completed the 48 week treatment period. The proportion of subjects with HIV-1 RNA less than 50 copies/mL and less than 400 copies/mL was 83.3% and 91.7%, respectively. The mean increase in CD4 +

cell count from baseline was 221 × 10⁶ cells/L. 16 HOW SUPPLIED/STORAGE AND HANDLING

Darunavir 400 mg tablets are supplied as orange, oval shaped, bevel edged, biconvex, film-coated tablets de-bossed with "H" on one side and "189" on the other side. They are supplied as follows: NDC 31722-567-60

Bottles of 60 Darunavir 600 mg tablets are available as orange, oval shaped, biconvex, film-coated tablets de-bossed with "J" on one side and "7" on the other side. They are supplied as follows:

NDC 31722-568-60

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]

Keep darunavir tablets out of reach of childr

Bottles of 60

Storage

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instruction for Use).

Instructions for Use Advise patients to take darunavir tablets and ritonavir with food every day on a regular dosing schedule, as missed doses can result in development of resistance. Darunavir tablets must always be used with ritonavir in combination with other antiretroviral drugs. Advise patients not to alter the dose of either darunavir tablets or ritonavir, discontinue ritonavir, or discontinue therapy with darunavir tablets without consulting their physician/see Dosage and Administration (2)).

Hepatotoxicity inform patients that drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with darunavir tablets co-administered with 100 mg of ritonavir. Advise patients about the signs and symptoms of liver problems [see Warnings and Precautions (5.2)].

Severe Skin Reactions Inform patients that skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, drug rash with eosinophilia and systemic symptoms, and table plants of the control of the second se fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia /see Warnings and Precautions (5.3)/.

Drug Interactions Darunavir tablets/ritonavir may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort (see Contraindications (4), Warnings and Precautions (5.4, 5.5) and Drug Interactions (7)]. Contraception

Instruct patients receiving combined hormonal contraception or the progestin only pill to use an effective alternative (non-hormonal) contraceptive method or add a barrier method during therapy with darunavir tablets/ritonavir because hormonal levels may decrease /see Drug Interactions (7.3) and Use in Specific Populations (8.3)/. Fat Redistribution

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including darunavir tablets/ritonavir, and that the cause and long-term health effects of these conditions are not known at this time [see Warnings and Precautions (5.7)].

Immune Reconstitution Syndrome Advise nationts to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and

nation from previous infections may occur soon after anti-HIV treatment is started *(see Warnings and Precautions (5.8))*.

Pregnancy Registry Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to darunavir tablets [see Use in Specific Populations (8,1)].

Lactation

struct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk /see Use in Specific Populations (8.2)/.



Camber Pharmaceuticals, Inc taway, NJ 08854 factured by: Γ**ERO**™

Labs Limited metla, Hyderabad - 500 055,

ed: 04/2023

^b. Johnson VA. Brun-Vézinet F. Clotet B. et al. Undate of the drug resistance mutations in HIV-1: December 2008. Ton HIV Med 2008: 16(5): 138 to 145 Dnly counting ARVs, excluding low-dose ritonavi $Week\,48\,outcomes\,for\,subjects\,on\,darunavir/ritonavir\,800/100\,mg\,once\,daily\,from\,trial\,TMC114-C229\,are\,shown\,in\,Table\,22.$ Table 22: Virologic Autoome of Randomized Treatment of Trial TMC114-C229 at A8 Week

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. 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.

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 if MC 114-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. ° 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 2st Trimester of Pregnancy, the 3st Trimester of Pregnancy and Postpartum

Pharmacokinetics of total darunavir (mean ± standard deviation)	2 nd Trimester of pregnancy (n=12) ^a	3 rd Trimester of pregnancy (n = 12)	Postpartum (6 to 12 Weeks) (n=12)
C _{max} , ng/mL	4668 ± 1097	5328 ± 1631	6659 ± 2364
AUC ₂₄₆ , ng·h/mL ^b	78740 ± 19194	91760 ± 34720	113780 ± 52680
Cmin, ng/mL	1922 ± 825	2661 ± 1269	2851 ± 2216

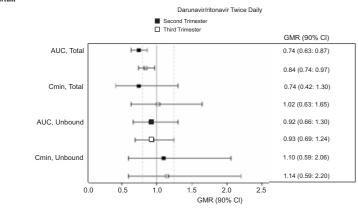
^b AUC _{24b} is calculated as AUC _{12b}*2.

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 2st Trimester of Pregnancy, the 3st 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)
Cmax, ng/mL	4964 ± 1505	5132 ± 1198	7310 ± 1704
AUC24h, 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/rit 600/100 mg Twice Daily or 800/100 mg Once Daily as Part of an Antiretroviral Regimen, During the 2st and 3st Trimester of Pregnancy Compared to Postpartum



	In comparison to rifabutin 300 mg once daily.
y in	12.4 Microbiology
ie –	Mechanism of Action
	Darunavir is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV-1 encoded Gag-Pol polyp

Clinical trials of darunavir/ritonavir in treatment-naïve subjects: In the 192-week as-treated analysis censoring those who discontinued before Week 4 of the Phase 3 trial 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 darunavir/ritonavir 800/100 mg once daily compared to 29% (76/263) of subjects receiving lopinavir/ritonavir 800/200 mg per day. In the darunavir/ritonavir arm, emergent PI resistance associated substitutions were identified in 11 of the virologic failures with post-baseline genotypic data In a submittene of the second se none of the lopinavir/ritonavir virologic failures had decreased susceptibility to lopinavir (greater than 10-fold change) at failure. The reverse transcriptase M184V Window 42 to 54 Weeks

^c 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 daruna 800/100 mg once daily arm and the darunavir/ritonavir 600/100 mg twice daily arm, respectively).

TMC114-C214 TMC114-C214 is a randomized, controlled, open-label Phase 3 trial comparing darunavir/ritonavir 600/100 mg twice daily versus loginavir/ritonavir 400/100 mg twice daily in antiretrovinal treatment-experiment, pointerine, pointerine, and comparing unineminative HIV-1-infected adult subjects. Both arms used an optimized background regimen consisting of at least 2 antiretrovinals (NRTIs withor without NNRTIs).

HIV-1-infected subjects who were eligible for this trial had plasma HIV-1 RNA greater than 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 less than 400 copies/mL. Analyses included 595 subjects in trial TMC114-C214 who had completed 96 weeks of treatment or discontinued earlier.

Demonranhics and baseline characteristics were balanced between the darunavir/ritonavir arm and the loninavir/ritonavir arm (see Table 23). Table 23 compares the demographic and baseline characteristics between subjects in the darunavir/ritonavir 600/100 mg twice daily arm and subjects in the lopinavir/ri 400/100 mg twice daily arm in trial TMC114-C214.

	Darunavir/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 to 68)	41 (22 to 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 to 831)	230 (2 to 1096)
Percentage of patients with baseline viral load \geq 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 to 37.40)	0.60 (0.1 to 43.8)
Median lopinavir fold change (range)	0.70 (0.40 to 74.40)	0.80 (0.30 to 74.50)
Median number of resistance-associated ^a :		
PI mutations	4	4
NNRTI mutations	1	1
NRTI mutations	2	2
Percentage of subjects with number of baseline primary protease inhibitor mutations ⁸ :		
≤1	78%	80%
2	8%	9%
≥3	13%	11%
Median number of ARVs previously used ^b :		
NRTIS	4	4
NNBTIS	1	1
Pls (excluding low-dose ritonavir)	1	1
Percentage of subjects resistant ⁶ to all available ⁶ PIs at baseline,	1	· · · ·
excluding darunavir	2%	3%

OBR = optimized background regime * 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 to 130. ^bOnly counting ARVs, excluding low-dose ritona

⁶ Based on phenotype (Antivirogram[®]).

 Total ratio circuits is beneric the convert shalls: Tourist is a circuit is the same into a down or the farmany is tables a relation of the same into the same inthe same into the same in	You can ask your healthcare provider or pharmacist for a darunavir tablets. Do not start taking a new medicine without tellin healthcare provider can tell you if it is safe to take darunavi w should I take darunavir tablets?	e provider tells you. navir tablets. vith darunavir tablets without t	 healthcare provider. Take darunavir tablets and ritonavir with food. If you have difficulty swallowing darunavir tablets, darunavir oral suspension is also a Your healthcare provider will help decide whether darunavir tablets or oral suspension is 	 You. If your child is taking darunavir tablets, your child's healthcare provider will decide the rip based on your child's weight. Your child's healthcare provider will tell you how much d (tablets or oral suspension) and how much ritonavir (cansules, tablets or solution) you 	not tolerate ritonavir oral suspension, and now much monavir trablets of oral suspension, and now much in the should take. Your child should take darunavir tablets with ritonavir with food. If your child should take is a solution, ask your child's healthcare provider for advice. Darunavir oral suspension should be given with the supplied oral dosing syringe. St	Darunavir oral suspension snould be given with the supplied oral during symbols of suspension well before each use. See the "Instructions for Use" that come with da oral suspension for information about the right way to prepare and take a dose.	 It is important that you do not miss or skip doses of darunavir tablets during treatment. If you take too much darunavir, call your healthcare provider or go to the nearest emergency room right away. 	Vhat are the possible side effects of darunavir tablets? arunavir tablets may cause serious side effects, including:	See "What is the most important information I should know about darunavir table Diabetes and high blood sugar (hyperglycemia). Some people who take protease ir including darunavir tablets can get high blood sugar, develop diabetes, or your diabetes	te ofi es ma	and ar pen. T	Changes in your immune system (Immune Reconstitution Syndrome) can happy you start taking HIV-1 medicines. Your immune system may get stronger and begin infections that have been hidden in your body for a long time. Tell your healthcare provi away if you start having new symptome after starting your HIV-1 medicine	80	inal) pain offect that bothers you or that does not	nay report side effects	 How should I store darunavir tablets? Store darunavir tablets at room temperature 77°F (25°C). Keep darunavir tablets away from high heat. Keep darunavir tablets and all medicines out of the reach of children. 			;ol,	Manufactured for: Camber Pharmaceuticals, Inc.,	r: ted araharl - 500	ona his Patient Information has been approved by the U.S. Food and hvised: 04/2023	mation has been approved by the U.S. Food and }
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