Selected Properties of Darunavir

Other names	Prezista®, TMC-114 Combination formulation: • Prezcobix® (darunavir 800 mg/cobicistat 150 mg); Rezolsta® (EU trade name)
Manufacturer	Janssen Inc.
Pharmacology/Mechanism of Action	Protease inhibitor with potent in vitro activity against both wild-type HIV-1 and a large panel of viruses resistant to currently licensed PIs. Is a sulfonamide; to date, no cross-sensitivity observed in subjects with sulfonamide allergy. Molecular weight: 547.656 (active moiety), 593.724 (TMC114-ethanolate)
Activity	In vitro EC_{50} 4.2 nM (2.5 ng/mL), EC_{90} 10 nM (5.5 ng/mL). Comparative EC50 values were found against WT-HIV1 and multi-PI-resistant primary isolates. The EC50 value of darunavir increases by a median factor of 5.4 in the presence of human serum. EC50WT is approximately 55 ng/mL.
Resistance - genotypic	Resistance data are preliminary and limited. Reductions in response are associated with increasing numbers of the following mutations: V11I, V32I, L33F, I47V, I50V, I54M/L, G73S, L76V, I84V, L89V. Some of these mutations appear to have a greater effect on susceptibility than others (e.g., I50V versus V11I).
Resistance - phenotypic	
Cross-Resistance	
Oral Bioavailability	Absolute oral bioavailability: 37% (alone) and 82% (after coadministration with ritonavir 100 mg BID) Oral suspension for pediatric use (100 mg/mL) is under development [Sekar et al. ICAAC 2009]. When coadministered with low-dose ritonavir, exposures comparable to that of darunavir tablets are noted.
Effect of Food	Bioavailability ↑ 30% when taken in fed conditions with ritonavir versus fasting conditions. Type of meal (standard breakfast, high-fat breakfast, nutritional protein drink, croissant + coffee) had very little impact on exposure. Oral suspension for pediatric use (100 mg/mL) is under development [Sekar et al. ICAAC 2009]. Bioavailability of the suspension is similar with or without food.
Protein Binding	95% (humans), primarily alpha-1-acid glycoprotein
Vd	

Tmax	2.5-4 hours when given fed with ritonavir 100 mg BID
serum T ½	~ 15 hours when combined with ritonavir. 10.9-17.2 hours for various dosing regimens; ritonavir did not influence t1/2.
Drug Concentrations	Adult population PK (HIV-positive subjects): • 800/100 mg QD: median C0h: 1896-2041 ng/mL, AUC 87788-87854 ng.h/mL (studies TMC114-C211 and C229) • 600/100 mg BID: median C0h: 3197-3307 ng/mL, AUC 109401-123336 ng.h/mL (studies TMC114-C202, C213, C214, C229) Pediatric population PK: • 800/100 mg QD (12 to <18 years of age): median C0h 2234 ng/mL, AUC 86741 ng.h/mL • 20 mg/kg darunavir with ritonavir 3 mg/kg BID (10 to<15 kg): median C0h 4126 ng/mL, AUC 124044 ng.h/mL • 380 mg darunavir/48 mg ritonavir BID (15 to <20 kg): median C0h 3927 ng/mL, AUC 132698 ng.h/mL **Darunavir 800mg/100mg daily** for 7 days: conc remained above the protein-binding corrected in-vitro EC50 55ng/ml for ≥ 48 hours in healthy volunteers after last dose was administered (Boffito et al. 2008). Based on PK sampling data from the GRACE study, **exposure to darunavir was not influenced by age, body weight, hepatitis B co-infection status, or use of etravirine or tenofovir**. There were no clinically relevant differences in exposure to darunavir according to **race or gender**.(Kakuda et al. 2010) In healthy volunteers (n=23) who had previously participated in a pravastatin-darunavir/ritonavir interaction study, CYP3A5 and ABCB1 polymorphisms were not associated with variability in darunavir/ritonavir pharmacokinetics.(Torres et al. 2011) Darunavir concentrations were compared in 34 time-matched blood plasma and **seminal plasma samples** from 18 HIV-positive men. Good penetration of darunavir into the seminal fluid was observed, with concentrations approximately 10-20% of blood plasma levels. All seminal plasma darunavir were above the protein-corrected EC50 values for wild-type HIV-1 (55 ng/mL), and a third of all seminal plasma darunavir levels exceeded the protein-corrected EC50 required to inhibit protease inhibitor resistant HIV-1 (550 ng/mL).(Taylor et al. 2010) **Intracellular** darunavir concentrations are approximately 5-times higher than plasma concentrations, and are significantly correlated with plasma ritonavir exposures.(Dickinson et al. 2011) In healthy volunteers who received either darunavir 900/100 mg QD or efavirenz 600 mg QD alone or in combination, intracellular concentrations of both darunavir and efavirenz were significantly increased when the drugs were coadministered: intracellular darunavir AUC ↑ 124% and Cmax

	↑ 163% and intracellular efavirenz C24h ↑ 139%.[Soon et al. 2013] In a cross-sectional TDM database review of non-pregnant HIV-infected adults taking darunavir 800/100 mg QD, darunavir C24h obtained after morning dosing were significantly higher than those after evening dosing (1632 vs 1433 ng/mL, respectively, p<0.0001). The difference was more pronounced in women vs. men. Findings may represent Circadian variation in hepatic CYP3A4, intestinal P-gp and gastrointestinal mobility.[Ocadiz et al. 2012] Bioequivalence demonstrated with 800 mg darunavir tablet to two 400 mg darunavir tablets, both given with ritonavir 100 mg.[Kakuda et al. 2012] Bioequivalence demonstrated with darunavir 800/cobicistat 150 mg fixed dose tablet to darunavir and cobicistat administered as single agents under fasted and fed conditions.[Kakuda et al. 2013]
Minimum target trough concentrations (for wildtype virus)	
CSF (% of serum)	In 16 HIV-positive patients, darunavir concentrations were measured in matched CSF and plasma samples. Darunavir was present in all CSF with a median level of 56.9 ng/mL (IQR 39.6, 81.4). Median CSF-to-plasma ratio was 1.4% (IQR 0.9%, 1.8%) for total darunavir and 9.4% for unbound darunavir (IQR 6.8%, 14.2%) (z = 0.57, p > 0.10). Darunavir concentrations in CSF exceeded the IC50 of wild-type HIV in all specimens by a median of 20.7-fold (IQR 14.4, 29.6).[Letendre S et al. ICAAC 2009] CSF darunavir and ritonavir concentrations were compared in HIV-infected patients receiving darunavir/ritonavir 800/100mg once daily vs 600/100mg twice daily. HIV-infected patients on once-daily darunavir/ritonavir had significantly lower CSF darunavir trough concentrations and CSF-to-plasma ratios than patients on darunavir/ritonavir twice-daily (10.7 versus 38.2ng/ml and 0.32 versus 0.90%; *P*<0.05). No significant effect of single-nucleotide polymorphisms in the genes encoding for blood–brain barrier transporters was noted apart from slightly higher CSF darunavir penetration in patients carrying OATP1A2 uncommon variants.[Calcagno et al. 2012] Median CSF darunavir concentrations were 17.08 ng/mL with a CSF:plasma ratio of 0.0084 in subjects receiving darunavir 600 mg/100 mg once daily, and 13.23 ng/mL and 0.0104, respectively, in subjects receiving darunavir 800/100 mg daily in a PK-substudy of eudraCT2011-006272-39.[Di Yacovo et al. IWCPHT 2014] 2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]

<table>
<tr><td>Metabolism</td><td>Substrate and inhibitor of CYP3A4.</td></tr>
<tr><td>Excretion</td><td>After single dose administration of darunavir 400/ritonavir 100 mg, 79.5% and 13.9% of the administered dose of ^{14}C-darunavir was recovered in the feces and urine, respectively.</td></tr>
<tr><td>Dosing – Adult</td><td>Prezista®:
For treatment-experienced patients: 600/100 mg ritonavir po BID with food.

For treatment naïve patients or those with no darunavir resistance-associated mutations (RAMS): 800/100mg ritonavir po once daily with food.

In a multicentre open-label study (n=100) patients virally suppressed on darunavir 800/100 mg QD plus 2 NRTIs were randomized to continue on darunavir 800/100 mg QD or switched to darunavir 600/100 mg QD. At week 48, darunavir Ctrough levels were similar between treatment arms and the reduced darunavir dose showed non-inferior virologic efficacy to the standard dose arm. CD4 cell counts remained stable in both groups.[Molto et al. 2014 IWCPHT]

Prezcobix®: 1 tablet daily with food.</td></tr>
<tr><td>Dosing – Pediatric</td><td>(age 3 to < 18 years):
Once daily dosing is approved in treatment-naïve and treatment-experienced patients with no darunavir resistance-associated mutations.
• Pediatric patients weighing at least 10 kg but less than 15 kg

The weight-based dose is darunavir 35 mg/kg once daily with ritonavir 7 mg/kg once daily using the following table:
<table>
<tr><td colspan="2">Recommended dose for pediatric patients weighing 10 kg to less than 15 kg who are treatment-naïve or treatment-experienced with no darunavir resistance associated substitutions*</td></tr>
<tr><td>Body weight

(kg)</td><td>Formulation: darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL)</td></tr>
<tr><td></td><td>Dose: once daily with food</td></tr>
<tr><td>Greater than or equal to 10 kg to less than 11 kg</td><td>darunavir 3.6 mL‡ (350 mg) with ritonavir 0.8 mL (64 mg)</td></tr>
<tr><td>Greater than or equal to 11 kg to less than 12 kg</td><td>darunavir 4 mL‡ (385 mg) with ritonavir 0.8 mL (64 mg)</td></tr>
<tr><td>Greater than or equal to 12 kg to less than 13 kg</td><td>darunavir 4.2 mL (420 mg) with ritonavir 1 mL (80 mg)</td></tr>
</table></td></tr>
</table>

Greater than or equal to 13 kg to less than 14 kg	darunavir 4.6 mL‡ (455 mg) with ritonavir 1 mL (80 mg)
Greater than or equal to 14 kg to less than 15 kg	darunavir 5 mL‡ (490 mg) with ritonavir 1.2 mL (96 mg)
* darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V ‡ The 350 mg, 385 mg, 455 mg and 490 mg darunavir dose for the specified weight groups were rounded up for suspension dosing convenience to 3.6 mL, 4 mL, 4.6 mL and 5 mL, respectively.	

- *Pediatric patients weighing at least 15 kg*

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

Recommended dose for pediatric patients weighing at least 15 kg who are treatment-naïve or treatment-experienced with no darunavir resistance associated substitutions*		
Body Weight (kg)	Formulation: darunavir tablet(s) and ritonavir capsules or tablets (100 mg)	Formulation: darunavir oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL)
	Dose: once daily with food	Dose: once daily with food
Greater than or equal to 15 kg to less than 30 kg	darunavir 600 mg with ritonavir 100 mg	darunavir 6 mL (600 mg) with ritonavir 1.25 mL (100 mg)
Greater than or equal to 30 kg to less than 40 kg	darunavir 675 mg with ritonavir 100 mg	darunavir 6.8 mL§ʃ (675 mg) with ritonavir 1.25 mL (100 mg)
Greater than or equal to 40 kg	darunavir 800 mg with ritonavir 100 mg	darunavir 8 mLʃ (800 mg) with ritonavir 1.25 mL (100 mg)
* darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V § The 675 mg dose using darunavir tablets for this weight group is rounded up to 6.8 mL for suspension dosing		

	convenience. ∫ The 6.8 mL and 8 mL darunavir dose should be taken as two (3.4 mLor 4 mL, respectively) administrations with the included oral dosing syringe BID dosing in treatment-experienced children ages 3 to <6 years: • Darunavir 20 mg/ritonavir 3 mg per kg BID (<15 kg) • Darunavir 375 mg/ritonavir 50 mg BID (15 to <20 kg) [Kakuda et al. HIV PK 2013, O_13] The safety and efficacy of PREZISTA/rtv in pediatric patients less than 3 years of age have not been established. Darunavir should not be used in pediatric patients below 3 years of aged in view of the toxicity and mortality observed in juvenile rats observed up to post natal day 26.
Special instructions for pediatric patients	Darunavir 100mg/ml oral suspension approved in Europe & US for use in antiretroviral therapy-experienced paediatric patients age 3 years and above, weighing at least 15 kg body weight. Suspension must be coadministered with low-dose ritonavir and must be taken in combination with other antiretrovirals. No pharmacokinetic data are available on chewing or crushing of PREZISTA film-coated tablets. However, since the tablets are not formulated as an extended release formulation, no potential problem is anticipated if the tablets are chewed or crushed for administration through a nasogastric (NG) tube. It is unlikely that chewing or crushing PREZISTA tablets would have a significant impact on pharmacokinetics (Data on File, Tibotec, November 2006). In two patients, one with dysphagia and Candida esophagitis and one with a stomach tube, who received darunavir tablets crushed and dissolved and administered with ritonavir oral solution, adequate plasma darunavir levels were achieved along with good virologic response.(Scholten et al. 2010)
Adjust in Liver Dysfunction	The pharmacokinetics and safety of darunavir 600 mg/ritonavir 100 mg BID for 7 days was assessed in HIV-negative volunteers with **mild (Child-Pugh class A, n=8) and moderate (Child Pugh class B, n=8) hepatic impairment** and compared with HIV-negative, healthy control volunteers (n=16). There were no differences in levels of either drug in subjects with mild hepatic impairment and controls (least square mean (LSM) ratios (90% confidence intervals) for DRV exposure (AUC_{12h}), maximum (C_{max}) and minimum (C_{min}) plasma concentrations were 0.94 (0.75–1.17), 0.88 (0.73–1.07) and 0.83 (0.63–1.10), respectively). In those with moderate hepatic impairment there was

	approximately 20% increase in AUC for DRV, and levels of RTV were increased approximately 50% compared to healthy controls but neither increase was considered clinically significant. In conclusion, no dose adjustments of DRV/r are needed in individuals with mild or moderate liver impairment.[1] In an open-label observational study of 11 HIV+ and 13 HIV/hepatitis B or C (**Child Pugh score <6**) receiving darunavir/ritonavir 600/100 mg BID, no significant association between extent of liver fibrosis and darunavir kinetics was observed. Median darunavir AUC12 was 41.7 mg.h/L in HIV+/HEP+ vs. 42.6 in HIV+ patients, p=0649. Median darunavir Ctrough was 2.7 mg/L and 2.0, respectively, p=0.776.[Molto et al. 2009]. The kinetics of raltegravir and darunavir were studied in five HIV-HCV co-infected patients with **moderate to severe hepatic impairment** (2 with chronic active hepatitis, 3 with cirrhosis). Plasma Ctrough samples were collected at days 14 and 30 after this new regimen was initiated; 24 matched HIV-1 patients with normal liver function treated with raltegravir and darunavir were used as a control group. Mean darunavir Ctrough was 8519 vs. 3236 ng/mL in controls. Mean darunavir Ctrough was consistently higher in cirrhotic vs. non-cirrhotic patients (9820 vs. 2016 ng/mL, respectively). No differences in viral/immunologic outcome or safety parameters were found between cirrhotic and non-cirrhotic patients. Use darunavir with caution in patients with moderate to severe liver impairment because of the risk of additive toxicity.(Tommasi et al. 2010) Kinetics of darunavir 800/100 mg QD and 600/100 mg BID in **HIV-HCV coinfected patients with hepatic cirrhosis** (74% Child-Pugh A, median MELD score 9), total serum unbound darunavir concentrations were similar to historical data in non-cirrhotic patients.[Curran et al. HIVPK 2012, #O_16] Dose adjustments not necessary.
Adjust in Renal Failure/Dialysis	Population pharmacokinetic analysis in HIV-infected subjects (n=20) with moderate renal impairment (Clcr 30-60 mL/min) showed that darunavir pharmacokinetics were not significantly affected. There are currently no pharmacokinetic data of darunavir in HIV-infected subjects with severe renal impairment or endstage renal disease; however a significant increase in darunavir would not be expected in such subjects, due to the limited renal clearance of darunavir. Antiretroviral pharmacokinetics were studied in a 49-year old HIV-positive man virologically suppressed on darunavir/ritonavir 600/100 mg twice daily, etravirine 200 mg twice daily and raltegravir 400 mg twice daily while undergoing hemodialysis three times weekly. The morning dose of the antiretrovirals was taken after completion of the 4-hour morning hemodialysis session. After dialysis, darunavir, etravirine, raltegravir and

	ritonavir concentrations were decreased by 57%, 29%, 82% and 60%, respectively compared to predialysis levels. A supplemental dose of 600 mg darunavir administered prior to the hemodialysis session was successful in restoring darunavir concentrations approximately equal to expected levels, while administration of a supplemental dose of raltegravir 400 mg was not, likely due to wide intra- and inter-patient variability. Dose supplementation of etravirine was not deemed necessary given the relatively low amount removed during hemodialysis. After 1 year of therapy, the patient maintained viral suppression.[Giguere et al. 2009] An HIV-positive patient on continuous venovenous hemodiafiltration (CVVHDF) received raltegravir 400 mg BID, darunavir 600/100 mg BID, zidovudine 300 mg BID and 3TC 50 mg q24h in suspension via gastric port and simultaneous enteral feeding via the duodenal port of a double-lumen nasogastroduodenal tube. Pharmacokinetic sampling and analysis indicated that darunavir and raltegravir were removed by CVVHDF with approximately the same clearance as provided by a normally functioning kidney. Absorption of both drugs after suspension and application via the gastric port with continued administration of feed via the duodenal port of the double-lumen tube was good. As such, **dose adjustments are not required for patients receiving darunavir and/or raltegravir while undergoing CVVHDF** and that absorption of darunavir and raltegravir is not significantly affected by postpyloric enteral feeding.[Taegtmeyer et al. 2011]
Toxicity	Darunavir contains a sulfonamide moiety. Use with caution in patients with a **known sulfonamide allergy**. The potential for cross-sensitivity between darunavir and the sulfonamide class is unknown. **Drug-induced hepatitis** (e.g., acute hepatitis, cytolytic hepatitis) has been reported with darunavir/rtv (0.5% in clinical development program, n=3063). Patients with preexisting liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse events. Postmarketing cases of liver injury, including some fatalities, have been reported. These have generally occurred in patients with advanced HIV1 disease taking multiple concomitant medications, having comorbidities including hepatitis B or C coinfection, and/or developing immune reconstitution syndrome. A causal relationship with darunavir/rtv therapy has not been established. If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on

	darunavir/rtv, interruption or discontinuation of treatment must be considered."
Pregnancy & Lactation	Pregnancy category C. Use during pregnancy only if the potential benefit justifies the potential risk. In 2 HIV-infected pregnant women receiving darunavir/ritonavir (all VL<40 copies/mL at delivery), mean darunavir cord:mother blood concentration ratio was 0.11 (SD +/- 0.01); cord blood concentrations were below cut-off values in both samples. Mean amniotic fluid:maternal plasma ratio for darunavir was 0.16. Undetectable viral load was found in amniotic fluid and cord blood.[Ivanovic et al. 2010a]. In a treatment-naïve pregnant woman, darunavir 800/100 mg QD plus tenofovir/emtricitabine once daily was well-tolerated and resulted in undetectable viral load throughout the pregnancy. Darunavir concentrations were measured in pregnancy and post-partum. At week 21, darunavir Ctrough was 1877 ng/ml, and at week 37, darunavir Ctrough was 1407 ng/mL. Calculated cord blood, amniotic and cervicovaginal fluid to mother plasma ratios were 0.11, 0.24 and 0.09, respectively.[Ivanovic et al. 2010b]. In 11 HIV-positive women on cART including darunavir 600 mg/ritonavir 100 mg BID, plasma ART concentrations were measured in the 2nd and 3rd trimesters and post-partum. Total darunavir and ritonavir pharmacokinetics decreased during pregnancy likely due to pregnancy-related dilution of albumin and/or AAG. Total darunavir Cmax was 28% and 19% lower while total darunavir Cmin was 43% and 86% higher during the 2nd and 3rd trimesters, respectively, compared with the postpartum period. AUC12h was 24% and 17% lower in the 2nd and 3rd trimesters compared with the postpartum period. However, there was no clinically relevant change in unbound darunavir AUC12h and Cmin occurred during pregnancy, and there was no MTCT; therefore no dose adjustment is required for DRV/rtv 600/100mg BID in pregnant women.[Zorrilla et al. 2012] In 6 HIV-positive women treated with darunavir/ritonavir (600mg/100mg BID or 800mg/100mg QD) throughout pregnancy, darunavir exposures were significantly lower in the 3rd trimester compared to post-partum (GMR: 0.64 (0.47-0.86) for AUCtau; 0.71 (0.49-1.03) for Cmax; 0.45 (0.22-0.91) for Clast). The cord blood/maternal plasma concentration ratio was <0.076 for darunavir.[Colbers et al. 2012] In HIV-infected pregnant women receiving darunavir/r 800/100 mg QD with tenofovir/emtricitabine, steady-state PK analysis was performed in the 3rd trimester and at 12 weeks post-partum. All women had undetectable viral loads throughout pregnancy. Total darunavir Ctrough ↓ 47%, Cmax ↓ 27%, and AUC ↓ 41% in the 3rd trimester vs. postpartum. Unnbound darunavir Ctrough

	↓ 24%, Cmax ↓ 29%, and AUC ↓ 24% in the 3rd trimester vs. postpartum. Mean unbound darunavir Ctrough was 66 ng/mL in the 3rd trimester.[Curran et al. 2013] In a phase IIIb study, HIV-infected women (n=17) in their 2nd trimester received darunavir 800/100 mg QD with other antiretrovirals. Total darunavir exposures decreased in the 2nd and 3rd trimester compared to postpartum (34% ↓ AUC, 32% ↓ Cmin and 34% ↓ Cmax and 35% ↓ AUC, 50% ↓ Cmin and 31% ↓ Cmax, respectively). Unbound darunavir exposures decreased in the 2nd and 3rd trimester compared to postpartum (24% ↓ AUC, 132% ↓ Cmin and 34% ↓ Cmax and 20% ↓ AUC, 38% ↓ Cmin and 16% ↓ Cmax, respectively). Unbound darunavir was >10-fold above the unbound EC50 for wild-type HIV (2.75 ng/mL) in all subjects at all time points and there was no mother-to-child-transmission. No dose adjustment is required for darunavir/ritonavir 800/100 mg QD in pregnant women.[Crauwels et al. 2014 IWCPHT]
Drug Interactions	May be coadministered with omeprazole or ranitidine. Darunavir is an inhibitor of CYP3A4. Darunavir/r may induce CYP2C9, 2C19. Darunavir/r may possibly inhibit CYP2D6. See separate Drug Interaction Table.
Baseline Assessment	Appropriate laboratory testing of hepatic parameters should be conducted prior to initiating therapy with PREZISTA/rtv and patients should be monitored during treatment.
Routine Labs	Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pretreatment elevations of transaminases, especially during the first several months of PREZISTA/rtv treatment.
Dosage Forms	Prezista®: 75 mg (white) tablets, DIN 02338432 150 mg (white) tablets, DIN 02369753 400 mg (light orange) tablets, DIN 02324057 600 mg (orange) tablets, DIN 02324024 800 mg (dark red) tablets, DIN 02393050 100 mg/mL oral suspension (available in U.S. and Europe) *300 mg (orange) tablets, DIN 02284057 – discontinued* Prezcobix®: fixed dose combination of darunavir 800 mg and cobicistat 150 mg pink oval-shaped, film-coated tablet, DIN 02426501
Storage	Store tablets between 15-30C.

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