P-450 CYP3A4 inhibitor such as ritonavir or cobicistat, and in conjunction with other antiretroviral agents.

Guidelines from the USA, Australia, and Europe all list boosted darunavir as a preferred option for treatment-naive adults and adolescents (ASHM, 2015; DHHS, 2015a; Ryom *et al.,* 2015). Boosted darunavir in combination with a drug NRTI backbone is described as an alternate rather than preferred regimen for pediatric use in the US DHHS (2015b) guidelines.

Darunavir is available as 75-, 150-, 400-, 600-, and 800-mg film-coated tablets, as a 100 mg/ml oral suspension (in USA and Europe, not Australia) and as a fixed-dose combination of 800 mg darunavir–cobicistat 150 mg (Prezcobix). It is recommended that darunavir is taken with food. Halving of tablets is not recommended as dose equivalence with divided tablets has not been established (Janssen, 2015b).

4a. Adults

TREATMENT-NAIVE ADULTS

The recommended dose for treatment-naive adults is 800 mg taken once daily, co-administered with a pharmacological enhancer such as ritonavir 100 mg once daily or cobicistat 150 mg once daily.

TREATMENT-EXPERIENCED ADULTS

In the absence of darunavir resistance mutations or in protease inhibitor-naive adults where genotypic testing is not available and the HIV viral load is < 100,000 copies/ml, darunavir can be administered once daily in a dose of 800 mg with 100 mg ritonavir boosting.

The fixed-dose combination of darunavir–cobicistat (Prezcobix) is not currently recommended in treatment-experienced adults.

In the presence of one or more major darunavir resistance mutations (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V), darunavir should be administered at a dose of 600 mg twice daily, co-administered with ritonavir. Similarly, in treatment-experienced adults with prior protease inhibitor-exposure but no available genotype testing, twice-daily dosing is recommended. In the setting of a high viral load (≥ 100,000 copies/ml) in treatment-experienced adults, twice-daily dosing is recommended (Janssen, 2015b).

4b. Newborn infants and children

Darunavir should not be used in children aged < 3 years of age , due to adverse effects, including seizures and death, as seen in juvenile rats in preclinical studies.

Darunavir is approved in both the USA and EU for the treatment of children older than 3 years of age. In Australia, darunavir is currently registered for use in children aged 6 to under 18 years. Younger children should be assessed for their ability to swallow tablets.

Pediatric dosing in treatment-experienced and -naive patients aged 3–18 years is based on data from the DELPHI, ARIEL, and DIONE trials as well as pharmacokinetic modeling and simulation data (Blanche *et al.,* 2009; Brochot *et al.,* 2015; Flynn *et al.,* 2014; Violari *et al.,* 2015). The European PENTA 2015 guidelines list darunavir as an alternative agent in children aged 3 to 12 years, and a preferred agent in children aged over 12 (Bamford *et al.,* 2015). Dosing for both treatment-naive and -experienced pediatric patients, based on DHHS (2015c) guidelines and the European Medicines Agency (EMA) (2014) assessment report, is outlined in Table 245.2 and Table 245.3. Furthermore, the PENTA guidelines recommend twice-daily dosing in children aged 3–12 due to the lack of data regarding once-daily dosing in this group.

Table 245.2. Pediatric dosing for weight > 15 kg: treatment-naive and -experienced patients without darunavir-associated mutations.

Weight	Darunavir dose	Ritonavir dose
15–< 30 kg	600 mg once daily	100 mg once daily
≥ 30–< 40 kg	675 mg once daily	100 mg once daily
≥ 40 kg	800 mg once daily	100 mg once daily

4c. Pregnant and lactating mothers

Although there are no controlled trials evaluating the dose of darunavir during pregnancy, a number of small studies have provided information.

Once-daily dosing of darunavir boosted with ritonavir (800/100 mg) in 16 pregnant women during their second and third trimesters of pregnancy and postpartum has revealed an approximately 35% decrease in total darunavir exposure during pregnancy, compared to postpartum. The decrease in the area-under-the-concentration-time curve at 24 hours (AUC_{24}) was less for unbound (active) darunavir (AUC_{24} 20–24% lower, compared to postpartum). The changes are not considered to be sufficient for the authors to recommend dose modification (Crauwels *et al.,* 2016).

Similar findings were also observed in three earlier studies. Darunavir plasma trough concentrations were measured in 20 pregnant women receiving darunavir as part of their antiretroviral regimen. The mean darunavir plasma trough concentration deceased from 3790 ng/ml in the first trimester to 1288 ng/ml (p = 0.158 vs. postpartum) in the second trimester and 1086 ng/ml (p = 0.021 vs. postpartum) in the third trimester, rising again to 2324 ng/ml postpartum (Lambert *et al.,* 2014).

Table 245.3. Pediatric dosing for weight > 15 kg: treatment-experienced patients with at least one darunavir-associated mutation.

Weight	Darunavir dose	Ritonavir dose
15–< 30 kg	375 mg twice daily	50 mg twice daily
≥ 30–< 40 kg	450 mg twice daily	60 mg twice daily
≥ 40 kg	600 mg twice daily	100 mg twice daily