was lower at < 0.1% (Janssen, 2015b). Postmarketing surveillance has uncovered additional, possible, rare cases of toxic epidermal necrosis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), and Acute generalized exanthematous pustulosis (AGEP) A case report described a patient receiving darunavir (and other medications) who may have developed DRESS (Almudimeegh *et al,* 2014).

6c. Metabolic side effects

DYSLIPIDEMIA

The most common reported grade 3 or 4 laboratory abnormality in POWER 1 and 2 was an elevated triglyceride level after 48 weeks of treatment (Clotet *et al.,* 2007), occurring in 15% of darunavir-treated patients versus 7% in the control protease inhibitor arm.

Similarly, lipid abnormalities were common in the TITAN study, with grade 2–4 abnormalities in occurring in total cholesterol in 32% versus 29%, increased triglycerides in 19% versus 25%, and increased low-density lipoprotein (LDL) in 19% versus 17% of the darunavir and lopinavir-treated comparator groups respectively (Madruga *et al.*, 2007).

In the 192-week study ARTMEMIS, 24.3% of patients in the darunavir arm had elevated total cholesterol levels that met criteria for grades 2–4 laboratory abnormalities, with LDL abnormalities in this range in 22.9% of subjects (Clotet *et al.,* 2014). These rates of dyslipidemia compared favorably with the lopinavir-containing comparator arm.

In FLAMINGO, rates of dyslipidemia in the darunavir arm were significantly higher than in the dolutegravir arm (Molina *et al.*, 2015).

A substudy of the ATADAR study comparing 86 patients starting ritonavir-boosted atazanavir or ritonavir-boosted darunavir in combination with tenofovir and emtricitabine found that at week 48 there was a mild but significant increase in total cholesterol and high-density lipoprotein levels in patients receiving either combination, with improved LDL levels in only the darunavir arm (Saumoy *et al.,* 2015).

HYPERGLYCEMIA AND INSULIN RESISTANCE

Hyperglycemia has been reported in up to 11.7% in the TITAN trial, a similar proportion to the lopinavir arm (Madruga *et al.,* 2007). Elevated pancreatic enzymes occurred in 12.2% of darunavir-treated patients (versus 10% in the lopinavir arm). Similar results were found in the POWER trial analyses (Arasteh *et al.,* 2009). Boosted darunavir in combination with tenofovir–emtricitabine in a fixed dose did not increase insulin resistance in the STRIBILD-IR study (Spinner *et al.,* 2016). In a substudy of the METABOLIK trial, both boosted darunavir and boosted atazanavir had only modest effects on insulin sensitivity (Overton *et al.,* 2016).

BONE MINERAL DENSITY

The changes in bone mineral density after 96 weeks in patients starting therapy with ritonavir-boosted darunavir or boosted atazanavir or raltegravir, in combination with tenofovir–emtricitabine, were similar for patients receiving the boosted darunavir or atazanavir regimens and greater than in patients receiving the raltegravir-based regimen (Brown *et al.,* 2015).

There is also no consistent reduction in plasma markers of inflammation, immune activation, and coagulation at 96 weeks in patients randomized to receive these regimens, despite virologic suppression (Kelesidis *et al.,* 2015). And the incidence of metabolic syndrome was approximately 22% in patient groups on these regimens (Ofotokun *et al.,* 2015).

MITOCHONDRIAL TOXICITY

In vitro studies suggest that darunavir exerts no mitochondrial toxicity when tested in hepatic cells and neurons (Blas Garcia *et al.,* 2014).

7. CLINICAL USE OF THE DRUG

Darunavir is used solely for the treatment of HIV infection, in combination with other antiretroviral agents. The use of boosted darunavir has been evaluated in both treatment-naive and treatment-experienced adults, adolescents, and children as outlined in this section. The findings from ARTEMIS and ODIN evaluating once-daily darunavir in combination with other antiretroviral drugs provided evidence for revised treatment guidelines for the use of boosted darunavir for treatment-naive and -experienced patients who harbor no darunavir-associated resistance mutations

7a. Treatment-naive adults

ARTEMIS

The use of darunavir in treatment-naive adults was studied in ARTEMIS, a phase III, open-label, randomized control trial, which reported results at 48, 96, and 192 weeks (Mills *et al.*, 2009; Orkin *et al.*, 2013; Ortiz *et al.*, 2008). Boosted darunavir was compared to boosted lopinavir, used in combination with a backbone of tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg once daily. Darunavir was dosed at 800 mg once daily, in combination with 100 mg ritonavir, whereas lopinavir was administered at a total daily dose of 800 mg, in combination with 200 mg ritonavir and was dosed either once or twice daily. The primary end point was noninferiority in terms of virological response at 48 weeks, defined as the percentage of patients achieving a viral load < 50 copies/ml. A noninferiority analysis was conducted in the per protocol population, with a predefined 12% noninferiority margin; after this criterion was met, subsequent superiority testing was performed in the intent-to-treat population. At 48 weeks, boosted darunavir was noninferior to lopinavir in terms of the proportion of patients achieving virological suppression, with 83.7% achieving this end point in the darunavir arm versus 78.3% in the lopinavir arm. Darunavir was not found to be superior to lopinavir at this time point. Subsequent followup at 96 and 192 weeks demonstrated that darunavir was significantly more effective at maintaining