Darunavir-Cobicistat-Tenofovir alafenamide-Emtricitabine (Symtuza)

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Drug Summary

The fixed-dose combination tablet darunavir-cobicistat-tenofovir alafenamide-emtricitabine is a single-tablet regimen that can be considered for treatment-naïve or certain treatment-experienced adults living with HIV. This single-tablet regimen offers a one pill daily regimen with high barrier to resistance (due to the darunavir-cobicistat), with potentially less renal and bone toxicity as compared to regimens that include tenofovir DF; however, it has potential gastrointestinal adverse effects and drug-drug interactions, primarily due to the cobicistat component. In clinical trials, darunavir-cobicistat-tenofovir alafenamide-emtricitabine was compared to darunavir-cobicistat plus tenofovir DF-emtricitabine as initial therapy for treatment-naïve individuals and found to be equally effective in terms of viral suppression. A switch to the fixed-dose combination tablet was also compared to continuing a boosted protease inhibitor plus tenofovir DF-emtricitabine and again determined to have equivalent efficacy. The FDA has approved darunavir-cobicistat-tenofovir alafenamide-emtricitabine as a complete regimen for treatment-naïve individuals or treatment-experienced individuals who have a suppressed HIV RNA level on a stable regimen for at least 6 months and no resistance to darunavir or tenofovir.

Key Clinical Trials

A phase 3 trial in treatment-naïve individuals compared the fixed-dose single-tablet regimen darunavir-cobicistat-tenofovir alafenamide-emtricitabine with the regimen darunavir-cobicistat plus tenofovir DF-emtricitabine emtricitabine [AMBER]. In this trial, 725 treatment-naïve adults were randomized in 1:1 fashion to the two arms. At week 48, the proportion with HIV RNA level below 50 copies/mL was not statistically different (91.4% in the darunavir-cobicistat-tenofovir alafenamide-emtricitabine arm and 88.4% in the darunavir-cobicistat plus tenofovir DF-emtricitabine arm). Markers of bone mineral density and renal tubule wasting were better in the group who took the single-tablet, tenofovir alafenamide-containing regimen.

A phase 3 switch study enrolled individuals taking a boosted protease inhibitor plus tenofovir DF-
emtricitabine and randomized participants to continue the regimen or switch to darunavir-cobicistat-
tenofivir alafenamide-emtricitabine [EMERALD]. Overall, 1,141 enrollees were randomized in 2:1
fashion to the switch arm versus continue baseline therapy. All participants had a suppressed HIV
RNA level and individuals were excluded if they had resistance mutations known to affect the activity
of darunavir or tenofovir (past virologic failure on a non-darunavir-containing regimen was allowed).
At 48 weeks, rates of virologic rebound were low and not statistically different between the two
arms. Overall tolerability was similar between the two groups, though markers of bone mineral
density loss and renal tubulopathy favored the tenofovir alafenamide-containing single tablet
regimen. In this study, a retrospective analysis showed that 53 individuals had a history of
lamivudine/emtricitabine resistance, but all had HIV RNA below 50 copies/mL at follow-up.

Adverse Effects

Common adverse effects with tenofovir alafenamide-emtricitabine-darunavir-cobicistat include
nausea, diarrhea, and other gastrointestinal symptoms, which commonly occur secondary to
darunavir or cobicistat. Darunavir may also cause headache, rash, elevation of hepatic
aminotransferase levels, and worsening of serum lipid levels. Darunavir contains a sulfonamide
moiety and thus should be used cautiously in individuals with a history of sulfonamide allergy.
Cobicistat blocks tubular secretion of creatinine and thereby causes a mild benign elevation of serum
creatinine and reduction of estimated GFR (with no effect on true or measured GFR). Emtricitabine
infrequently causes adverse effects. The primary advantage of tenofovir alafenamide over tenofovir
DF is reduced adverse effects related to renal proximal tubule toxicity and bone mineral density loss;
the long-term clinical significance of these differences is not yet known. For more on potential
adverse effects, see the summary for each individual component.

Use In Pregnancy

Darunavir-cobicistat-tenofovir alafenamide-emtricitabine is not recommended for use in pregnancy.

Key Drug Interactions

For complete information on darunavir-cobicistat-tenofovir alafenamide-emtricitabine-related drug
interactions, see the Drug Interactions section in the Darunavir-Cobicistat-Tenofovir alafenamide-
Emtricitabine (Symtuza) Prescribing Information.