Fostemsavir (FTR, Rukobia) (Last updated April 7, 2021; last reviewed April 7, 2021)

Formulations

Extended-release tablet: 600 mg

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Child and Adolescent Dose

- The safety and efficacy of using fostemsavir (FTR) in children and adolescents aged <18 years have not been established.

Adult Dose

- One tablet twice daily

Selected Adverse Events

- QTc prolongation with higher than recommended dosages[1]
- Increased hepatic transaminases in patients with Hepatitis B or Hepatitis C co-infection

Special Instructions

- Can be taken with or without food.
- Extended-release tablet must be swallowed whole. Do not chew, crush, or split tablets.
- Should not be co-administered with strong cytochrome P450 (CYP) 3A4 inducers of metabolism, such as rifampin, carbamazepine, phenytoin, and phenobarbital
- Potential for multiple drug interactions. Check concomitant medications before prescribing FTR.
- Tablets have slight odor similar to vinegar.

Metabolism/Elimination

- FTR tromethamine is a prodrug of temsavir (TMR), an HIV-1 gp120-directed attachment inhibitor.
- FTR is rapidly converted to TMR after oral administration. Metabolic pathways of TMR include hydrolysis (esterases) (36.1% of oral dose), oxidation (CYP3A4) (21.1% of oral dose), and UGT (<1% of oral dose).
- TMR is a substrate of CYP3A, esterases, P-glycoprotein, and breast cancer resistance protein (BCRP).
- TMR is an inhibitor of organic anion transporter (OAT) P1B1 and OATP1B3; TMR and two of its metabolites are inhibitors of BCRP.

Fostemsavir Dosing in Patients with Hepatic Impairment

- No dose adjustment is required in patients with mild to severe hepatic impairment.

Fostemsavir Dosing in Patients with Renal Impairment

- No dose adjustment is required in patients with renal impairment or those on hemodialysis.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- *Metabolism:* Co-administration with strong cytochrome P450 3A inducers is contraindicated, because the plasma concentrations of the active metabolite, temsavir (TMR), are significantly reduced which could result in loss of virologic efficacy.
- *Cardiac toxicity:* Caution when used in combination with drugs that are associated with QTc prolongation.
- *Oral contraceptives:* Do not exceed 30 mcg ethinyl estradiol daily. Combination may increase ethinyl estradiol concentrations and risk of thrombosis.
- *HMG-CoA reductase inhibitors (statins):* TMR may increase plasma concentrations of statins.
- *Other antiretroviral agents:* Etravirine may decrease TMR plasma concentrations, but when it is used in combination with a ritonavir-boosted protease inhibitor (strong inhibitor), the overall effect on TMR metabolism is negligible and does not require dose modification.

Major Toxicities

- *More common:* Nausea reported in ≥5% of patients.
- *Less common (more severe):* QTc prolongation with higher than recommended doses. Increased hepatic transaminases in patients with hepatitis B or hepatitis C co-infection.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

TMR showed reduced antiviral activity against HIV subtype AE (the predominate subtype found in Southeast Asia but not commonly found elsewhere in the world). Treatment-emergent gp120 genotypic substitutions at four key sites (S375, M434, M426, and M475) have been found in evaluable subjects with virologic failure in clinical trials.

Pediatric Use

Approval

Fostemsavir (FTR) is not approved for use in pediatric patients. FTR was approved by the Food and Drug Administration in 2020 for use in adults in combination with other antiretroviral (ARV) drugs, with approval limited to heavily treatment-experienced adults with multidrug-resistant HIV failing their current (ARV) regimen due to resistance, intolerance, or safety considerations.

A pharmacokinetic and safety study of FTR in adolescent patients is planned.

Efficacy in Clinical Trials

The safety and efficacy of FTR in heavily treatment-experienced adults living with HIV were evaluated in the BRIGHTE trial, a Phase 3, double-blind placebo-controlled trial. A total of 371 participants were enrolled into two cohorts (randomized and nonrandomized), depending on remaining treatment options.

The randomized cohort included 272 participants, with at least one fully active drug in at least one but no more than two ARV classes that could be added to FTR. Participants received either FTR or a placebo twice daily for 8 days, in addition to their failing ARV regimen. On Day 8, participants treated with FTR had a significantly greater decrease in levels of HIV-RNA compared with those taking the placebo (0.79 versus 0.17 $\log_{10}$ copies, respectively).[2] After Day 8, all participants received FTR as part of an optimized regimen. In results reported through 48 weeks,[2] 54% of participants had an HIV viral load of <40 copies/mL. At Week 96,[3] 60% of participants had HIV viral loads of <40 copies/mL and a mean increase in CD4+ counts of 205 cells/mm³. In 51% (27 out of 53) of evaluable subjects with virologic failure, treatment-emergent gp120 genotypic substitutions were detected at four key sites (S375, M434, M426, and M475).

An additional nonrandomized cohort of 99 patients who had no active drugs as treatment options but had FTR added to an optimized ARV regimen was studied. Of these, 38% achieved an HIV viral load of <40 copies/mL at 48 weeks.[2] For this cohort, at 96 weeks,[3] 37% of participants had HIV viral loads of <40 copies/mL, and the mean increase in CD4+ counts was 119 cells/mm^3.

Mechanism of Action

FTR tromethamine is a prodrug of TMR, an HIV-1 gp120-directed attachment inhibitor. FTR is rapidly converted to TMR after oral administration. TMR binds directly to the HIV-1 gp120 and prevents viral attachment and subsequent entry of virus into host T cells. FTR has a novel mechanism of action and no *in vitro* cross-resistance with other ARVs, and it can be used regardless of HIV-1 tropism.

References

1. Lagishetty C, Moore K, Ackerman P, Llamoso C, Magee M. Effects of temsavir, active moiety of antiretroviral agent fostemsavir, on QT interval: results from a Phase I study and an exposure-responses analysis. *Clin Transl Sci*. 2020;13(4):769-776. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32027457.

2. Kozal M, Aberg J, Pialoux G, et al. Fostemsavir in adults with multidrug-resistant HIV-1 infection. *N Engl J Med*. 2020;382(13):1232-1243. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32212519.

3. Food and Drug Administration. Rukobia (Fostemsavir) [package insert]. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212950s000lbl.pdf.