Fostemsavir (FTR, Rukobia)

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Formulations

Extended-release tablet: 600 mg

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Child and Adolescent (Aged <18 years) 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 (corrected QT) prolongation with higher than recommended dosages
- Increased hepatic transaminases in patients with hepatitis B or hepatitis C coinfection

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 coadministered 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 uridine diphosphate glucotransferase (UDG) (<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

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

Metabolism: Coadministration 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 is required when used in combination with drugs that are associated with prolongation of the QTc interval of the echocardiogram.

Oral contraceptives: Do not exceed 30 mcg ethinyl estradiol daily. The 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: QTc prolongation with higher than recommended doses.[1] Increased hepatic transaminases in patients with hepatitis B or hepatitis C coinfection.

Resistance

The International AIDS Society–USA maintains a list of HIV drug 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 glycoprotein (gp120) genotypic substitutions at four key sites (S375, M434, M426, and M475) have been found in evaluable subjects with virologic failure in clinical trials. However, overall frequency of polymorphisms previously associated with the potential to reduce susceptibility to TMR is low and should not be a barrier to its usage in patients with multidrug resistance. [2]

Pediatric Use

Fostemsavir (FTR) is a HIV-1 gp120-directed attachment inhibitor that is not approved for use in pediatric patients. FTR was approved by the U.S. 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.[3] A pharmacokinetic and safety study of FTR in children and adolescents ≥20 kg will soon be open to enrollment. (PENTA Foundation: NCT04648280)

Efficacy in Clinical Trials

The safety and efficacy of FTR in heavily treatment-experienced adults 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 than those taking the placebo (0.79 versus 0.17 $\log_{10}$ copies, respectively).[4] After Day 8, all participants received FTR as part of an optimized regimen. In results reported through 48 weeks,[4] 54% of participants had an HIV viral load of <40 copies/mL. At Week 96, 60% of participants[3] had HIV viral loads of <40 copies/mL and a mean increase in CD4 T lymphocyte (CD4) cell counts of 205 cells/mm^3. 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). In the randomized cohort, virologic response rates increased over time, between the 24-week and 96-week analyses. Response rates were associated with better susceptibility scores for new optimized treatment regimens.[5] Patients with the lowest CD4 counts at baseline were more likely to experience serious adverse events or death.[5]

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.[4] 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.

Improvements in patient-reported outcomes in health-related quality of life were observed among participants in both cohorts of the BRIGHTE trial at 48 weeks.[6]

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.[2]

Pharmacokinetics

FTR is pre-systemically metabolized to the active moiety TMR by alkaline phosphatase in the luminal surface of the small intestine, and then TMR is rapidly absorbed. In healthy adults, the estimated $t_{½}$ is approximately 11 hours.[7]

References

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5. Ackerman P, Thompson M, Molina JM, et al. Long-term efficacy and safety of fostemsavir among subgroups of heavily treatment-experienced adults with HIV-1. *AIDS*. 2021;35(7):1061-1072. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33946085.

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