Fostemsavir (FTR, Rukobia)

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Formulations
Extended-Release Tablet: 600 mg For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations	Selected Adverse Events
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	• QTc (QT corrected for heart rate) interval prolongation with higher-than-recommended dosages • Increased hepatic transaminases in children 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 a slight odor similar to vinegar.
	Metabolism/Elimination
	• FTR tromethamine is a prodrug of temsavir (TMR), an HIV-1 glycoprotein 120–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 (<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 OATP1B1 and OATP1B3; TMR and two of its metabolites are inhibitors of BCRP. **FTR Dosing in Children With Hepatic Impairment** • No dose adjustment is required in children with mild-to-severe hepatic impairment. **FTR Dosing in Children With Renal Impairment** • No dose adjustment is required in children 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 QT corrected for heart rate (QTc) interval of the echocardiogram.
- *Oral contraceptives and gender-affirming hormonal therapy*: TMR may increase ethinyl estradiol concentrations and risk of thrombosis. Do not exceed 30 mcg ethinyl estradiol daily when fostemsavir is co-administered with estrogen-based therapies. For gender-affirming hormonal therapy, estrogen concentrations can be monitored with dose adjustments as needed.[1]
- *3-hydroxy-3-methylglutaryl coenzyme A (or HMG-CoA) reductase inhibitors (statins):* TMR may increase plasma concentrations of statins, including rosuvastatin, atorvastatin, fluvastatin, pitavastatin, and simvastatin. Use the lowest possible starting dose of statin and monitor for statin-associated adverse effects.
- *Hepatitis C virus direct-acting antivirals:* TMR may increase plasma concentrations of grazoprevir and voxilaprevir due to organic anion transporting polypeptide OATP1B1 and OATP1B3 inhibition.
- *Other antiretroviral (ARV) agents*: Drug interaction studies of fostemsavir (FTR) in combination with darunavir/cobicistat, darunavir/ritonavir, etravirine, and maraviroc have been conducted in healthy volunteers. FTR given in combination with these other ARVs was generally well tolerated, and no dose adjustments were required.[2,3]

Major Toxicities

- *More common:* Nausea, fatigue, diarrhea (reported in ≥5% of people)
- *Less common*: QTc prolongation with higher-than-recommended doses[4]
- *Less common:* Increased hepatic transaminases in people 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 predominant subtype found in Southeast Asia but not commonly found elsewhere in the world). Treatment-emergent glycoprotein 120 (gp120) genotypic substitutions at four key sites—S375, M434, M426, and M475—have been found in evaluable participants 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 people with multidrug resistance.[5] At this time, standard HIV drug resistance testing does not include FTR.

Pediatric Use

FTR is an HIV-1 gp120-directed attachment inhibitor that is not approved for use in children. FTR was approved by the U.S. Food and Drug Administration in 2020 for use in adults in combination with other ARV drugs, with approval limited to heavily treatment-experienced adults with multidrug-resistant HIV who are experiencing virologic failure on their current regimen due to resistance, intolerance, or safety considerations.[6] A pharmacokinetic, safety, acceptability, and swallowability study of FTR in children and adolescents weighing ≥20 kg is open to enrollment (PENTA Foundation: NCT04648280). The dose selection of FTR for children and adolescents weighing ≥20 kg utilized a population pharmacokinetic model–based approach to achieve similar adult TMR exposures following FTR 600 mg twice daily dosing that was demonstrated to be safe and effective in the BRIGHTE study in heavily treatment-experienced children and adolescents.[7]

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 vs. 0.17 $\log_{10}$ copies, respectively).[8] After Day 8, all participants received FTR as part of an optimized regimen. In results reported through 48 weeks,[8] 54% of participants had an HIV viral load of <40 copies/mL. At Week 96, 60% of participants[6,9] 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 participants 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.[10] Participants with the lowest CD4 counts at baseline were more likely to experience serious adverse events or death.[10] 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.[11]

An additional nonrandomized cohort of 99 adults 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.[8] For this cohort, at 96 weeks,[6] 37% of participants had HIV viral loads of <40 copies/mL, and the mean increase in CD4 counts was 119 cells/mm^3.

Recently, long-term efficacy and safety of FTR plus optimized therapy at 240 weeks has been reported for participants enrolled in the Phase 3 BRIGHTE study. Durable virologic responses were observed with no new safety concerns.[12,13]

The real-world OPERA prospective cohort study, using a large database of electronic medical records, was conducted in the United States in 182 heavily treatment-experienced adults who initiated therapy with FTR and were followed for up to 1 year.[14] Most participants virologically suppressed at FTR initiation were able to maintain suppression regardless of CD4 count at start. Only 52% of participants viremic at initiation with CD4 counts ≥350 cells/mm^3 achieved viral suppression, and only 33% of those with CD4 counts <350 cells/mm^3 achieved viral suppression.[14] Immunologic responses were variable, but improvements were seen in CD4 counts (increase of 66 cells/ mm^3) among participants who were virologically suppressed with low CD4 counts at initiation.[14]

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.[5]

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 half-life is approximately 11 hours.[15,16]

FTR has a novel mechanism of action, lacks significant drug–drug interactions with other ARVs, and does not require dosage adjustment in people with renal or hepatic impairment.[16] The PENTA study "Safety and Pharmacokinetics Evaluation of Fostemsavir + (OBT) in HIV-1 Infected Children and Adolescents Who Are Failing Their CART and Have Dual- or Triple-Class Antiretroviral Resistance" is currently recruiting participants.

References

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