PDL DRUG REVIEW

Proprietary Name: Rukobia®
Common Name: fostemsavir tromethamine, extended release
PDL Category: Antiretrovirals

Comparable Products	Preferred Drug List Status
Trogarzo	Medical Coverage

Summary

Pharmacology/Usage: Fostemsavir tromethamine, the active ingredient of Rukobia®, is a prodrug of temsavir, an HIV-1 gp120-directed attachment inhibitor. Fostemsavir is a prodrug without significant biochemical or antiviral activity that is hydrolyzed to the active moiety, temsavir. Temsavir is an antiretroviral agent that binds directly to the gp120 subunit within the HIV-1 envelope glycoprotein gp160 and selectively inhibits the interaction between the virus and cellular CD4 receptors, thus preventing attachment. In addition, temsavir can inhibit gp120-dependent post-attachment steps required for viral entry into host cells.

Indication: In combination with other antiretroviral(s) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

There is no pregnancy category for this medication; however, the risk summary indicates that there are not sufficient human data on the use during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage. There is a pregnancy exposure registry that monitors pregnancy outcomes in those exposed to Rukobia® during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film Coated Tablets, Extended Release: 600mg fostemsavir (equivalent to 725mg fostemsavir tromethamine). Do not chew, crush or split tablets. Swallow whole.

Recommended Dosage: Take 600mg PO BID with or without food.

Dose adjustments are not required with hepatic impairment or renal impairment, or those on hemodialysis.

Drug Interactions: Refer to the contraindications section for a list of drugs contraindicated with Rukobia® use.

Exposures of grazoprevir or voxilaprevir may increase if use concomitantly with Rukobia®; however, the magnitude of increase in exposure is not known. Increased exposures of grazoprevir may increase the risk of ALT elevations. Use an alternative hepatitis C virus regimen if possible.

Concentrations of ethinyl estradiol, a component of oral contraceptives, may increase if used concomitantly with Rukobia®. Ethinyl estradiol daily dose should not exceed 30mcg, and caution is advised especially in patients with additional risk factors for thromboembolic events.

Statin concentrations, including rosuvastatin, atorvastatin, fluvastatin, pitavastatin, and simvastatin, may increase if use concomitantly with Rukobia®. Use the lowest possible starting dose for statins and monitor for statin-associated adverse events if use concomitantly with Rukobia®.

Coadministration of Rukobia® with a drug with a known risk of Torsade de Pointes may increase the risk of Torsade de Pointes. Use Rukobia® with caution when co-administered with drugs with a known risk of Torsade de Pointes.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Rukobia®) plus optimized background therapy (OBT).* The most frequently reported adverse events included nausea (10%), diarrhea (4%), headache (4%), abdominal pain (3%), dyspepsia (3%), fatigue (3%), rash (3%), sleep disturbance (3%), immune reconstitution inflammatory syndrome (2%), somnolence (2%), and vomiting (2%).

Laboratory abnormalities included ALT >5.0X upper limit of normal (ULN; 5%), AST >5X ULN (4%), direct bilirubin >ULN (7%), bilirubin ≥2.6X ULN (3%), cholesterol ≥300mg/dl (5%), creatinine >1.8X ULN or 1.5X baseline (19%), creatine kinase ≥10X ULN (2%), hemoglobin <9g/dL (6%), hyperglycemia >250mg/dL (4%), lipase >3X ULN (5%), LDL cholesterol ≥190mg/dL (4%), neutrophils ≤599 cells/mm^3 (4%), triglycerides >500mg/dL (5%), and urate >12mg/dL (3%).

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including Rukobia®. Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barre syndrome, and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after the start of treatment.

Rukobia® at 4 times the recommended daily dose has been shown to significantly prolong the QTc interval of the electrocardiogram. Rukobia® should be used with caution in patients with a history of QTc interval prolongation, when co-administered with a drug with a known risk of Torsade de Pointes, or in patients with relevant pre-existing cardiac disease. Elderly patients may be more susceptible to drug-induced QT interval prolongation.

Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection. Elevations in hepatic transaminases were seen in a greater proportion of subjects with HBV and/or HCV co-infection compared with those with HIV mono-infection.

Contraindications: In patients:

- With previous hypersensitivity to fostemsavir or any components of the product
- Co-administered strong P450 CYP3A inducers, including but not limited to
    - Androgen receptor inhibitor: enzalutamide
    - Anticonvulsants: carbamazepine, phenytoin
    - Antimycobacterial: rifampin
    - Antineoplastic: mitotane
    - Herbal products: St. John's wort

Manufacturer: ViiV Healthcare Company

Analysis: The efficacy of Rukobia® in heavily treatment-experienced adults with HIV-1 infection was based on 96-week data from a phase 3, partially randomized, international, double-blind, placebo-controlled trial (BRIGHTE) that included heavily treatment-experienced subjects with multi-class HIV-1 resistance. All adults were required to have a viral load ≥400 copies/ml and ≤2 classes of antiretroviral medications remaining at baseline due to resistance, intolerance, contraindication, or other safety concerns. Subjects were enrolled in either a randomized or non-randomized cohort defined as follows:

- In the randomized cohort (N=272), subjects had 1 but no more than 2, fully active and available antiretroviral agent(s) at screening which could be combined as part of an efficacious background regimen. Subjects were randomized to either blinded Rukobia® or placebo in addition to their current failing regimen for 8 days of functional monotherapy. Beyond 8 days, randomized adults received open-label Rukobia® plus an investigator-selected optimized background therapy (OBT). This cohort provides primary evidence of efficacy of Rukobia®.

- In the non-randomized cohort (N=99), subjects had no fully active and approved antiretroviral agent(s) available at screening. Non-randomized subjects were treated with open-label Rukobia® plus OBT from day 1 onward. The use of an investigational drug(s) as a component of the OBT was permitted in this cohort.

Of the included adults, the median age was 49 years (range 17 to 73 years), while most were male (78%) and white (70%). At baseline, the median HIV-1 RNA was 4.6 $\log_{10}$ copies/ml and the median CD4+ cell count was 80 cells/mm^3 (100 and 41 cells/mm^3 for randomized and non-randomized subjects, respectively). In addition, 75% of all treated subjects had a CD4+ cell count <200 cells/mm^3 at baseline, 86% had a history of AIDS, 8% had a history of hepatitis B and/or C virus co-infection at baseline, and 71% had been treated for HIV for >15 years.

Of the randomized cohort, 52% had 1 fully active agent within their initial failing background regimen, 42% had 2, and 6% had no fully active agent. Within the non-randomized cohort, 81% had no fully active agent(s) in their original regimen and 19% had 1 fully active agent.

The primary efficacy endpoint in the randomized cohort was the adjusted mean decline in HIV-1 RNA from day 1 to day 8 with Rukobia® versus placebo. Results demonstrated the superiority of Rukobia® as compared with placebo ($p<0.0001$). Results can be seen in the table below, which was adapted from the prescribing information.

Plasma HIV1 RNA log 10 change from day 1 to day 8	Rukobia® (N=201)	Placebo (N=69)
Adjusted mean	-0.791	-0.166
Difference (Rukobia® minus placebo)	-0.625	

At day 8, 65% (N=131/203) and 46% (N=93/203) of subjects who received Rukobia® had a reduction in viral load from baseline >0.5 $\log_{10}$ copies/ml and >1 $\log_{10}$ copies/ml, respectively, compared with 19% (N=13/69) and 10% (N=7/69) of subjects, respectively, in the placebo group.

By subgroup analysis, randomized subjects who received Rukobia® with baseline HIV RNA >1000 copies/ml achieved a mean decline in viral load of 0.86 $\log_{10}$ copies/ml at day 8 compared with 0.2 $\log_{10}$ copies/ml in subjects treated with blinded placebo. Subjects with baseline HIV-1 RNA ≤1000 copies/ml achieved a mean decline in viral load of 0.22 $\log_{10}$ copies/ml at day 8 compared with a mean increase of 0.1 $\log_{10}$ copies/ml in subjects treated with blinded placebo.

Virologic outcomes by ITT-E population snapshot analysis at weeks 24 and 96 can be seen in the table below for the randomized cohort, which was adapted from the prescribing information. Most subjects (84%) received dolutegravir as a component of OBT, of which about 51% overall also received darunavir with ritonavir or cobicistat. Virologic outcomes by ITT-E snapshot analysis at week 48 were consistent with those seen at week 24.

	Rukobia® 600mg BID plus OBT	
	Week 24 (N=272)	Week 96 (N=272)
HIV-1 RNA <40 copies/ml	53%	60%
HIV-1 RNA ≥40 copies/ml	40%	30%
Data in window not <40 copies/ml	32%	12%
Discontinued for lack of efficacy	<1%	4%
Discontinued for other reasons while not suppressed	1%	6%
Change in antiretroviral treatment regimen	6%	8%

	Rukobia® 600mg BID plus OBT	
	Week 24 (N=272)	Week 96 (N=272)
No virologic data	7%	10%
Reasons:		
Discontinued study/study drug due to adverse event or death	4%	6%
Discontinued study/study drug for other reasons	2%	3%
Missing data during window but on study	1%	2%

The following table includes virologic outcomes (HIV-1 RNA <40 copies/ml) by baseline covariates at weeks 24 and 96 in the ITT-E population, snapshot algorithm for the randomized cohort.

	Rukobia® 600mg BID plus OBT	
	Week 24 (N=272)	Week 96 (N=272)
Baseline plasma viral load (copies/ml)		
<100,000	60% (116/192)	65% (124/192)
≥100,000	35% (28/80)	49% (39/80)
Baseline CD4+ (cells/mm^3)		
<20	32% (23/73)	46% (33/72)
20 to <50	48% (12/25)	56% (14/25)
50 to <200	58% (59/102)	61% (62/102)
≥200	68% (50/73)	74% (54/73)
# of fully active & available antiretroviral classes in initial background regimen		
0	31% (5/16)	19% (3/16)
1	56% (80/142)	65% (92/142)
2	52% (59/114)	60% (68/114)
Use of dolutegravir (DTG) and darunavir (DRV) as a component of OBT		
DTG and DRV	58% (68/117)	64% (75/117)
With DTG, without DRV	54% (61/112)	63% (71/112)
Without DTG, with DRV	29% (5/17)	47% (8/17)
Without DTG/DRV	38% (10/26)	35% (9/26)
Gender		
Male	52% (104/200)	59% (118/200)

	Rukobia® 600mg BID plus OBT	
	Week 24 (N=272)	Week 96 (N=272)
Female	56% (40/72)	63% (45/72)
Race		
White	49% (90/185)	56% (103/185)
Black or African American/Others	62% (54/87)	69% (60/87)
Age (years)		
<50	50% (81/162)	59% (96/162)
≥50	57% (63/110)	61% (67/110)

In the randomized cohort, HIV-1 RNA <200 copies/ml was achieved in 68% and 64% of subject at weeks 24 and 96, respectively. Mean changes in CD4+ cell count from baseline increased over time, including 90 cells/mm^3 at week 24 and 205 cells/mm^3 at week 96.

In the non-randomized cohort, HIV-1 RNA <40 copies/ml was achieved in 37% of subjects at week 24 and 96. At these timepoints, the proportion of subjects with HIV-1 RNA <200 copies/ml was 42% and 39%, respectively. Mean changes in CD4+ cell count from baseline increased over time, including 41 cells/mm^3 at week 24 and 119 cells/mm^3 at week 96.

Place in Therapy: Rukobia®, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations. In a double-blind, randomized cohort, Rukobia® demonstrated superiority over placebo for the primary endpoint of adjusted mean decline in HIV-1 RNA from day 1 to day 8 in a population infected with HIV-1 and current regimen failure. Rukobia® should be used with caution in patients with a history of QTc interval prolongation, when co-administered with a drug with a known risk of Torsade de Pointes, or in patients with relevant pre-existing cardiac disease.

It is recommended that Rukobia® should be non-recommended as it is not a first-line therapy.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended**

References

[1] Rukobia [package insert]. Research Triangle Park, NC: ViiV Healthcare; 2020.