RXADVANCE
2 Park Central Drive
Southborough, MA 01772

NEW DRUG APPROVAL

Brand Name	Rukobia™
Generic Name	fostemsavir
Drug Manufacturer	GlaxoSmithKline

New Drug Approval

FDA Approval Date: July 2, 2020
Review Designation: Priority
Type of Review: New Drug Application 212950

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Acquired immunodeficiency syndrome (AIDS) is a chronic, potentially life-threatening condition caused by the human immunodeficiency virus (HIV). By damaging your immune system, HIV interferes with your body's ability to fight infection and disease.

HIV is a sexually transmitted infection (STI). It can also be spread by contact with infected blood or from mother to child during pregnancy, childbirth or breast-feeding. Without medication, it may take years before HIV weakens your immune system to the point that you have AIDS.

HIV-1 is the most common type of Human Immunodeficiency Virus. It attacks your body's immune system. The virus destroys CD4 cells. These cells help your body fight infections.

Since the beginning of the epidemic, 76 million people have been infected with the HIV virus and about 33 million people have died of HIV/AIDS. Globally, 38.0 million [31.6–44.5 million] people were living with HIV at the end of 2019. An estimated 0.7% [0.6-0.9%] of adults aged 15–49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. The WHO African region remains most severely affected, with nearly 1 in every 25 adults (3.7%) living with HIV and accounting for more than two-thirds of the people living with HIV worldwide.

Efficacy

The efficacy of RUKOBIA in heavily treatment-experienced adult subjects with HIV-1 infection is based on 96-week data from a Phase 3, partially-randomized, international, double-blind, placebo-controlled trial (BRIGHTE [NCT02362503]).

The BRIGHTE trial was conducted in 371 heavily treatment-experienced subjects with multiclass HIV-1 resistance. All subjects were required to have a viral load 400 copies/mL and classes of antiretroviral medications remaining at baseline due to resistance, intolerability, contraindication, or other safety concerns. Subjects were enrolled in either a randomized or nonrandomized cohort defined as follows: Within 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. Randomized subjects received either blinded RUKOBIA 600 mg twice daily (n = 203) or placebo (n = 69) in addition to their current failing regimen for 8 days of functional monotherapy. Beyond Day 8, randomized subjects received open label RUKOBIA 600 mg twice daily plus an investigator-selected OBT.

This cohort provides primary evidence of efficacy of RUKOBIA. Within the nonrandomized cohort (n = 99), subjects had no fully active and approved antiretroviral agent(s) available at screening. Nonrandomized subjects were treated with 23 Reference ID: 4635448 open-label RUKOBIA 600 mg twice daily plus OBT from Day 1 onward. The use of an

investigational drug(s) as a component of the OBT was permitted in the nonrandomized cohort. Overall, the majority of subjects were male (78%), white (70%), and the median age was 49 years (range: 17 to 73 years). At baseline, the median HIV-1 RNA was 4.6 log10 copies/mL and the median CD4+ cell count was 80 cells/mm3 (100 and 41 cells/mm3 for randomized and nonrandomized subjects, respectively). Seventy-five percent (75%) of all treated subjects had a CD4+ cell count 15 years; 85% had been exposed to 5 different HIV treatment regimens upon entry into the trial. Fifty-two percent (52%) of subjects in the randomized cohort had 1 fully active agent within their initial failing background regimen, 42% had 2, and 6% had no fully active agent. Within the nonrandomized cohort, 81% of subjects had no fully active agent(s) in their original regimen and 19% had 1 fully active agent, including 15% (n = 15) who received ibalizumab, which was an investigational agent at the time of the BRIGHTE trial start-up.

Safety

ADVERSE EVENTS

The most common adverse reaction (all grades) observed in 5% of subjects was nausea.

WARNINGS & PRECAUTIONS

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapies.

QTc prolongation: Use RUKOBIA with caution in patients with a history of QTc prolongation or with relevant pre-existing cardiac disease or who are taking drugs with a known risk of Torsade de Pointes.

Elevations in hepatic transaminases in patients with hepatitis B or C virus co-infection: Elevations in hepatic transaminases were observed in a greater proportion of subjects with HBV and/or HCV co-infection compared with those with HIV mono-infection.

CONTRAINDICATIONS

Hypersensitivity to fostemsavir or any of the components of the formulation.

Coadministration with strong cytochrome P450 (CYP)3A inducers as significant decreases in temsavir plasma concentrations may occur, which may result in loss of virologic response

Clinical Pharmacology

MECHANISMS OF ACTION

RUKOBIA is an HIV-1 antiretroviral agent. Fostemsavir is a prodrug without significant biochemical or antiviral activity that is hydrolyzed to the active moiety, temsavir, which is an HIV-1 attachment inhibitor. Temsavir 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, thereby preventing attachment. Additionally, temsavir can inhibit gp120-dependent post-attachment steps required for viral entry 17 Reference ID: 4635448 into host cells. Temsavir inhibited the binding of soluble CD4 to surface immobilized gp120 with an IC50 value of 14 nM using an enzyme-linked immunosorbent assay (ELISA).

Dose & Administration

ADULTS

One 600 mg tablet taken orally twice daily with or without food.

PEDIATRICS

The safety and effectiveness of RUKOBIA have not been established in pediatric patients.

GERIATRICS

Clinical trials of RUKOBIA did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in administration of RUKOBIA in elderly patients reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

RENAL IMPAIRMENT

No dosage adjustment is required for patients with renal impairment or those on hemodialysis.

HEPATIC IMPAIRMENT

No dosage adjustment is required in patients with mild to severe hepatic impairment (Child-Pugh Score A, B, or C).

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Extended-release tablets: 600 mg