<table>
<thead>
<tr>
<th>Application Type</th>
<th>NDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application Number</td>
<td>212950</td>
</tr>
<tr>
<td>PDUFA Goal Date</td>
<td>July 7, 2020</td>
</tr>
<tr>
<td>OSE RCM #</td>
<td>2019-2484; 2019-2486</td>
</tr>
<tr>
<td>Reviewer Name(s)</td>
<td>Till Olickal, Ph.D., Pharm.D.</td>
</tr>
<tr>
<td>Team Leader</td>
<td>Naomi Boston, Pharm.D.</td>
</tr>
<tr>
<td>Division Director</td>
<td>Cynthia LaCivita, Pharm.D.</td>
</tr>
<tr>
<td>Review Completion Date</td>
<td>June 22, 2020</td>
</tr>
<tr>
<td>Subject</td>
<td>Review to determine if a REMS is necessary</td>
</tr>
<tr>
<td>Established Name</td>
<td>fostemsavir</td>
</tr>
<tr>
<td>Trade Name</td>
<td>Rukobia</td>
</tr>
<tr>
<td>Name of Applicant</td>
<td>ViiV Healthcare Co</td>
</tr>
<tr>
<td>Therapeutic Class</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>Formulation(s)</td>
<td>600 mg Extended-release tablets</td>
</tr>
<tr>
<td>Dosing Regimen</td>
<td>The recommended dose is 600-mg tablet taken orally twice daily with or without food.</td>
</tr>
</tbody>
</table>
# Table of Contents

EXECUTIVE SUMMARY ......................................................................................................................................................... 3

1 Introduction..................................................................................................................................................................... 3

2 Background.................................................................................................................................................................. 4
    2.1 Product Information ........................................................................................................................................... 4
    2.2 Regulatory History ........................................................................................................................................... 4

3 Therapeutic Context and Treatment Options .................................................................................................... 4
    3.1 Description of the Medical Condition .......................................................................................................... 4
    3.2 Description of Current Treatment Options ............................................................................................... 5

4 Benefit Assessment....................................................................................................................................................... 6

5 Risk Assessment & Safe-Use Conditions .............................................................................................................. 7

6 Expected Postmarket Use........................................................................................................................................... 9

7 Risk Management Activities Proposed by the Applicant .............................................................................. 9

8 Discussion of Need for a REMS .............................................................................................................................. 10

9 Conclusion & Recommendations .......................................................................................................................... 10

10 References ...................................................................................................................................................................... 11
EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity fostemsavir (Rukobia) is necessary to ensure the benefits outweigh its risks. ViiV Healthcare Co submitted a New Drug Application (NDA) 212950 for fostemsavir with the proposed 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. The serious risks associated with the use of fostemsavir are immune reconstitution syndrome, QTc prolongation with higher than recommended dosages, elevations in hepatic transaminases in patients with hepatitis B or C virus co-infection and risk of adverse reactions or loss of virologic response due to drug interactions. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information, and a Patient Package Insert (patient labeling or PPI).

Division of Risk Management (DRM) and Division of Antiviral (DAV) have determined that if approved, a REMS is not necessary to ensure the benefits of fostemsavir outweigh its risks. HIV, the virus that causes AIDS, is a serious global public health challenge. The standard of care in HIV management is to maximally suppress plasma HIV RNA to prevent HIV disease progression and the emergence of drug-resistant virus. Achieving virologic suppression can be difficult for HIV-infected patients with drug-resistant virus. Treatment failure may result in selection of virus with resistance to one or more ART agents. Heavily treatment-experienced (HTE) patients are failing their current ART regimen, have MDR virus, and have few remaining therapeutic options. Despite the availability of different classes of ART agents providing a variety of treatment options, treatment failure continues to occur as a result of ART drug resistance, drug-associated toxicity and tolerability problems, and poor adherence. Therefore, new alternative modalities of medical treatment with improved long-term safety and efficacy are still needed beyond the existing medical therapies for the HTE population. In the clinical trial, fostemsavir appeared efficacious in both its primary outcome of decline in HIV RNA and supportive efficacy outcome of durability of antiviral response at weeks 24 and 96. Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of fostemsavir in combination with other antiretroviral(s), for the treatment of HIV-1 infection in HTE adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations. The most concerning adverse reactions observed with the use of fostemsavir are immune reconstitution syndrome, QTc prolongation with higher than recommended dosages, elevations in hepatic transaminases in patients with hepatitis B or C virus co-infection and risk of adverse reactions or loss of virologic response due to drug interactions. If fostemsavir is approved, labeling, which will include Warnings and Precautions, Patient Counseling Information to be included in section 17, and in the PPI will be used to communicate the safety issues and management of toxicities associated with fostemsavir.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) fostemsavir (Rukobia) is necessary to ensure the benefits outweigh its risks. ViiV Healthcare Co submitted a New Drug Application (NDA) 212950 for fostemsavir with the proposed 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. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information and a Patient Package Insert (patient labeling or PPI).

2 Background

2.1 PRODUCT INFORMATION

Fostemsavir (FTR) is an NME NDA type 505(b)(1) pathway application. It is a prodrug of temsavir (TMR), an HIV-1 attachment inhibitor, a first-in-class drug. Temsavir binds directly to the glycoprotein, gp120 subunit within the HIV-1 envelope gp160 and selectively inhibits the interaction between the virus and cellular CD4 receptors, thereby preventing attachment, subsequent viral entry into, and infection of, host cells. Fostemsavir will be supplied as 600 mg extended-release tablets. The recommended dose is 600-mg tablet taken orally twice daily with or without food. Fostemsavir was granted fast track designation on February 16, 2011 and breakthrough therapy designation on June 24, 2015. Fostemsavir is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for fostemsavir (NDA 212950) relevant to this review:

- 11/08/2005: Investigation New Drug IND 073916 submission for fostemsavir was received.
- 02/16/2011: Fast track designation granted
- 06/24/2015: Breakthrough therapy designation
- 10/08/2019: NDA 212801 submission for fostemsavir with the proposed indication in combination with other antiretroviral(s), for the treatment of 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, received.
- 03/12/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for fostemsavir.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

HIV, the virus that causes acquired immunodeficiency syndrome (AIDS), is a serious global public health challenge. There were approximately 37.9 million people across the globe with HIV/AIDS in 2018. Of

---

a Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

b Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

c Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.
these, 36.2 million were adults and 1.7 million were children (<15 years old). An estimated 1.7 million individuals worldwide became newly infected with HIV in 2018. In the United States (US), approximately 1.1 million people are living with HIV today. About 14% of them (1 in 7) don’t know that they were infected and need testing. In 2018, 37,832 people received an HIV diagnosis in the U.S. and 6 dependent areas. An estimated 38,000 new HIV infections still occur in the United States each year. In 2017, there were 16,350 deaths among adults and adolescents with diagnosed HIV in the United States and 6 dependent areas.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

HIV attacks and destroys the infection-fighting CD4 cells of the immune system. Loss of CD4 cells makes it hard for the body to fight off infections. The most significant advance in the medical management of HIV-1 infection has been the treatment of patients with antiviral drugs, which can suppress HIV-1 replication to undetectable levels. The treatment for HIV is called antiretroviral therapy (ART) involves taking a combination of HIV medicines called an HIV treatment regimen, every day. The Department of Health and Human Services guideline for the Use of Antiretroviral Agents in Adults and Adolescent with HIV recommend antiretroviral therapy in all patients with HIV infection. With the advent of highly active antiretroviral therapy (HAART), HIV-1 infection is now manageable as a chronic disease in patients who have access to medication and who achieve durable virologic suppression. Treatment with antiretroviral drugs decreases the morbidity and mortality associated with HIV infection. Since 1987, a large number of antiretroviral drugs have been approved by the FDA for the treatment of HIV infection, with over 22 drugs in 8 mechanistic classes, such as nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors (INSTIs), fusion inhibitors (FIs), chemokine receptor antagonists (CCR5 antagonists), entry inhibitors (CD4-directed post-attachment inhibitors) and pharmacokinetic enhancers and over 22 drugs as combination HIV medicines contain two or more HIV medicines from one or more drug classes.

The standard of care in HIV management is to maximally suppress plasma HIV RNA to prevent HIV disease progression and the emergence of drug-resistant virus. Achieving virologic suppression can be difficult for HIV-infected patients with drug-resistant virus. There is no standard definition of antiretroviral treatment failure: failure can be defined by clinical, immunologic, or virologic measures. However, since the effect of antiretroviral therapy is to reduce viral load, the success of antiretroviral treatment is defined most specifically by viral suppression. Treatment failure may result in selection of virus with resistance to one or more ART agents. Designing a new regimen for patients who are experiencing treatment failure should always be guided by ART history and results from current and past resistance testing. Estimating the prevalence of heavily treatment-experienced (HTE) patients among the HIV-infected population is challenging due to lack of a standardized definition for HTE, and the inherent heterogeneity of this subset of patients. When constructing a new regimen in the setting of virologic failure, the potential reasons for failure should be considered, including adverse effects, exacerbation of comorbidities, drug interactions, pill burden, and dosing frequency, all of which can affect adherence. HTE patients that are failing their current ART regimen and have MDR virus, have few remaining therapeutic options. Based on the concern that incomplete viral suppression will lead to the emergence of drug resistance, current guidelines recommend that therapy be switched as soon as virologic failure is confirmed, and that complete viral suppression remain the immediate goal of therapy.

\[\text{Reference ID: 4628964}\]
Many patients, however, do not have enough sufficiently potent agents remaining to achieve durable viral suppression. The ART drugs most frequently used for advanced salvage therapy are ritonavir-boosted darunavir, dolutegravir, etravirine, maraviroc, and enfuvirtide. Ibalizumab is a recently approved anti-CD4 monoclonal antibody that is administered every two weeks by intravenous infusion, with a targeted indication for use in HTE adults with MDR HIV-1 infection who are failing their current ARV regimen. The optimal therapeutic approach to virologic failure remains unclear. One of the central unanswered questions pertains to the virologic goal of therapy in pre-treated patients with limited therapeutic options.

Despite the availability of different classes of ART agents providing a variety of treatment options, treatment failure continues to occur as a result of ART drug resistance, drug-associated toxicity and tolerability problems, and poor adherence. Therefore, new alternative modalities of medical treatment with improved long-term safety and efficacy are still needed beyond the existing medical therapies for the HTE population.

4 Benefit Assessment

The efficacy and safety of fostemsavir was evaluated in heavily treatment-experienced adult subjects living with HIV is based on 96-week data from a Phase 3 study (205888), partially-randomized, international, double-blind, placebo-controlled trial (BRIGHTE; NCT02362503). The study was conducted in 371 heavily treatment-experienced subjects with multi-class HIV-1 resistance. All subjects were required to have a viral load ≥400 copies/mL and ≤2 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. 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. Randomized subjects received either blinded fostemsavir 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 fostemsavir 600 mg twice daily plus an investigator-selected optimized background therapy (OBT). This cohort provides primary evidence of efficacy of fostemsavir. In the nonrandomized cohort (n = 99), subjects had no fully active and approved antiretroviral agent(s) available at screening. Nonrandomized subjects were treated with open-label fostemsavir 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. This cohort provides additional safety data with fostemsavir.

At the time of this review, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for fostemsavir. The primary endpoint analysis, based on the adjusted mean decline in HIV-1 RNA from Day 1 at Day 8 in the randomized cohort, demonstrated superiority of fostemsavir to placebo as shown in Table 1 (0.79 vs. 0.17 log₁₀ copies/mL decline, respectively; \( P<0.0001 \), Intent-to-Treat-Exposed [ITT-E] population). At Day 8, 65% (131/203) and 46% (93/203) of subjects who received fostemsavir had a reduction in viral load from baseline >0.5 log₁₀ copies/mL and >1 log₁₀ copies/mL, respectively, compared with 19% (13/69) and 10% (7/69) of subjects, respectively, in the placebo group.

*Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*
Table 1. Plasma HIV-1 RNA Log10 (copies/mL) Change from Day 1 at Day 8 (Randomized Cohort) in BRIGHTE Trial – ITT-E Population¹,²,³

<table>
<thead>
<tr>
<th>Randomized Treatment</th>
<th>n</th>
<th>Adjusted Mean⁴ (95% CI)</th>
<th>Difference⁵ (95% CI)</th>
<th>P-value⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fostemsavir 600 mg twice daily</td>
<td>201</td>
<td>-0.791 (-0.885, -0.698)</td>
<td>-0.625 (-0.810, -0.441)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>69</td>
<td>-0.166 (-0.326, -0.007)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

¹ Mean adjusted by Day 1 log₁₀ HIV-1 RNA.
² Difference: fostemsavir minus placebo.
³ Mean value of viral load change from baseline (fostemsavir = placebo).
⁴ Two subjects who received fostemsavir with missing Day 1 HIV-1 RNA values were not included in the analysis.

The key supportive efficacy endpoint was the durability of antiviral response at weeks 24 and 96. In the randomized cohort, HIV-1 RNA <200 copies/mL was achieved in 68% and 64% of subjects at weeks 24 and 96, respectively. Mean changes in CD4+ cell count from baseline increased over time: 90 cells/mm³ at week 24 and 205 cells/mm³ at week 96. In the non-randomized cohort, HIV-1 RNA <40 copies/mL was achieved in 37%, of subjects at weeks 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: 41 cells/mm³ at Week 24 and 119 cells/mm³ at week 96.¹,²,³,⁵

5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were ongoing with the applicant. The following section is a summary of relevant safety information to date for fostemsavir. The safety analysis of fostemsavir primarily focuses on data of 96 weeks from a Phase 3 Study (205888) partially randomized, international, multicenter, double-blind, placebo-controlled trial (BRIGHTE; NCT02362503) conducted in 371 heavily treatment-experienced adult subjects (see Section 4: Benefit Assessment).¹ A total of 370 subjects (271 randomized and 99 nonrandomized) received at least 1 dose of fostemsavir 600 mg twice daily in the BRIGHTE trial.¹

The most common adverse reaction (all grades) observed in ≥5% of subjects was nausea.¹

Deaths

A total of 30 deaths have been reported under the FTR clinical development program, one subject died during screening period, prior to randomization (lymphoma) and another subject randomized to placebo, who died before starting open-label FTR due to pneumonia. Out of 28 deaths one event was considered as treatment-related due to immune reconstitution inflammatory syndrome (IRIS) (See Section on IRIS). The majority of these fatalities occurred in Phase 3 Study with the most common causes of death related to complications of malignancies and acute infections. Out of 28 deaths, 20 had baseline CD4 cell count < 50 cells and 5 subjects died after discontinuing from the study were non-treatment-emergent events. Out of 28 deaths, 13 death were due to infection/sepsis, 8 deaths were due to complications of malignancies, 5 deaths were due to organ failure such as CV disorder, hepatic/renal failure and 2 deaths were reported as progressive multifocal leukoencephalopathy and IRIS.
Serious Adverse Events (SAE)

Overall, most (81%) of the adverse reactions reported with fostemsavir were mild or moderate in severity. The proportion of subjects who discontinued treatment with fostemsavir due to an adverse event was 7% at Week 96 (randomized: 5% and nonrandomized: 12%). The most common adverse events leading to discontinuation were related to infections (3% of subjects receiving fostemsavir). Serious drug reactions occurred in 3% of subjects and included three cases of severe immune reconstitution inflammatory syndrome.1

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 IMMUNE RECONSTITUTION SYNDROME

In Study 205888 (n=370), 8 (2%) patients had experienced an IRIS event; six out of 8 were in randomized and 2 were in nonrandomized cohorts. One of the cases was fatal, Grade 4 due to atypical mycobacteria infection. Three of these events, including the fatal event were reported as SAEs as Grade 3, due to cerebral toxoplasmosis and due to past John Cunningham (JC) virus (CNS lesions), respectively. Of the remaining 5 nonserious reports, one case due to Grade 2 cryptococcal meningitis and HCV, 2nd case was due to Grade 2 CMV (retinitis/colicitis) and cerebral toxoplasmosis, 3rd case was due to Grade 2 PML, 4th case was due to Grade 3 PML and bacterial pneumonia and 4th case was due to Grade 2 folliculitis. The clinical reviewer stated that IRIS reactions are expected to occur in the HTE population when treated with effective ART, including FTR reactions vary in severity but are often severe or life-threatening.18 The labeling instructs that during the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves’ disease, polymyositis, and Guillain-Barré syndrome) 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 initiation of treatment. If approved, the risk of IRIS will likely be communicated with in the Warnings and Precautions section of the label.1

5.2 QTc PROLONGATION WITH HIGHER THAN RECOMMENDED DOSAGES

Although no cardiac arrhythmias were reported in the nonclinical safety pharmacology studies, QTc prolongation was detected in vivo in the telemetered dog study. At a 600 mg BID FTR dose selected for Phase 3 Study 205888, the estimated QTc prolongation risk was 3.2 msec and with a PK enhancer was 5.0 msec. Fostemsavir at 2,400 mg twice daily, which is 4 times the recommended daily dose, has been shown to significantly prolong the QTc interval of the electrocardiogram. The labeling instructs that fostemsavir 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 and also stated that elderly patients may be more susceptible to drug-induced QT interval prolongation. If approved, the risk of QTc prolongation will likely be communicated with in the Warnings and Precautions section of the label.1
5.3 **Elevations in Hepatic Transaminases in Patients with Hepatitis B or C Virus Co-infection**

The majority of laboratory abnormalities were low-grade and did not interfere with treatment. Hepatic enzyme elevations occurred more frequently in the Phase 3 trial compared to the Phase 2b trial, suggesting that underlying illness is likely contributing to the events.\(^{19}\) Labeling recommends to monitor the liver chemistries for patients with hepatitis B and/or C co-infection. Elevations in hepatic transaminases were observed in a greater proportion of subjects with HBV and/or HCV co-infection compared to those with HIV mono-infection. Some of these elevations occurred in subjects who were not receiving treatment for HBV. Labeling instructs to be diligent in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting fostemsavir in patients co-infected with hepatitis B. If approved, the risk of elevations in hepatic transaminases in patients with hepatitis B or C virus co-infection will likely be communicated with in the Warnings and Precautions section of the label.\(^1\)

5.4 **Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interaction**

The concomitant use of fostemsavir and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of fostemsavir, possible development of resistance due to reduced exposure of temsavir and possible prolongation of QTc interval from increased exposure to temsavir. If approved, the risk of adverse reactions or loss of virologic response due to drug interactions will likely be communicated with in the Warnings and Precautions section of the label. Steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations will be included in both Contraindications and Drug Interactions. Labeling instructs to consider the potential for drug interactions prior to and during therapy with fostemsavir, review concomitant medications during therapy with fostemsavir, and monitor for the adverse reactions associated with the concomitant drugs.\(^1\)

6 **Expected Postmarket Use**

According to the current proposed indication, if approved, fostemsavir is an oral medication that will be used in both inpatient and outpatient settings, and will be prescribed by wide variety of healthcare providers who are involved in the management and treatment of patients infected with HIV. There were no new AEs in the clinical trial setting that healthcare providers in the HIV field were not already familiar with.

7 **Risk Management Activities Proposed by the Applicant**

The applicant did not propose any risk management activities for fostemsavir beyond routine pharmacovigilance and labeling. The applicant proposed a PI that includes Warnings and Precautions to address the risks of immune reconstitution syndrome, QTc prolongation with higher than recommended dosages, elevations in hepatic transaminases in patients with hepatitis B or C virus co-infection and risk of adverse reactions or loss of virologic response due to drug interactions, as well as a PPI.
8 Discussion of Need for a REMS

Fostemsavir is a HIV-1 attachment inhibitor, with the proposed indication in combination with other antiretroviral(s), for the treatment of 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.1 When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for fostemsavir, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population. The likely prescribers for fostemsavir will be wide variety of healthcare providers who are involved in the management and treatment of patients infected with HIV. The risks identified in the draft label are risks that these providers have likely encountered in their practice experience and can management without additional risk mitigation measures.

At the time of this review, labeling negotiations were still ongoing with the Applicant. HIV, the virus that causes AIDS, is a serious global public health challenge. The standard of care in HIV management is to maximally suppress plasma HIV RNA to prevent HIV disease progression and the emergence of drug-resistant virus. Achieving virologic suppression can be difficult for HIV-infected patients with drug-resistant virus. Treatment failure may result in selection of virus with resistance to one or more ART agents. HTE patients that are failing their current ART regimen and have MDR virus have few remaining therapeutic options. Despite the availability of different classes of ART agents providing a variety of treatment options, treatment failure continues to occur as a result of ART drug resistance, drug-associated toxicity and tolerability problems, and poor adherence. Therefore, new alternative modalities of medical treatment with improved long-term safety and efficacy are still needed beyond the existing medical therapies for the HTE population. Fostemsavir appeared efficacious both in its primary and secondary outcomes and its risks can be communicated and managed through labeling.20,21,22

DRM and DAV have determined that if approved, a REMS is not necessary to ensure the benefits of fostemsavir outweigh its risks. The most concerning adverse reactions observed with the use of fostemsavir are immune reconstitution syndrome, QTc prolongation with higher than recommended dosages, elevations in hepatic transaminases in patients with hepatitis B or C virus co-infection and risk of adverse reactions or loss of virologic response due to drug interactions. The AEs reported in the clinical trials for fostemsavir were similar to the currently approved drugs used to treat HIV infection, and have been well described in the guidelines6 and literature for ART for several years. If fostemsavir is approved, labeling, including Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with fostemsavir, as well as information to be included in section 17, Patient Counseling Information and in the PPI to inform patients. At this time, none of these risks will receive a boxed warning in the label.

9 Conclusion & Recommendations

If approved, DRM and DAV have determined that a REMS is not necessary to ensure the benefits outweigh the risks of fostemsavir. The management of the risks associated with fostemsavir treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.
10 References

1 Draft Prescribing Information for fostemsavir as currently edited by the FDA, last updated May 16, 2020.


11 Deeks SG, Barbour JD, Grant RM, Martin JN. Duration and predictors of CD4 T-cell gains in patients who continue combination therapy despite detectable plasma viremia. Aids. 2002;16(2):201-207.

12 Prezista. Prescribing Information (last updated 05/2019).

13 Trivicay. Prescribing Information (last updated 03/2020).

14 Intelence. Prescribing Information (last updated 07/2019).

15 Selzentry. Prescribing Information (last updated 07/2018).

16 Fuzeon. Prescribing Information (last updated 08/2019).

17 Trogarzo. Prescribing Information (last updated 04/2020).


This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

-------------------------------------------------------------

TILL OLICKAL
06/22/2020 11:51:34 AM

NAOMI S BOSTON
06/22/2020 12:48:20 PM

CYNTHIA L LACIVITA
06/22/2020 07:58:43 PM