CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

New Molecular Entity (NME) Risk Management Review

Date:	July 11, 2013; *Revised July 15, 2013*
Reviewer:	Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)
Team Leader:	Kendra Worthy, Pharm. D., DRISK
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Drug Name:	TIVICAY® (dolutegravir) Oral Tablets
Therapeutic Class:	Anti-retroviral, Integrase Inhibitor
Indication(s):	For the treatment of Human Immunodeficiency Virus Type-1 Infection
Application Type/Number:	NDA 204-790/Supplement 01/Sequence 01
Applicant:	On behalf of ViiV Healthcare Company (ViiV Healthcare, ViiV), GlaxoSmithKline, LLC submitted the original NDA for Tivicay (dolutegravir)
OSE RCM #:	2013-117
TSI:	Not Applicable

1 INTRODUCTION

This Division of Risk Management (DRISK) review evaluates GlaxoSmithKline/ViiV Healthcare's (ViiV) Risk Management Plan submitted for dolutegravir (Tivicay), proposed as a Human Immunodeficiency Virus Type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated, in combination with other retroviral agents, for the treatment of HIV-1 infection in adults and children aged 12 years and older. This New Drug Application (NDA) 204-790 [received on December 17, 2012/ Supplement (Suppl.) 01/Sequence (Seq.) 01], was submitted to the Division of Antiviral Drugs (DAVP). The DRISK was consulted by the DAVP to evaluate whether or not a risk evaluation and mitigation strategy (REMS) is required to ensure that the benefits outweigh the risks associated with use of dolutegravir.

2 BACKGROUND

Dolutegravir (DTG/Tivicay) is an integrase inhibitor (INI), a new class of antiretroviral therapy designed to block the action of the integrase viral enzyme which catalyzes two key steps in the HIV life cycle and is responsible for insertion the viral genome into the deoxyribonucleic acid (DNA) of the host cell. According to the applicant, since genome integration is a vital step in retroviral replication, dolutegravir is proposed as a target for HIV therapy.[1]

The applicant claims that dolutegravir is a potent low nanomolar inhibitor of HIV integrase, which demonstrates antiviral activity and tolerability for the INI class, and is once-daily dosing (or twice daily dosing) without the requirement for pharmacokinetic boosters. According to the applicant, most HIV isolates with resistance to the approved antiretroviral INI products, ralegravir (RAL) and elvitegravir (EVG), remain susceptible to dolutegravir, making dolutegravir an important option for treatment-experienced patients with multi-class drug resistance. [1]

Integrase Inhibitors

The INIs have shown potent antiviral activity in treatment-naïve and treatment-experienced patient populations and have been well-tolerated in clinical trials. Clinical resistance to the two approved INI products, RAL and EVG, has been reported from Phase 2 studies [Hazuda 2007; McColl, 2007] in treatment-experienced patients and from Phase 3 studies in both treatment-experienced [Cooper, 2008; Molina, 2012] and treatment naive subjects. [1] The development of new INIs with different resistance profiles is desirable and, in the case of treatment-experienced patients with clinical resistance to RAL and EVG, is essential for providing HIV-infected individuals additional options for an effective antiretroviral therapy (ART).[1]

Approved ART INI Products

- **Isentress** (Raltegravir/RAL) - Approved October 12, 2007 as the first marketed INI shown to be non-inferior to an efavirenz (EFV) containing a standard-of-care regimen. RAL requires twice-daily (BID) dosing and is currently not available in a

[1] See Global submit submission NDA 204-790, Module 2.7.3 Summary of Clinical Efficacy, Section 1.2, page 8 of 166; Section 6., pages 117 – 119.

fixed-dose combination regimen.[1] Isentress labeling (section 17) includes PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

- **Clinical Safety** (*approved labeling on June 28, 2013*):
  WARNINGS AND PRECAUTIONS section
  - Severe, potentially life-threatening and fatal skin reactions have been reported. This includes cases of Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal nercrolysis (5.1)
  - Monitor for Immune Reconstitution Syndrome (5.2)
  - Inform patients with phenylketonuria that the 100 mg and 25 mg chewable tablet contains phenylalanine (5.3)

- **Stribild** [Elvitegravir (EVG); Cobicistat; Emtrivitabine; Tenofovir Disoproxil Fumarate] - Approved August 27, 2012 as a combination product. Elvitegravir is an INI drug that requires co-administration with a pharmacokinetic (PK) booster, such as ritonair or cobicist [German, 2010] and, therefore, has the potential for clinically significant drug-drug interactions with drugs that depend on CYP3A4 for clearance. Stribild is not recommended for patients with creatinine clearance < 70 mL/minute. [1] Stribild labeling (section 17) includes PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

  - **Clinical Safety** (*approved labeling on August 27, 2013*)
    BOX WARNING
    - Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of Stribil. (5.1)
    - Stribild is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients co-infected with HIV-1 and HBV who have discontinued Emtriva or Viread. (5.2)

    CONTRAINDICATIONS section:
    - Co-administration of Stribild with drugs that:
      - are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening adverse events (4.0)
      - strongly induce CYP3A which may lead to lower exposure for one or more compounds and loss of efficacy of Stribild which may result in loss of virologic response and possible resistance (4.0)

    WARNINGS AND PRECAUTIONS section:
    - New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (Clcr), urine glucose and urine protein before initiating treatment with Stribild. Monitor CLcr, urine glucose,

and urine protein in all patients. Avoid administering Stribild with concurrent or recent use of nephrotoxic drugs (5.3)

- Coadministration with other products: Do not use with drugs containing emtricitabine or tenofovir disoproxil fumarate including Atripla, Complera, Emtriva, Truvada, or Viread. (5.4)
- Decrease in bone mineral density (BMD) (5.5)
- Redistribution/accumulation of body fat (5.6)
- Immune reconstitution syndrome (5.7)

The risk management of Isentress and Stribild is via routine pharmacovigilance and labeling that does not include a Medication Guide. The Agency did not require a REMS for either of these two antiretroviral therapies.

2.1 Materials Reviewed

- December 17, 2012: NDA 204-790, Suppl. 01, Seq. 01 for dolutegravir (Tivicay) proposed as a Human Immunodeficiency Virus Type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other retroviral agent for the treatment of HIV-1 infection in adults and children aged 12 years and older. This NDA includes a proposed Risk Management Plan for dolutegravir.
- July 9, 2013: Substantially complete proposed labeling for Tivicay per the DAVP

3 Overview of the Clinical Development Program

The clinical development program for dolutegravir consisted of four pivotal clinical trials conducted under Investigational New Drug (IND) application 075-382: ING113-086 (SPRING-1), ING114467 (SINGLE), ING112574 (VIKING-3) and ING111762 (SAILING).

Efficacy

The efficacy of Tivicay is based on analyses of data from 2 trials, SPRING-1 (ING113086) and SINGLE (ING114467), in treatment-naïve, HIV-1 infected subjects (n=1,641); one trial, SAILING (ING111762), in treatment-experienced, INSTI-naïve HIV-1 infected subjects (n=715); and from VIKING-3 (ING112574) trial in INSTI-experienced HIV-1 infected subjects (n=183).

The use of Tivicay in pediatric patients aged 12 years and older is based on evaluation of safety, PK, and efficacy through 24 weeks in a multi-center, open-label trial in subjects (n=23) without INSTI resistance.

The efficacy results are briefly summarized below (see the substantially complete Tivicay labeling, Section 14. for details of the clinical efficacy):

- Significantly improved efficacy for treatment-naïve patients over FEV-based regimen (Study SINGLE ING114467)
- Significant increase in efficacy for treatment-experienced (INI-naïve) patients over RAL [Study SAILING (ING111762)]

- Efficacy in treatment-experienced (INI-resistant) patients, where no satisfactory alternative exists [Study VIKING-3 (ING112574)]
- Higher barrier to resistance, with no INI or NRTI resistance seen to-date in treatment naives on dolutegravir regimen and significantly lower resistance versus RAL in treatment-experienced patients.
- Once daily dosing (treatment-naïve and treatment-experienced, INI naïve) without need for PK booster
- New treatment option for pediatric patients > 12 years of age and older (weighing ≥ 40 kg) HIV-infected, INI-naïve patients.

Dosage and Administration - Adults
The proposed dolutegravir oral tablet will be 50 mg and may be taken without regard to meals. The proposed adult dosage and administration follows:

- Treatment-naive or treatment-experienced INS-TI: → 50 mg once daily
- Treatment-naïve or treatment-experienced, INSTI-naïve when co-administered with the following potent UGTIA/CYP3A inducers: efavirenz, fosamprenavir, tipranavir/ritonavir, or rifampin: → 50 mg twice daily
- INSTI-experienced with documented or clinically suspected resistance to other INSTIs (raltegravir, elvitegravir): → 50 mg twice daily

Dosage and Administration - Pediatrics
The proposed dolutegravir dosing and administration in pediatric patients (treatment-naïve or treatment-experienced, INSTI-naïve, aged ≥ 12 years and weighing ≥ 40 kg) follows:

- The recommended dose is Tivicay 50 mg once daily
- If efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin are co-administered, then the dose if Tivicay 50 mg twice daily.

3.1 Clinical Safety

Exposure
Dolutegravir has been used in 637 healthy volunteers and 2,026 patients with HIV-1 infection for up to ≥ 96 weeks in doses up to 50 mg daily (ART-naïve patients) and 50 mg twice daily [ART-experienced (INI resistant patients)]. The total number of healthy volunteers and patients (regardless of indication) who have received dolutegravir to-date is 2,663.

Key Safety Risks associated with use of Tivicay

- Hypersensitivity Reactions
Hypersensitivity reactions were observed to be characterized by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Dolutegravir is primarily metabolized and eliminated by the liver via uridine diphosphate glucuronyltransferase with a minor CYP3A component. The WARNINGS and PRECAUTIONS section (5.1) of the proposed Tivicay labeling states, "discontinue Tivicay and other suspect agent immediately if signs or symptoms of hypersensitivity reactions develop, (b) (4) delay in stopping treatment may result in a life-threatening

reaction. Tivicay should not be used in patients who have experienced a previous hypersensitivity reaction to Tivicay.

- Hepatobiliary Disorders
Worsening or development of transaminase elevations may occur in patients with hepatitis B or C with use of Tivicay. The WARNINGS and PRECAUTIONS section (5.2) of the proposed Tivicay labeling states, "appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with Tivicay is recommended in patients with underlying hepatic disease such as hepatitis B or C."

- Accumulation of Body Fat and Immune Reconstitution Syndrome
Redistribution/accumulation of body fat and immune reconstitution syndrome (IRIS) have been reported in patients treated with combination ART. See the WARNINGS and PRECAUTIONS section (5.3. 5.4) of the proposed Tivicay labeling for comment on this risk with combination ART.

Adverse Reactions
The most common adverse reactions of moderate to severe intensity and incidence ≥ 2% (in those patients receiving Tivicay in any one adult trial) are insomnia and headache. See the ADVERSE REACTIONS section (6.1) in the proposed Tivicay labeling.

3.2 Applicant's Proposed Risk Management Plan

The applicant's proposed risk management plan includes routine risk minimization through labeled contraindications, limitations of use, warnings and precautions and AE information communicated through the label and Patient Counseling Information.

The applicant plans to employ routine pharmacovigilance and risk minimization with systematic, regular review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, pediatrics, and the elderly. The applicant's Clinical Safety Database contains information on AEs received from spontaneous sources, literature, regulatory agencies, and serious AEs (SAEs) from post-marketing surveillance studies and clinical studies. Periodic safety issues identified from individual case reviews, monthly summaries, signal detection with data mining activities, Periodic Safety Update Reports (PSURs), or other sources will be evaluated.

4 CONCLUSION

The DRISK and the DAVP are in agreement that Tivicay does not require a REMS to ensure that the benefits outweigh the risks associated with use of this proposed drug. Both divisions agree that the benefit risk profile of dolutegravir for treatment of HIV-1 infected patients offers an additional antiretroviral agent as part of combination ART, favorable tolerability, and ease of use (once daily or twice daily dosing) without regard to food or major drug interactions.

The DAVP should consult the DRISK if additional safety information is identified that warrants reevaluation of risk mitigation measures.

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