Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	NDA 204,790
Applicant Name	ViiV Healthcare Company
Date of Submission	December 17, 2012
PDUFA Goal Date	August 17, 2013
Proprietary Name / **Established (USAN) Name**	Tivicay dolutegravir
Dosage Forms / Strength	tablet, 50 mg
Indication(s)	TIVICAY® is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children aged 12 years and older and weighing at least 40 kg. The following should be considered prior to initiating treatment with TIVICAY: • Poor virologic response was observed in subjects treated with TIVICAY 50 mg twice daily with an integrase strand transfer inhibitor (INSTI)-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S/, or G193E/R
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Charu Mullick, Wendy Carter, Yodit Belew
Statistical Review	Thomas Hammerstrom, Greg Soon
Pharmacology Toxicology Reviews	Mark Seaton, Hanan Ghantous
CMC Review/OBP Reviews (including the 7/24/2013 amendment)	Lin Qi, Maotang Zhou, Deepika Arora Lakhani, Kui Zeng, Sandra Suarez, Rapti Madurawe, Michael
Clinical Virology (including the amendment of 7/11/2013)	Lisa Naeger, Jules O'Rear
Clinical Pharmacology Review	Su-Young Choi, Assadollah Noory, Shirley Seo, Jeffry Florian, Yaning Wang, Jeffrey Kraft, Mike Pacanowski
OSI	Antoine El-Hage, Susan Leibenhaut, Susan Thompson
CDTL Review	Kim Struble
Division Director's Review	Debbie Birnkrant

OND=Office of New Drugs

OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Tivicay (dolutegravir) is an HIV integrase strand transfer inhibitor (INSTI) developed for the treatment of HIV-1 infection in adults in combination with other antiretroviral agents. There are two previously approved HIV INSTIs; Isentress (raltegravir) and elvitegravir, which is approved as part of a fixed dose combination tablet, Stribild (elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate).

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of Tivicay. For a detailed discussion of NDA 204,790, the reader is referred to the individual discipline specific reviews. In addition the Cross-Discipline Team Leader Review and the Division Director Review summarize key issues in the NDA submission. This memorandum will focus on select issues from the NDA review.

The Office of New Drug Quality Assessment finds that the CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of Tivicay (dolutegravir) 50 mg tablets. The available data support a shelf-life of 24 months for dolutegravir tablets when stored in the primary packaging at 25°C (77°F); excursions permitted 15-30°C (59° to 86°F). The CMC review amendment #1 updates the review noting that the Office of Compliance has provided an overall recommendation of "Acceptable" for the establishments filed in this NDA, as of July 23, 2013. The Product Quality Microbiology Review recommends approval. The CMC recommendation is for approval of NDA 204,790 Tivicay (dolutegravir) 50 mg tablets.

The recommendation from the pharmacology/toxicology reviewers is for approval. Findings from the nonclinical toxicology studies included gastrointestinal inflammation and gastrointestinal hemorrhage in short-term, subchronic, and chronic studies. Hepatocellular single-cell necrosis was observed in male monkeys in the high dose group. Hepatic toxicity was not noted in subchronic or chronic studies. Dolutegravir is labeled as Pregnancy Category B reflecting that there have not been studies in pregnant women and no significant embryo/fetal toxicity was observed in animal studies.

The Clinical Virology Reviewer recommends that the data in NDA 204,790 support approval. The Review includes an evaluation of mutations associated with reduced response rates to dolutegravir. Mutations identified associated with reduced susceptibility to dolutegravir are described in the product labeling. The product labeling provides information in the Dosage and Administration section to guide selection of the once daily or the twice daily dosing regimen based upon patient factors and information in the Microbiology subsection of the product labeling regarding integrase substitutions.

The Clinical Pharmacology reviewers find the data in the application are acceptable. The moderate increase in dolutegravir exposure that was observed when taken with food is not considered clinically significant. Hence, labeling recommends that dolutegravir can be taken without regard to food. Dolutegravir is chelated by divalent cations and therefore should be taken 2 hours before or 6 hours after taking polyvalent cation containing drugs.

A mass balance study indicates that 53% of the total oral dose of dolutegravir is excreted unchanged in the feces. Thirty-one percent of the oral dose is excreted in the urine as glucuronide, N-dealkylated, and other metabolites.

Dolutegravir inhibits the renal organic transporter 2 (OCT2). Dolutegravir may increase plasma concentrations of drugs for which excretion is highly dependent upon OCT2 transport (e.g., dofetilide, and metformin). Moderate to strong inducers of UGT1A1 and/or CYP 3A4 including etravirine, efavirenz, fosamprenavir/ritonavir, tipranavir, and rifampin reduce the plasma concentrations of dolutegravir. The product labeling provides information on drug interactions and dose adjustment, when appropriate.

No dose adjustment of dolutegravir is required in the setting of mild to moderate hepatic impairment. Dolutegravir has not been studied in persons with severe hepatic impairment. Dolutegravir exposures were decreased in patients with severe renal impairment. In patients that are treatment naïve or treatment experienced and INSTI-naïve, no dosage adjustment is necessary. In patients who are INSTI-experienced avoidance of co-administration of metabolic inducers that can further reduce exposures is recommended. The effect of dolutegravir was evaluated on the QT interval was found to be below the threshold of regulatory concern.

Clinical Trials of dolutegravir were performed in treatment-naïve, treatment-experienced INSTI-naïve, and treatment-experienced and INSTI-experienced adult patients. Data was also provided for pediatric patients. The results from the trials support the indications for treatment of human immunodeficiency virus type 1 (HIV-1) in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg. The labeling provides dosing instructions for treatment-naïve, treatment-experienced, and INSTI-experienced patients. The labeling also notes mutations associated with poor virologic response in the Indications and Usage section as follows:

> *Poor virologic response was observed in subjects treated with TIVICAY 50 mg twice daily with an INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions including L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R.*

The efficacy of dolutegravir for treatment-naïve patients was evaluated in studies ING 113086 (SPRING-2) and ING 114467 (SINGLE). These studies were randomized, double-blind, active-controlled trials in treatment naïve subjects. In SPRING-2 patients were randomized to either dolutegravir 50 mg once daily or raltegravir 400 mg once daily in combination with dual nucleoside reverse transcriptase inhibitors. In SINGLE patients were randomized to either dolutegravir with fixed-dose abacavir sulfate and lamivudine or fixed dose efavirenz/emtricitabine/tenofovir. Outcomes at 48-weeks are summarized in the following table for the SPRING-2 and SINGLE studies.

Table. Virologic Outcomes of Randomized Treatment in SPRING-2 and SINGLE at Week 48 (Snapshot Algorithm)

	SPRING-2		SINGLE	
	TIVICAY 50 mg Once Daily + 2 NRTIs (N = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (N = 405)	TIVICAY 50 mg + EPZICOM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
HIV-1 RNA <50 copies/mL	88%	86%	88%	81%
Treatment difference[a]	2.6% (95% CI: -1.9%, 7.2%)		7.4% (95% CI: 2.5%, 12.3%)	
Virologic nonresponse[b]	5%	7%	5%	6%
No virologic data at Week 48 window	7%	7%	7%	13%
Reasons				
Discontinued study/study drug due to adverse event or death[c]	2%	1%	2%	10%
Discontinued study/study drug for other reasons[d]	5%	6%	5%	3%
Missing data during window but on study	0	0	0	<1%
Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL at Week 48 by Baseline Category				
Plasma viral load (copies/mL)				
≤100,000	91%	90%	90%	83%
>100,000	82%	75%	83%	76%
Gender				
Male	89%	86%	88%	82%
Female	84%	82%	85%	75%
Race				
White	88%	86%	90%	84%
Non-white	85%	85%	84%	74%

[a] Adjusted for pre-specified stratification factors.

[b] Includes subjects who changed BR to new class or changed BR not permitted per protocol or due to lack of efficacy prior to Week 48 (for SPRING-2 only), subjects who discontinued prior to Week 48 for lack or loss of efficacy, and subjects who were HIV-1 RNA ≥50 copies/mL in the Week 48 window.

[c] Includes subjects who discontinued due to an adverse event or death at any time point from Day 1 through the Week 48 window if this resulted in no virologic data on treatment during the Week 48 window.

[d] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

The results demonstrate non-inferiority in the SPRING-2 study vs. a raltegravir-based regimen and superiority in the SINGLE study of dolutegravir with fixed-dose abacavir sulfate and lamivudine vs. fixed dose efavirenz/emtricitabine/tenofovir.

The efficacy of dolutegravir for treatment-experienced, INSTI-naïve patients was evaluated in study ING 111762 (SAILING). Patients in SAILING were randomized to either dolutegravir

50mg QD or raltegravir, each in combination with an optimized background regimen. Outcomes at 24-weeks are summarized in the following table for the SAILING.

Table. Virologic Outcomes of Randomized Treatment in SAILING at 24 Weeks (Snapshot Algorithm)

	TIVICAY 50 mg Once Daily + BR[a] (N = 354)	Raltegravir 400 mg Twice Daily + BR[a] (N = 361)
HIV-1 RNA <50 copies/mL	79%	70%
Adjusted[b] treatment difference	9.7% (95% CI: 3.4%, 15.9%)	
Virologic nonresponse	15%	24%
No virologic data at Week 24 window	6%	6%
Reasons		
Discontinued study/study drug due to adverse event or death	2%	2%
Discontinued study/study drug for other reasons[c]	3%	3%
Missing data during window but on study	<1%	<1%
Proportion (%) With HIV-1 RNA <50 copies/mL at Week 24 by Baseline Category		
Plasma viral load (copies/mL)		
≤50,000 copies/mL	83%	77%
>50,000 copies/mL	70%	53%
Background regimen		
No darunavir use or use of darunavir with primary PI substitutions	79%	67%
Use of darunavir without primary PI substitutions	80%	81%
Gender		
Male	78%	70%
Female	83%	69%
Race		
White	79%	69%
Non-white	80%	71%

[a] BR = Background regimen. Background regimen was restricted to ≤2 antiretroviral treatments with at least 1 fully active agent.
[b] Adjusted for pre-specified stratification factors.
[c] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

The results demonstrate superiority of dolutegravir 50 mg QD with OBR over raltegravir 400 mg BID with OBR.

The efficacy of dolutegravir 50 mg BID was also evaluated in treatment-experienced, INSTI-experienced patients in the VIKING-3 study. The study examined virologic response at Day 8 following the addition of dolutegravir. The study showed a mean decline from baseline to Day 8 of 1.4 log10, an event unlikely to happen by chance alone. Dolutegravir was then continued along with an OBR and virologic response and CD4 cell count were assessed at week 24. A

virologic response rate of 63% along with an increase in median CD4 cell counts of 65 cells/mm^3 was observed at week 24. This information, considered along with the data from the previously described trials in other patient populations support labeling for use in the treatment experienced, INSTI-experienced patients.

Data supporting extending the indication to pediatric patients 12 years of age and weighing at least 40 kg were provided. The data included pharmacokinetic analyses of exposure in pediatric patients and limited evidence of safety and activity in pediatric patients with data at 24 weeks.

The safety database included 2026 patients that received at least one dose of dolutegravir including 856 treatment-naïve patients that received 50mg QD for at least 48 weeks, 311 treatment-experienced INSTI-naïve patients that received 50 mg QD for at least 24 weeks, and 207 patients that received 50 mg BID, 127 of who received 50 mg BID for at least 24 weeks.

The product labeling includes statements in Warnings and Precautions on the potential for hypersensitivity reactions, effects on serum liver biochemistries, fat redistribution, and immune reconstitution syndrome. Hypersensitivity reactions characterized by rash, constitutional findings, and in some instances organ dysfunction, including liver injury were reported in 1% or fewer subjects. Elevations in serum transaminases were observed in patients co-infected with hepatitis B or hepatitis C. It is unclear if the observed transaminase elevations are related to immune reconstitution, flare in the setting of withdrawal of therapy for hepatitis B, or drug related. The labeling describes the observed effects on serum liver biochemistries in patients with hepatitis B or C co-infection. The product labeling also includes a Warning and Precautions statement on fat redistribution and immune reconstitution syndrome. In addition, a patient package insert for dolutegravir is also included.

NDA 204,790 was not referred to an advisory committee for review for the following reasons: There are two previously approved HIV integrase strand transfer inhibitor class, raltegravir and elvitegravir (as a component of the fixed dose combination of Stribild). Evaluation of the safety data did not reveal particular safety issues that were unexpected for an INSTI antiretroviral drug, and the design and results of the efficacy trials did not pose particular concerns.

We are waiving the pediatric study requirement for ages 0 to 4 weeks in the HIV-infected population who are naïve to INSTIs and for ages 0 to 23 months in HIV-infected children who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs for the following reasons.

We are waiving the pediatric study requirement for 0 to less than 4 weeks of age in INSTI-naïve and INSTI-experienced patients because with improvement in perinatal transmission prevention strategies there are insufficient numbers of neonatal subjects to be enrolled. Further, even when neonates are identified for enrollment, by the time enrollment is accomplished, dosing is initiated, and drug concentrations have reached steady state, the subjects are likely to be older than 4 weeks of age. Additionally, we are waiving the pediatric study requirement in HIV-infected children ages 4 weeks to less than 2 years who are INSTI-

experienced with documented or clinically suspected resistance to other INSTIs because only one integrase inhibitor, raltegravir, is currently approved for pediatric use in the US and European Union. Raltegravir is not yet available in most developing countries, where the burden of pediatric HIV infection is greatest. Therefore enrollment of pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs is expected to be challenging, and the necessary pediatric study will be impossible or highly impracticable.

We are deferring submission of pediatric study for ages 4 weeks to 11 years in the HIV-infected INSTI-naïve population and for ages 2 years to 17 years in HIV-infected INSTI experienced population with documented or clinically suspected resistance to other INSTIs. This is because the product is ready for approval for use in adults and INSTI-naïve pediatric patients ages 12 years and older, and studies in the remaining pediatric populations are either not initiated or completed.

In summary, I agree with the review team, CDTL, and the Division Director, that the overall benefits and risks support the approval of NDA 204,790 for TIVICAY (dolutegravir) 50 mg tablets in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children aged 12 years and older and weighing at least 40 kg. The product labeling adequately describes the safety and efficacy findings. Postmarketing studies will provide additional information to evaluate selected safety issues and provide additional pediatric safety and efficacy in children less than 12 years of age.

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OND/CDER/FDA

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