PDL NEW DRUG REVIEW

Proprietary Name: Tivicay®
Common Name: dolutegravir sodium
PDL Category: Antiretrovirals

Comparable Products	Preferred Drug List Status
Isentress	Recommended

Summary

Indications and Usage: For use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children ≥12 years of age and weighing at least 40kg. Prior to starting therapy it should be considered that poor virologic response was seen in those treated with Tivicay® 50mg BID with an integrase strand transfer inhibitor (INSTI)-resistance Q148 substitution plus 2 more additional INSTI-resistance substitutions, including L741/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R. This is a pregnancy category B medication. The safety and efficacy of use in children under 12 years of age or weighing less than 40kg have not been established.

Drug Interactions: Dolutegravir is metabolized by UGT1A1, along with CYP3A4. Dolutegravir is also a substrate of UGT1A3, UGT1A9, and P-glycoprotein (P-gp) *in vitro*. Concomitant use of Tivicay® with nevirapine, oxcarbazepine, phenytoin, phenobarbital, carbamazepine, and St. John's wort should be avoided. The concomitant use of rifampin, efavirenz, fosamprenavir/ritonavir, or tipranavir/ritonavir with Tivicay® should result in a dose adjustment of Tivicay® to 50mg BID in treatment-naïve or treatment-experienced, INSTI-naïve patients. It is recommended to closely monitor the combination of metformin with Tivicay®, and that a metformin dose adjustment may be needed. Tivicay® should not be used concomitantly with etravirine without the co-administration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir. Also, Tivicay® should be given 2 hours before or 6 hours after taking medications containing polyvalent cations (eg Mg, Al-containing antacids, Ca supplements, oral iron supplements, buffered medications).

Dosage Forms: Film-coated Tablets: 50mg

Recommended Dosage: For treatment naïve or treatment-experienced INSTI-naïve patients, the recommended dose is 50mg QD, with or without food. For treatment naïve or treatment-experienced INSTI-naïve patients when given concomitantly with the following potent UGT1A/CYP2A inducers efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin, then the recommended dose is 50mg BID with or without food. For INSTI-experienced with certain INSTI-associated substitutions or clinically suspected INSTI resistance, then the recommended dosing is also 50mg BID, with or without food.

The recommended dose for pediatric patient's ≥12 years and weighing ≥40kg is 50mg QD; however, if efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin is given concomitantly, the recommended dose is 50mg BID.

Dosage adjustments are not required in those with mild to moderate hepatic impairment; however, as the effect of use in those with severe hepatic impairment has not been studied, use in this population is not recommended. Dosage adjustment is not needed in those with renal impairment for treatment-naïve or treatment-experienced and INSTI-naïve patients, or for those with mild or moderate renal impairment for INSTI-experienced patients (with certain INSTI-associated resistance

substitutions or clinically suspected INSTI resistance). Use with caution in those with severe renal impairment for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance).

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug (Tivicay®) PLUS Epzicom® QD minus reported % incidence for Atripla® QD. If an incidence of 0% is listed, the results suggest that the incidence was the same as or less with Tivicay® Plus Epzicom® minus Atripla®.* The most common adverse event reporteds included insomnia (1%), abnormal dreams (0%), dizziness (0%), headache (0%), nausea (0%), diarrhea (0%), and rash (0%).

Contraindications: The concomitant use of Tivicay® with dofetilide, due to the potential for increased dofetilide plasma levels and the risk for serious and/or life-threatening events.

Manufacturer: GlaxoSmithKline/ViiV Healthcare

Analysis: Dolutegravir sodium, the active ingredient of Tivicay®, is an HIV-1 antiviral agent. It's an HIV INSTI to be used in combination with other antiretroviral agents.

The SINGLE (N=833) and SPRING-2 (N=822) were 2 multicenter, randomized, double-blind, active-controlled 48-week trials that assessed the efficacy of Tivicay® in HIV-1 infected treatment-naïve adults. In SPRING-2, Tivicay® or raltegravir were given in combination with dual NRTI treatment (either abacavir and lamivudine or emtricitabine/tenofovir), while in the SINGLE trial adults were randomized to Tivicay® plus abacavir and lamivudine or fixed-dose efavirenz/emtricitabine/tenofovir (Atripla®). Results of the SPRING-2 study suggest 88% of the Tivicay® group had HIV-1 RNA <50copies/ml vs 86% of the raltegravir group, and the virologic nonresponse was 5% vs 7%, respectively. In the SINGLE study, results suggested that 88% of the Tivicay® group had HIV-1 RNA <50 copies/ml vs 81% of the Atripla group, and the virologic nonresponse was 5% vs 6%, respectively.

The SAILING study was a multicenter, international, double-blind 24-week study that included HIV-1 infected antiretroviral treatment-experienced adults (N=719) who were randomized to either Tivicay® or raltegravir with investigator selected background regimen of at least 2 agents. Results suggested that 79% of the Tivicay® group had HIV-1 RNA <50 copies/ml vs 70% of the raltegravir group, and the virologic nonresponse was 15% vs 24%, respectively.

The VIKING-3 study was a multicenter, randomized, open-label, single-arm study that assessed the efficacy of Tivicay® in HIV-1 infected, antiretroviral treatment-experienced adults (N=183) with virologic failure and current or historical evidence of raltegravir and/or elvitegravir resistance. All received Tivicay® with the current failing background regimen for 7 days, and then received it with optimized background therapy from day 8 until week 24. The primary outcome was the mean reduction from baseline in HIV-1 RNA at day 8, which was 1.4 $\log_{10}$. 63% had HIV-1 RNA <50 copies/ml, and the virologic nonresponse was 32%.

The IMPAACT study was a multicenter, open-label Phase 1/2 study to assess the safety, tolerability, and efficacy of Tivicay® in combination treatment regimens in children and adolescents aged 12-17 years infected with HIV-1 (N=23). Results suggested that at 24 weeks, 70% treated with Tivicay® plus background therapy achieved a viral load <50 copies/ml. The median CD4+ count increase from baseline to week 24 was 63 cells/mm^3 (5%).

It is recommended that Tivicay® be placed as non-recommended on the Recommended Drug List as more cost effective alternatives are available.

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

References

[1] Tivicay [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2013.