PDL NEW DRUG REVIEW

Proprietary Name: Tybost®
Common Name: cobicistat
PDL Category: Antiretrovirals

Comparable Products	Preferred Drug List Status
Norvir	Recommended

Summary

Indications and Usage: This is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir or darunavir (QD dosing regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection. Tybost® is not interchangeable with ritonavir to increase systemic exposure of darunavir 600mg BID, fosamprenavir, saquinavir, or tipranavir due to lack of exposure data. Use of Tybost® is not recommended with darunavir 600mg BID, fosamprenavir, saquinavir, or tipranavir. In addition, complex or unknown mechanisms of drug interactions preclude extrapolation of ritonavir drug interactions to certain Tybost® interactions. Tybost® and ritonavir when administered with either atazanavir or darunavir may result in different drug interactions when used with concomitant medications.

This is a pregnancy category B medication. The safety and efficacy of use in children have not been established.

Dosage Forms: Film-coated Tablets: 150mg

Recommended Dosage: 150mg PO QD, administered in conjunction with atazanavir 300mg QD or darunavir 800mg QD and other antiretroviral agents. These agents must be co-administered at the same time as atazanavir or darunavir and taken with food.

Prior to starting therapy, estimated creatinine clearance (eCrCl) should be assessed. Tybost® should not be given with tenofovir DF in those who have an eCrCl <70ml/min. In addition to assessing eCrCl, urine glucose and urine protein should be assessed at baseline if Tybost® is given with tenofovir DF. Dose adjustment is not required in those with renal impairment or in those with mild-to-moderate hepatic impairment. Data on use in severe hepatic impairment is not available.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Tybost® + atazanavir + Truvada®) minus reported % incidence for ritonavir + atazanavir + Truvada®. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than its comparator.* The most frequently reported adverse events included jaundice (2%), rash (1%), ocular icterus (2%), and nausea (0%).

The following were lab abnormalities reported in clinical trials: total bilirubin >2.5X upper limit of normal (ULN; 9%), creatine kinase ≥10X ULN (0%), serum amylase >2X ULN (2%), ALT >5X ULN (1%), AST >5X ULN (1%), gamma-glutamyl transpeptidase >5X ULN (GGT, 1%), urine glucose ≥1g/dl (2%), and urine RBC (hematuria, 1%).

Contraindications: The concomitant use of Tybost® with atazanavir or darunavir and the following drugs is contraindicated (due to potential for serious and/or life-threatening events or loss of therapeutic effect): alfuzosin, dronedarone, rifampin, irinotecan, dihydroergotamine, ergotamine, methylergonovine, cisapride, St. John's wort, lovastatin, simvastatin, pimozide, nevirapine, sildenafil (when given as Revatio® for treatment of PAH), indinavir, triazolam, or PO midazolam.

Manufacturer: Gilead Sciences, Inc

Analysis: Cobicistat, the active ingredient of Tybost®, is a mechanism-based inhibitor of CYP3A. Inhibition of CYP3A-mediated metabolism increases the systemic exposure of CYP3A substrates atazanavir and darunavir. As such, the coadministration with other CYP3A substrates may require dose adjustments and additional monitoring.

In addition, cobicistat is also an inhibitor of CYP2D6. Overall, there is a significant list of drug-interactions associated with this product. Some may require dose adjustment, some are not recommended to be used concomitantly, and some may be contraindicated. Please refer to the prescribing information (PI) for further information on DDIs. In addition, there are several antiretroviral agents that are not recommended to be used in combination with Tybost®, as recommendations for such combinations have not been established and concomitant use may result in decreased plasma levels of the antiretroviral agents. Please refer to the warnings section of the PI for a complete list. Overall, it is recommended to consider the potential for drug interactions prior to and during Tybost® treatment, to review concomitant medications during Tybost® treatment, and to monitor for adverse reactions associated with the concomitant drugs.

Pharmacokinetic trials have shown that Tybost® administered with atazanavir or darunavir resulted in exposure of the latter that was consistent with that seen with ritonavir 100mg. The safety and efficacy of Tybost® were assessed in a double-blind, active-controlled trial that included HIV-1 infected treatment-naïve subjects. Tybost® plus atazanavir plus Truvada® was compared with ritonavir plus atazanavir plus Truvada®. Results suggested that the percent with HIV-1 RNA<50 copies/ml was 85% vs 87%, respectively. The mean increase from baseline in CD4+ cell count at week 48 was 213 cells/mm^3 vs 219 cells/mm^3, respectively. Furthermore, 6% vs 4%, respectively, had HIV RNA ≥50copies/ml while 6% vs 7%, respectively, discontinued the drug due to an adverse event or death.

Tybost® is only indicated for use with atazanavir or darunavir as a mechanism to increase drug exposure. There was no data found that suggested it is safer or more effective than the alternative drug, ritonavir. It is recommended that Tybost® be added to the Recommended Drug List as non-recommended since a more cost effective pharmacokinetic booster is available.

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

References

[1] Tybost [package insert]. Foster City, CA: Gilead Sciences, Inc; 2014.