Product Information

TYBOST® (cobicistat) 150 mg tablets

NAME OF THE MEDICINE

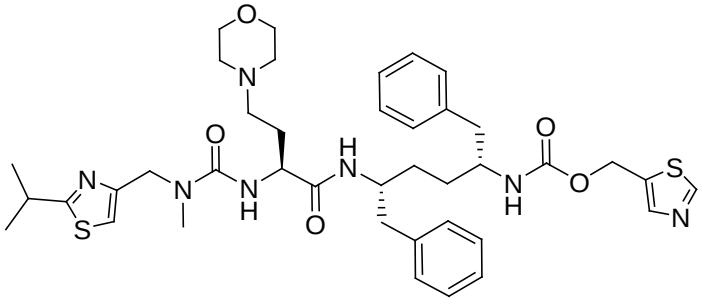
TYBOST (cobicistat) 150 mg tablets.

The active substance in TYBOST tablets is cobicistat.

Cobicistat is a mechanism-based inhibitor of cytochrome P-450 (CYP) enzymes of the CYP3A family. Cobicistat is one of the active substances in the single tablet regimen; STRIBILD®.

DESCRIPTION

Cobicistat: the chemical name for cobicistat is 1,3-Thiazol-5-ylmethyl [(2*R*,5*R*)-5-{[(2*S*)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate. It has a molecular formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.0. It has the following structural formula:



CAS registry number: 1004316-88-4

Cobicistat is a white to pale yellow solid with a solubility of 0.1 mg/mL in water at 20 °C. The partition coefficient (*log p*) for cobicistat is 4.3 and the pKa is 6.4.

TYBOST tablets each contain 150 mg of cobicistat and the following ingredients as excipients: *Tablet core:* cellulose-microcrystalline (E460), silicon dioxide, croscarmellose sodium, magnesium stearate (E572). *Film-coating:* Sunset yellow FCF (FD&C yellow #6) aluminum lake (E110), polyethylene glycol, polyvinyl alcohol, talc (E553B), titanium dioxide (E171), yellow iron oxide (E172).

Each TYBOST tablet is round, film-coated and orange in colour. Each tablet is debossed with 'GSI' on one side and plain faced on the other side. The tablets are supplied in bottles with child resistant closures.

PHARMACOLOGY

Pharmacotherapeutic group: all other therapeutic products, ATC code: V03AX03.

Mechanism of action

Cobicistat is a selective, mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as atazanavir or darunavir, where bioavailability is limited and half-life is shortened due to CYP3A-dependent metabolism.

Antiviral Activity

Cobicistat has no detectable antiviral activity against HIV-1, HBV or HCV and does not antagonize the antiviral effect of HIV inhibitors.

Pharmacodynamics

Effects on Pharmacokinetic Enhancement

The effect of cobicistat on atazanavir pharmacokinetics was demonstrated in the pharmacokinetic substudy (N=48) of the Phase III Study GS-US-216-0114 in which HIV-1 infected patients received atazanavir+cobicistat or atazanavir+ritonavir, both in combination with TRUVADA® Tenofovir DF 300mg/emtricitabine 200 mg) The steady-state pharmacokinetic parameters of atazanavir were comparable when boosted with cobicistat versus ritonavir as shown in Table 1 (see CLINICAL TRIALS).

Table 1 Pharmacokinetic Parameters (Mean ± SD) of Atazanavir in the Pharmacokinetic Substudy of Phase III trial (Study 114)

Atazanavir Pharmacokinetics Parameters	Atazanavir + cobicistat + TRUVADA (N=22)	Atazanavir + ritonavir + TRUVADA (N=26)
AUC_{tau} (mg·h/mL)	46.13 ± 26.18	47.59 ± 24.39
C_{max} (mg/mL)	3.91 ± 1.94	4.76 ± 1.94
C_{tau} (mg/mL)	0.80 ± 0.72	0.85 ± 0.72

The pharmacokinetic enhancing effect of cobicistat on darunavir was evaluated in a Phase I clinical trial (Study GS-US-216-0115) in 31 healthy patients that were administered darunavir 800 mg in combination with cobicistat 150 mg or ritonavir 100 mg, all once daily, for 10 days. The steady-state pharmacokinetic parameters of darunavir were comparable when boosted with cobicistat versus ritonavir as shown in Table 2 and these results were similar to those reported in previous clinical studies of darunavir 800 mg with ritonavir 100 mg once daily (refer to PREZISTA Product Information).

Table 2 Pharmacokinetic Parameters (Mean ± SD) of Darunavir 800 mg Coadministered with Cobicistat 150 mg or Ritonavir 100 mg once daily

Darunavir Pharmacokinetics Parameters	Darunavir 800 mg + cobicistat 150 mg once daily (N=31)	Darunavir 800 mg + ritonavir 100 mg once daily (N=31)
AUC_{tau} (mg·h/mL)	81.08 ± 25.15	79.99 ± 27.20
C_{max} (mg/mL)	7.74 ± 1.69	7.46 ± 1.52
C_{0h} (mg/mL)	2.40 ± 1.22	2.48 ± 0.85

Effects on Electrocardiogram
The electrocardiographic effects of cobicistat were determined in a study of 48 healthy adult patients. Cobicistat did not prolong QTcF interval at doses of 250 mg and 400 mg, providing exposures 2- and 4-fold above the recommended therapeutic dose. A modest increase in PR interval (+9.6 msec) occurred around C_{max}, 3 to 5 hours after dosing. This finding was not considered to be clinically significant.

Effects on serum creatinine
The effect of TYBOST on serum creatinine was investigated in a Phase I study in patients with normal renal function (eGFR ≥ 80 mL/min, N=18) and mild to moderate renal impairment (eGFR 50-79 mL/min, N=12). A statistically significant change of estimated glomerular filtration rate calculated by Cockcroft-Gault method ($eGFR_{CG}$) from baseline was observed after 7 days of treatment with cobicistat 150 mg among subjects with normal renal function (-9.9 ± 13.1 mL/min) and mild to moderate renal impairment (-11.9 ± 7.0 mL/min). These decreases in $eGFR_{CG}$ were reversible after cobicistat was discontinued. The actual glomerular filtration rate, as determined by the clearance of probe drug iohexol, was not altered from baseline following treatment of TYBOST among subjects with normal renal function and mild to moderate renal impairment, indicating cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in $eGFR_{CG}$, without affecting the actual glomerular filtration rate.

Pharmacokinetics

Absorption
Following oral administration of TYBOST with food in HIV-1 infected patients, peak plasma concentrations were observed 4 hours post-dose for cobicistat. The steady-state mean C_{max}, AUC_{tau}, and C_{trough} (mean ± SD) following multiple doses of TYBOST in HIV-1 infected patients (N=68), respectively, were 1.2 ± 0.3 µg/mL, 10.9 ± 3.8 µg•hr/mL, and 0.07 ± 0.07 µg/mL.

Distribution
Cobicistat is 97-98% bound to human plasma proteins and the mean plasma to blood drug concentration ratio was 2.

Metabolism
Cobicistat is metabolized via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. Following oral administration of [^{14}C] cobicistat, 99% of circulating radioactivity in plasma was unchanged cobicistat. Low levels of metabolites are

observed in urine and faeces and do not contribute to the CYP3A inhibitory activity of cobicistat. Eighty-six percent and 8.2% of the dose were recovered in faeces and urine, respectively. The median terminal plasma half-life of cobicistat following administration of TYBOST is approximately 3.5 hours.

Effect of food
A food effect study was not conducted for TYBOST. In clinical studies, TYBOST was coadministered with atazanavir or darunavir under fed conditions, in accordance with the prescribing information for these agents. It is recommended that TYBOST be administered with food.

Age, Gender and Ethnicity
No clinically relevant pharmacokinetic differences due to gender or ethnicity have been identified for cobicistat. (see PRECAUTIONS).

The pharmacokinetics of cobicistat in paediatric patients have not been established. Pharmacokinetics of cobicistat have not been fully evaluated in the elderly (65 years of age and older).

No clinically relevant pharmacokinetic differences have been observed between men and women for cobicistat.

Patients with Impaired Renal Function
A study of the pharmacokinetics of cobicistat was performed in non HIV-1 infected subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min). No meaningful differences in cobicistat pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects, consistent with low renal clearance of cobicistat.

Patients with Hepatic Impairment
Cobicistat is primarily metabolized and eliminated by the liver. A study of the pharmacokinetics of cobicistat was performed in non-HIV-1 infected patients with moderate hepatic impairment (Child-Pugh Class B). No clinically relevant differences in cobicistat pharmacokinetics were observed between patients with moderate hepatic impairment and healthy patients. No dosage adjustment of TYBOST is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of cobicistat has not been studied.

Hepatitis B and/or hepatitis C virus co-infection
Pharmacokinetics of cobicistat have not been fully evaluated in the hepatitis B and/or C co-infection patients.

Assessment of Drug Interactions
In drug interaction studies conducted with cobicistat, there was no clinically significant interaction observed between cobicistat and famotidine or omeprazole.

The effects of coadministered drugs on the exposure of cobicistat are shown in Table 3. The effects of cobicistat on the exposure of coadministered drugs are shown in Table 4.

Table 3 Drug Interactions: Changes in Pharmacokinetic Parameters for Cobicistat in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Cobicistat Dose (mg)	N	% Change of Cobicistat Pharmacokinetic Parameters[b] (90% CI)		
				C_{max}	AUC	C_{min}
Rifabutin	150 once every other day	150 once daily[c]	12	Û [d]	Û [d]	¯66[d] (¯74 to ¯54)
Rosuvastatin	10 single dose	150 single dose[c]	10	Û [d]	Û [d]	Û [d]

a. All interaction studies conducted in healthy volunteers
b. - = Increase; ¯ = Decrease; Û = No Effect
c. Study was conducted in the presence of 150 mg elvitegravir
d. Comparison based on elvitegravir/cobicistat 150/150 mg once daily.

Table 4 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Cobicistat[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Cobicistat Dose	N	% Change of Coadministered Drug Pharmacokinetic Parameters[b] (90% CI)		
				C_{max}	AUC	C_{min}
Desipramine	50 single dose	150 once daily	8	- 24 (- 8 to - 44)	- 65 (- 36 to - 102)	ND
Digoxin	0.5 single dose	150 once daily	22	- 41 (- 29 to - 55)	Û	ND
Efavirenz	600 single dose	150 once daily	17	¯13 (¯20 to ¯6)	Û	ND
Rifabutin	150 once every other day	150 once daily[c]	12	Û [d]	Û [d]	Û [d]
25-O-desacetyl-rifabutin				- 384[d] (- 309 to - 474)	- 525[d] (- 408 to - 669)	- 394[d] (- 304 to - 504)
Rosuvastatin	10 single dose	150 single dose[c]	10	- 89 (- 48 to - 142)	- 38 (- 14 to - 67)	- 43 (- 8 to - 89)

a. All interaction studies conducted in healthy volunteers
b. - = Increase; ¯ = Decrease; Û = No Effect, ND = not determined
c. Study was conducted in the presence of 150 mg elvitegravir
d. Comparison based on rifabutin 300 mg once daily.

Attachment 1: Product information for AusPAR Cobicistat Tybost Gilead Sciences Pty Ltd PM-2012-02160-3-2 Final 16 December 2013. This Product Information was approved at the time this AusPAR was published.

CLINICAL TRIALS

The activity of cobicistat as a pharmacokinetic enhancer to atazanavir or darunavir has been demonstrated in pharmacokinetic studies. In these pharmacokinetic studies, the exposure of atazanavir or darunavir boosted with cobicistat 150 mg were consistent with those observed with ritonavir 100 mg (see PHARMACOLOGY). For clinical efficacy of darunavir/ritonavir 800/100 mg once daily, please refer to darunavir product information.

The safety and efficacy of TYBOST with atazanavir in HIV-1 infected patients were evaluated in a randomized, double-blind, active-controlled Phase III trial (Study GS-US-216-0114) in HIV-1 infected patients with baseline estimated creatinine clearance above 70 mL/min who were treatment-naïve (N=692). In Study GS-US-216-0114, patients were randomized in a 1:1 ratio to receive either atazanavir 300 mg + cobicistat 150 mg once daily or atazanavir 300 mg + ritonavir 100 mg once daily, each administered with a fixed background regimen (BR) containing tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg administered as single tablet TRUVADA®. Randomization was stratified by screening HIV-1 RNA level (≤ 100,000 copies/mL or >100,000 copies/mL).
The mean age of patients was 37 years (range 19-70), 83% were male, 60% were White, 18% were Black and 12% were Asian. The mean baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL (range 3.2–6.4). The mean baseline CD4+ cell count was 352 cells/mm^3 (range 1–1455) and 17% had CD4+ cell counts ≤200 cells/mm^3. Forty percent of patients had baseline viral loads >100,000 copies/mL.

Treatment outcomes at 48 weeks are presented in Table 5.

Table 5 Virologic Outcome of Randomized Treatment of Study 114 at Week 48 [a]

	Week 48	
	Atazanavir + cobicistat + TRUVADA (N=344)	**Atazanavir +ritonavir + TRUVADA (N=348)**
Virologic Success HIV-1 RNA < 50 copies/mL	85%	87%
Treatment Difference[b]	-2.2% (95% CI = -7.4%, 3.0%)	
Virologic Failure[c]	6%	4%
No Virologic Data at Week 48 Window	9%	9%
Discontinued Study Drug Due to AE or Death[d]	6%	7%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[e]	3%	2%
Missing Data During Window but on Study Drug	0%	0%

a. Week 48 window is between Day 309 and 378 (inclusive)
b The treatment difference was stratified by baseline HIV-1 RNA (HIV-1 RNA ≤ 100,000 copies/mL or > 100,000 copies/mL)
c. Includes patients who had ≥50 copies/mL in the Week 48 window, patients who discontinued early due to lack or loss of efficacy, patients who discontinued for reasons other than an adverse event, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL.
d. Includes patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
e. Includes patients who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Atazanavir + cobicistat + TRUVADA was non-inferior in achieving HIV-1 RNA < 50 copies/mL when compared to atazanavir + ritonavir + TRUVADA.

In Study GS-US-216-0114, the mean increase from baseline in CD4+ cell count at Week 48 was 213 cells/mm^3 in patients receiving atazanavir + cobicistat + TRUVADA and 219 cells/mm^3 in patients receiving atazanavir + ritonavir + TRUVADA.

Drug Resistance
In an analysis of treatment-failure patients in Study GS-US-216-0114 through Week 48, evaluable genotypic data from paired baseline and treatment-failure isolates were available for 11 of the 12 virologic failures in the TYBOST group. Among the 11 patients, 2 developed the emtricitabine (FTC)-associated resistance substitution M184V. No subject developed the tenofovir (TDF) associated resistance substitution K65R or any primary resistance substitution associated with protease inhibitors. In the ritonavir group, evaluable genotypic data were available for all 12 virologic failures and no patient had emergent resistance to any component of the regimen.

INDICATIONS

TYBOST is indicated as a pharmacokinetic enhancer of appropriate HIV-1 protease inhibitors in adults (See Dosage and Administration).

CONTRAINDICATIONS

Coadministration with the following drugs is contraindicated due to the potential for serious and/or life-threatening events or loss of virologic response and possible resistance to TYBOST (See Drug Interactions):

- Alpha 1-adrenoreceptor antagonists: alfuzosin
- Antimycobacterials: rifabutin, rifampin, rifapentine
- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine
- GI motility agents: cisapride
- Herbal products: St. John's wort (*Hypericum perforatum*)
- HMG CoA reductase inhibitors: lovastatin, simvastatin
- Neuroleptics: pimozide
- PDE-5 inhibitors: sildenafil and tadalafil for the treatment of pulmonary arterial hypertension
- Sedative/hypnotics: orally administered midazolam, triazolam

PRECAUTIONS

Drug Interactions

TYBOST is a potent mechanism-based CYP3A inhibitor. Initiating treatment with TYBOST in patients receiving medications metabolized by CYP3A or initiating medications metabolized by CYP3A in patients already receiving TYBOST may result in increased plasma concentration of these concomitant medications. Higher plasma concentrations of concomitant medications can result in increased or prolonged therapeutic or adverse effects, potentially leading to severe, life-threatening or fatal events. The potential for drug-drug interactions must be considered prior to and during therapy with TYBOST. Review of other medications taken by patients and monitoring of patients for adverse effects is recommended during therapy with TYBOST.

See CONTRAINDICATIONS for a listing of drugs that are contraindicated due to potentially life-threatening adverse events, significant drug interactions or loss of effectiveness. Also, see Table 6 for a listing of drugs with established and other potentially significant drug-drug interactions (see CONTRAINDICATIONS).

TYBOST is a pharmacokinetic enhancer of atazanavir and darunavir. Prescribers should consult the Product Information of atazanavir and darunavir for a description of additional contraindicated drugs and significant drug-drug interactions associated with these drugs.

Use with Antiretrovirals

Dosing recommendations have only been established for use of TYBOST with either atazanavir or darunavir once daily. TYBOST should not be used as a pharmacokinetic enhancer to boost any

other HIV-1 protease inhibitor, since dosing recommendations for such coadministration have not been established and may result in insufficient plasma level of the protease inhibitor leading to loss of therapeutic effect and development of resistance. (see DOSAGE AND ADMINISTRATION).

TYBOST coadministered with atazanavir or darunavir should not be used in combination with another antiretroviral that requires boosting (i.e., another protease inhibitor or VITEKTA), since dosing recommendations for such combination have not been established and may result in decreased plasma concentrations of atazanavir, darunavir and/or the other antiretroviral leading to loss of therapeutic effect and development of resistance.

TYBOST should not be used concurrently with products containing ritonavir or regimens containing ritonavir due to similar effects of cobicistat and ritonavir on CYP3A.

TYBOST should not be used in combination with the fixed-dose combination product STRIBILD since cobicistat is a component of STRIBILD.

Renal

Effects on Serum Creatinine

TYBOST has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when interpreting changes in estimated creatinine clearance in patients initiating TYBOST, particularly in patients with medical conditions or receiving drugs needing monitoring with estimated creatinine clearance, or when coadministered with drugs with dosing adjustment recommendations guided by estimated creatinine clearance.

Although cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function, patients who experience a confirmed increase in serum creatinine of greater than 35 µmol/L f from baseline should be monitored and evaluated for evidence of tubulopathy.

New Onset or Worsening Renal Impairment When Used with Tenofovir Disoproxil Fumarate

Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported when TYBOST is used in an antiretroviral regimen that contains tenofovir disoproxil fumarate (tenofovir DF).

- Do not initiate TYBOST as part of a regimen containing tenofovir DF in patients who have an estimated creatinine clearance below 70 mL/min because dose adjustment of tenofovir DF is required below 50 mL/min and such dose adjustments have not been established for coadministration with TYBOST. Patients should be switched to an

alternative antiretroviral regimen if estimated creatinine clearance decreases to less than 50 mL/min.

- Document estimated creatinine clearance, urine glucose and urine protein (ratio) at baseline and perform routine monitoring during treatment when TYBOST is used with tenofovir DF.
- Proteinuria, normoglycemic glycosuria and increased fractional excretion of phosphorous may represent the first signs of tubulopathy and precede any decline in renal function.
- Measure serum phosphorus in patients with or at risk for renal impairment.
- Avoid use of TYBOST with tenofovir DF in combination with concomitant or recent use of a nephrotoxic agent.

Effects on Fertility
Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 3-fold higher than human exposures at the recommended 150 mg daily dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) approximately similar to human exposures at the recommended 150 mg daily dose.

Use in Pregnancy
Pregnancy Category B1.

There are no adequate and well controlled clinical studies of TYBOST in pregnant women. Because animal reproductive studies are not always predictive of human response, TYBOST should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Because TYBOST must be used in combination with atazanavir or darunavir, also refer to the Product Information for pregnancy category of atazanavir and darunavir.
In a rat study, foetal development was unaffected by an oral dose of cobicstat resulting in a drug exposure (AUC) that was 1.9-fold higher than in humans receiving the 150 mg daily dose. There was a tendency for reduced foetal weight and increases in skeletal variations with a higher dose that was associated with reduced maternal food consumption and bodyweight gain. Treatment of rabbits with a dose resulting in a drug exposure approximately 3 times that in humans receiving the 150 mg daily dose did not affect foetal development.

Use in Lactation
Studies in rats have demonstrated that cobicistat is secreted into milk.

It is not known whether cobicistat is excreted in human milk. Because of the potential for both HIV transmission and for serious adverse events in nursing infants, mothers should be instructed not to breast feed if they are receiving TYBOST.

Paediatric Use
Safety and effectiveness of TYBOST in children less than 18 years of age have not been established.

Use in the Elderly
Clinical studies of TYBOST did not contain sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Caution should be exercised when prescribing TYBOST to the elderly, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Effects on Laboratory Tests
There are no known interactions of TYBOST with any laboratory tests.

Genotoxicity
Cobicistat was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

Carcinogenicty
In a long-term carcinogenicity study in mice, no drug-related increases in tumor incidence were observed at doses up to 50 and 100 mg/kg/day (males and females, respectively). Cobicistat exposures at these doses were approximately 7 (male) and 16 (females) times, respectively, the human systemic exposure at the therapeutic daily dose. In a long-term carcinogenicity study of cobicistat in rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses of 25 and 50 mg/kg/day in males, and at 30 mg/kg/day in females. The follicular cell findings are considered to be rat-specific, secondary to hepatic microsomal enzyme induction and thyroid hormone imbalance, and are not relevant for humans. At the highest doses tested in the rat carcinogenicity study, systemic exposures were approximately 2 times the human systemic exposure at the therapeutic daily dose.

INTERACTIONS WITH OTHER MEDICINES

Effect of Cobicistat on the Pharmacokinetics of Concomitant Drugs
TYBOST is a potent mechanism-based inhibitor of cytochrome P450 3A (CYP3A) and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. Drugs that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in exposure when co-administered with TYBOST. Thus, coadministration of TYBOST with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Coadministration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 6.

TYBOST is a weak inhibitor of CYP2D6. TYBOST is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19. TYBOST is not expected to induce CYP1A2, CYP3A4, CYP2C9, CYP2C19, UGT1A1, or MDR1.

Effect of Concomitant Drugs on the Pharmacokinetics of Cobicistat

TYBOST is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of TYBOST. Coadministration of TYBOST with drugs that induce CYP3A may result in decreased plasma concentration of the booster cobicistat and consequently that of atazanavir or darunavir., leading to loss of therapeutic effect and possible development of resistance. Coadministration of TYBOST with drugs that inhibit CYP3A may result in increased plasma concentration of cobicistat.

Established and Other Potentially Significant Interactions

Table 6 provides dosing recommendations as a result of drug interactions with TYBOST. These recommendations are based on either drug interactions studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of therapeutic effect.

For additional drug-drug interactions with atazanavir or darunavir, consult their respective Product Information when using TYBOST.

The table is not all-inclusive (see CONTRAINDICATIONS).

Table 6 Established Significant [a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiretroviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
didanosine	« didanosine « cobicistat	Coadministration of didanosine buffered tablets is expected to decrease atazanavir plasma concentration. Consult the atazanavir prescribing information for atazanavir dosing recommendation when used concomitantly with didanosine. When didanosine is coadministered with darunavir/cobicistat, didanosine should be administered one hour before or two hours after darunavir/cobicistat (which are administered with food).
tenofovir disoproxil fumarate	- tenofovir « cobicistat	Coadministration of tenofovir disoproxil fumarate with TYBOST is expected to increase tenofovir plasma concentration. This increase is not expected to be clinically relevant and does not necessitate dose adjustment of tenofovir disoproxil fumarate.
Antiretroviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
efavirenz	¯ cobicistat	Coadministration of efavirenz and TYBOST is expected to decrease cobicistat plasma concentration and consequently that of atazanavir or darunavir, which may result in loss of therapeutic effect and development of resistance. Such coadministration is not recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
etravirine	¯ cobicistat	Coadministration of etravirine and TYBOST is expected to decrease cobicistat plasma concentration and consequently that of atazanavir or darunavir, which may result in loss of therapeutic effect and development of resistance. Such coadministration is not recommended.
delavirdine	- cobicistat - delavirdine	Coadministration of delavirdine and TYBOST may increase delavirdine and/or cobicistat plasma concentration. The appropriate dose of delavirdine in combination with atazanavir/cobicistat or darunavir/cobicistat has not been established.
nevirapine	¯ cobicistat - nevirapine	Coadministration of nevirapine and TYBOST is expected to decrease cobicistat plasma concentration and consequently that of atazanavir or darunavir, which may result in loss of therapeutic effect and development of resistance. Such coadministration is not recommended.
rilpivirine	- rilpivirine « cobicistat	Coadministration of rilpivirine and TYBOST is expected to increase the plasma concentration of rilpivirine. Rilpivirine is not expected to affect the plasma concentration of cobicistat. Concomitant use of rilpivirine with boosted PIs may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.
Antiretroviral Agents: CCR5 Antagonists		
maraviroc	- maraviroc	Maraviroc is a substrate of CYP3A and its plasma concentration increases when coadministered with potent CYP3A inhibitors. When coadministering maraviroc and atazanavir/cobicistat or darunavir/cobicistat, patients should receive maraviroc 150 mg twice daily. For further details, see local prescribing information for maraviroc.
Other Agents:		
Acid Reducing Agents: antacids	« cobicistat	No dose adjustment of cobicistat is required when coadministered with antacids. Concomitant use of antacids, including buffered medications, is expected to decrease atazanavir plasma concentration. Consult the atazanavir prescribing information for atazanavir dosing recommendation when used concomitantly with acid-reducing agents.
Alpha 1-Adrenoreceptor Antagonist: alfuzosin	- alfuzosin	Alfuzosin is primarily metabolized by CYP3A. Coadministration with TYBOST may result in increased plasma concentrations of alfuzosin, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of TYBOST and alfuzosin is contraindicated.
Analeptics: modafinil	¯ cobicistat	Coadministration of modafinil, a CYP3A inducer, may decrease cobicistat plasma concentrations and consequently that of atazanavir or darunavir, which may result in loss of therapeutic effect and development of resistance. Alternative analeptics should be considered.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiarrhythmics: amiodarone bepridil disopyramide flecainide systemic lidocaine mexiletine propafenone quinidine	- antiarrhythmics	Concentrations of these antiarrhythmic drugs may be increased when coadministered with TYBOST. Caution is warranted and clinical monitoring is recommended upon coadministration of these agents with TYBOST.
digoxin	- digoxin	The peak concentration of digoxin is increased when coadministered with TYBOST. The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effects.
Antibacterials: clarithromycin	- clarithromycin - cobicistat ¯ 14-OH clarithromycin	Concentrations of clarithromycin may be increased upon coadministration of TYBOST, consult the prescribing information of atazanavir or darunavir for dosing recommendations when these agents are used concomitantly with clarithromycin.
Anticancer Agents: dasatinib nilotinib vinblastine vincristine	- anticancer agents	Concentrations of these drugs may be increased when coadministered with TYBOST resulting in the potential for increased adverse events usually associated with these anticancer agents.
Anticoagulants: warfarin	- or ¯ warfarin	Concentrations of warfarin may be affected upon coadministration with TYBOST. It is recommended that the international normalized ratio (INR) be monitored upon coadministration with TYBOST.
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	¯ cobicistat	Coadministration of carbamazepine, oxcarbazepine, phenobarbital or phenytoin, CYP3A inducers, may significantly decrease cobicistat plasma concentrations and consequently that of atazanavir or darunavir, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered.
clonazepam ethosuximide	- clonazepam - ethosuximide	Concentrations of clonazepam and ethosuximide may be increased when coadministered with TYBOST. Clinical monitoring is recommended upon coadministration with TYBOST.
Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs) desipramine trazodone	- SSRIs - desipramine - trazodone	Concentrations of these antidepressant agents may be increased when coadministered with TYBOST. Dose titration may be required for most drugs of the SSRI class. The concentration of desipramine is increased when coadministered with TYBOST. Concentrations of trazodone may increase upon coadministration with TYBOST. If trazodone or desipramine is used with TYBOST, the combination should be used with caution, and a lower dose of trazodone or desipramine should be considered.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antifungals: itraconazole ketoconazole voriconazole	- antifungals - cobicistat	Concentrations of ketoconazole, itraconazole and/or cobicistat may increase with coadministration of TYBOST. When administering with TYBOST, the maximum daily dose of ketoconazole and itraconazole should not exceed 200 mg per day. Concentrations of voriconazole may be increased when coadministered with TYBOST. Clinical monitoring may be needed upon coadministration with TYBOST.
Anti-gout: colchicine	- colchicine	TYBOST should not be coadministered with colchicine to patients with renal or hepatic impairment. Treatment of gout-flares – coadministration of colchicine in patients receiving TYBOST: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. Prophylaxis of gout-flares – coadministration of colchicine in patients receiving TYBOST: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. Treatment of familial Mediterranean fever – coadministration of colchicine in patients receiving TYBOST: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterial: rifabutin rifampin rifapentine	– cobicistat	Coadministration of rifampin, rifabutin, and rifapentine, potent CYP3A inducers, may significantly decrease cobicistat plasma concentrations and consequently that of atazanavir or darunavir, which may result in loss of therapeutic effect and development of resistance. Coadministration of TYBOST with rifampin, rifabutin, and rifapentine are contraindicated.
Beta-Blockers: metoprolol timolol	- beta-blockers	Concentrations of beta-blockers may be increased when coadministered with cobicistat. Clinical monitoring is recommended and a dose reduction may be necessary when these agents are coadministered with TYBOST.
Calcium Channel Blockers: amlodipine diltiazem felodipine nicardipine nifedipine verapamil	- calcium channel blockers	Concentrations of calcium channel blockers may be increased when coadministered with TYBOST. Caution is warranted and clinical monitoring is recommended upon coadministration with TYBOST.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Systemic Corticosteroids: dexamethasone fluticasone	¯ cobicistat - fluticasone	Coadministration of dexamethasone, a CYP3A inducer, may significantly decrease cobicistat plasma concentrations and consequently that of atazanavir or darunavir, which may result in loss of therapeutic effect and development of resistance. Coadministration of fluticasone and TYBOST is not recommended unless the potential benefit to the patient outweighs the risks of systemic corticosteroid side effects. Alternative corticosteroids should be considered. Coadministration of inhaled or oral corticosteroids with TYBOST is not recommended unless the potential benefit to the patient outweighs the risks.
Endothelin Receptor Antagonists: bosentan	- bosentan ¯ cobicistat	Coadministration of bosentan with TYBOST may lead to decreased cobicistat plasma concentrations and consequently that of atazanavir or darunavir, which may result in loss of therapeutic effect and development of resistance. Coadministration is not recommended.
Ergot Derivatives: dihydroergotamine ergonovine ergotamine methylergonovine	- ergot derivatives	Ergot derivatives are primarily metabolized by CYP3A. Coadministration with TYBOST may result in increased plasma concentrations of these drugs, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of TYBOST and dihydroergotamine, ergonovine, ergotamine,or methylergonovine is contraindicated.
GI Motility Agents: cisapride	- cisapride	Cisapride is primarily metabolized by CYP3A. Coadministration with TYBOST may result in increased plasma concentrations of cisapride, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of TYBOST and cisapride is contraindicated.
H_2-Receptor Antagonists: famotidine	« cobicistat	No dose adjustment of cobicistat is required when atazanavir/cobicistat or darunavir/cobicistat is coadministered with H_2-receptor antagonists. H_2-receptor antagonists are expected to decrease atazanavir plasma concentration. Consult the atazanavir prescribing information for atazanavir dosing recommendation when used concomitantly with H_2-receptor antagonists.
Herbal Products: St. John's wort (*Hypericum perforatum*)	¯ cobicistat	Coadministration of St. John's wort, a potent CYP3A inducer, may significantly decrease cobicistat plasma concentrations and consequently that of atazanavir or darunavir, which may result in loss of therapeutic effect and development of resistance. Coadministration of TYBOST with St. John's wort is contraindicated.
HMG-CoA Reductase Inhibitors: lovastatin simvastatin	- lovastatin - simvastatin	HMG-CoA reductase inhibitors are primarily metabolized by CYP3A. Coadministration with TYBOST may result in increased plasma concentrations of lovastatin or simvastatin, which are associated with the potential for serious and/or life-threatening reactions. Coadministration of TYBOST with lovastatin and simvastatin is contraindicated.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
atorvastatin pravastatin rosuvastatin	- atorvastatin - pravastatin - rosuvastatin	Plasma concentrations of atorvastatin, pravastatin or rosuvastatin isexpected to increase when coadministered with atazanavir/cobicistat or darunavir/cobicistat. Consult the local prescribing information of atazanavir or darunavir when used in combination with these drugs.
Hormonal Contraceptives: norgestimate/ethinyl estradiol	With atazanavir/cobicistat: - norgestimate - ethinyl estradiol With darunavir/cobicistat: – or - ethinyl estradiol	No data are available to make recommendations on the use of atazanavir/cobicistat with oral contraceptives. Alternative forms of contraception should be considered. No dosing recommendations can be made on the use of darunavir/cobicistat with oral contraceptives. Alternative forms of contraception should be considered.
Immunosuppressants: cyclosporine rapamycin sirolimus tacrolimus	- immunosuppressants	Concentrations of these immunosuppressant agents may be increased when coadministered with TYBOST. Therapeutic monitoring is recommended upon coadministration with TYBOST.
Inhaled Beta Agonist: salmeterol	- salmeterol	Coadministration with TYBOST may result in increased plasma concentrations of salmeterol, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of salmeterol and TYBOST is not recommended.
Neuroleptics: perphenazine pimozide risperidone thioridazine	- neuroleptics	Pimozide is primarily metabolized by CYP3A. Coadministration with TYBOST may result in increased plasma concentrations of pimozide, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of TYBOST with pimozide is contraindicated. For other neuroleptics, consider reducing the dose of the neuroleptic upon coadministration with TYBOST.
Phosphodiesterase-5 (PDE5) Inhibitors: sildenafil tadalafil vardenafil	- PDE5 inhibitors	PDE5 inhibitors are primarily metabolized by CYP3A. Coadministration with TYBOST may result in increased plasma concentrations of sildenafil and tadalafil, which may result in PDE5 inhibitor-associated adverse reactions. Coadministration of TYBOST with sildenafil for the treatment of pulmonary arterial hypertension is contraindicated. Caution should be exercised, including consideration of dose reduction, when coadministering TYBOST with tadalafil for the treatment of pulmonary arterial hypertension. For the treatment of erectile dysfunction, it is recommended that a single dose of sildenafil no more than 25 mg in 48 hours, vardenafil no more than 2.5 mg in 72 hours, or tadalafil no more than 10 mg in 72 hours be coadministered with TYBOST.
Proton-pump Inhibitors omeprazole	« cobicistat	No dose adjustment of cobicistat is required when atazanavir/cobicistat or darunavir/cobicistat is coadministered with proton-pump inhibitors. Proton-pump inhibitors are expected to decrease atazanavir plasma concentration. Consult the atazanavir prescribing information for atazanavir dosing recommendation when used concomitantly with proton-pump inhibitors.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Sedative/hypnotics: buspirone clorazepate diazepam estazolam flurazepam orally-administered midazolam triazolam zolpidem	- sedatives/hypnotics	Midazolam and triazolam are primarily metabolized by CYP3A. Coadministration with TYBOST may result in increased plasma concentrations of these drugs, which are associated with the potential for serious and/or life-threatening reactions. Coadministration of TYBOST and orally administered midazolam and triazolam are contraindicated. For other sedative/hypnotics, dose reduction may be necessary and concentration monitoring is recommended.

a. This table is not all inclusive.
b. - = increase, ¯ = decrease, ↔ = no effect

Effects on ability to drive and use machines
No studies on the effects of TYBOST on the ability to drive and use machines have been performed.

ADVERSE EFFECTS

Experience from Clinical Trials
The safety of TYBOST has been established in a Phase III randomized, active-controlled clinical trial (GS-US-216-0114), in which 692 treatment-naïve patients received TYBOST -boosted atazanavir (ATV) (N=344) or ritonavir-boosted atazanavir (N=348) administered with TRUVADA for at least 48 weeks. Adverse reactions for TYBOST -boosted atazanavir were consistent with the safety profile of ritonavir-boosted atazanavir.

The most frequently reported adverse reactions were associated with elevated bilirubin levels. Table 7 below lists the frequency of adverse reactions (Grade 2-4) occurring in at least 3% of patients receiving TYBOST -boosted atazanavir + TRUVADA in Study GS-US-216-0114.

Table 7 Selected Treatment-Emergent Adverse Drug Reactions[a] (Grades 2-4) Reported in ≥ 3% of Subjects Receiving TYBOST -boosted Atazanavir + TRUVADA in Study GS-US-216-0114. (Week 48 analysis)

	TYBOST -boosted Atazanavir + TRUVADA	Ritonavir-boosted Atazanavir + TRUVADA
	N=344	N=348
EYE DISORDERS		
Ocular icterus	3%	1%
GASTROINTESTINAL DISORDERS		
Diarrhoea	3%	5%
Nausea	4%	3%
HEPATOBILIARY DISORDERS		
Jaundice	7%	3%
Hyperbilirubinaemia	10%	8%
NERVOUS SYSTEM DISORDERS		
Headache	4%	3%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drugs

Laboratory Abnormalities: the frequency of treatment-emergent laboratory abnormalities (Grade 3-4) occurring in at least 3% of patients receiving TYBOST -boosted atazanavir + TRUVADA in Study GS-US-216-0114 are presented in Table 8.

Table 8: Laboratory Abnormalities (Grades 3-4) Reported in ≥ 3% of Patients Receiving TYBOST -boosted atazanavir + TRUVADA in Study GS-US-216-0114 (Week 48 analysis)

	TYBOST -boosted Atazanavir + TRUVADA	Ritonavir-boosted Atazanavir + TRUVADA
Laboratory Parameter Abnormality	N=344	N=348
Total Bilirubin (> 2.5 × ULN)	65%	57%
Creatine Kinase (³ 10.0 x ULN)	6%	6%
Serum Amylase[a] (> 2.0 × ULN)	3%	2%
ALT (>5.0 x ULN)	3%	2%
Urine RBC (Haematuria) (> 75 RBC/HPF)	4%	2%

a. For patients with serum amylase > 1.5 x upper limit of normal, lipase test was also performed. The frequency of increased lipase (Grade 3-4) occurring in TYBOST -boosted atazanavir plus TRUVADA (N=38) and ritonavir-boosted atazanavir plus TRUVADA (N=28) treatment groups was 5% and 4%, respectively.

TYBOST has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. An increase in serum

creatinine due to TYBOST's inhibitory effect generally does not exceed 35 µmol/L from baseline. In Study GS-US-216-114, decreases in estimated creatinine clearance occurred early in treatment with TYBOST, after which they stabilized. The mean (± SD) change in estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method after 48 weeks of treatment was -13.4 ± 15.2 mL/min in the TYBOST -boosted atazanavir + TRUVADA group and -8.7 ± 14.5 mL/min in the ritonavir-boosted atazanavir + TRUVADA group (see PHARMACOLOGY).

Serum Lipids: changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides are presented in Table 9:

Table 9 Lipid Values, Mean Change from Baseline, Reported in Patients Receiving TYBOST -boosted atazanavir + TRUVADA or Ritonavir-boosted atazanavir + TRUVADA in Study GS-US-216-0114 (Week 48 analysis)

	TYBOST -boosted Atazanavir + TRUVADA		**Ritonavir-boosted Atazanavir + TRUVADA**	
	Baseline	**Week 48**	**Baseline**	**Week 48**
	Mean (mg/nmol/L)	Mean (Change from baseline mg/nmol/L[a])	Mean (mg/nmol/L)	Mean (Change from baseline mg/nmol/L[a])
Total Cholesterol (fasted)	4 [N=323]	0.1 [N=278]	4 [N=328]	0.2 [N=287]
HDL-cholesterol (fasted)	1 [N=322]	0. 1 [N=277]	1 [N=328]	0.1 [N=287]
LDL-cholesterol (fasted)	3 [N=322]	0.2 [N=278]	3 [N=328]	0.2 [N=288]
Triglycerides (fasted)	1.4 [N=323]	0.2 [N=278]	1.5 [N=328]	0.4 [N=287]

a. The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values.

DOSAGE AND ADMINISTRATION

TYBOST must be coadministered with atazanavir or darunavir. The recommended dose of TYBOST is one tablet, once daily taken orally with food.

The recommended dose of TYBOST and that of the coadministered protease inhibitor, atazanavir or darunavir, are presented in Table 10. As TYBOST is used in combination with atazanavir or darunavir, also consult the Product Information for atazanavir or darunavir.

Table 10 Recommended Dosing Regimens

Dose of TYBOST	**Dose of Recommended HIV-1 Protease Inhibitor**
150 mg once daily	atazanavir 300 mg once daily
	darunavir 800 mg once daily

TYBOST is not recommended for use with HIV-1 protease inhibitors other than those presented in Table 10.

Renal impairment: No dose adjustment of TYBOST is required in patients with renal impairment, including those with severe renal impairment (see PHARMACOLOGY).

TYBOST has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when TYBOST is coadministered with a drug that has dosing adjustment recommendations guided by estimated creatinine clearance. For example, TYBOST should not be initiated as part of a regimen containing emtricitabine, lamivudine, tenofovir disoproxil fumarate or adefovir dipivoxil in patients who have an estimated creatinine clearance below 70 mL/min since dose adjustment of these drugs is required below 50 mL/min and such dose adjustments have not been established in combination with TYBOST (see PRECAUTIONS; Effects on Serum Creatinine).

Hepatic impairment: No dose adjustment of TYBOST is required in patients with mild or moderate hepatic impairment (see PHARMACOLOGY).

OVERDOSAGE

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with TYBOST consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) and 0800 764 766 (New Zealand).

Limited clinical experience is available at doses higher than the therapeutic dose of cobicistat. In two studies, single dose of cobicistat 400 mg was administered to a total of 60 healthy subjects. No severe adverse reactions were reported. The effects of higher doses are not known. As cobicistat is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis**.**

PRESENTATION AND STORAGE CONDITIONS

TYBOST is available as tablets. Each tablet contains 150 mg of cobicistat. The tablets are round, film-coated and orange in colour. Each tablet is debossed with 'GSI' on one side and plain faced on the other side.

TYBOST is supplied in high density polyethylene (HDPE) bottles containing 30 tablets and a silica gel desiccant, polyester coil and is closed with a child resistant closure.

TYBOST should be stored below 25 °C.

NAME AND ADDRESS OF THE SPONSOR

Gilead Sciences Pty Ltd
Level 6, 417 St Kilda Road
Melbourne, Victoria 3004

POISON SCHEDULE OF THE DRUG

S4

DATE OF FISRT INCLUSION ON ARTG:

23 October 2013

Attachment 1: Product information for AusPAR Cobicistat Tybost Gilead Sciences Pty Ltd PM-2012-02160-3-2 Final 16 December 2013. This Product Information was approved at the time this AusPAR was published.