HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TYBOST safely and effectively. See full prescribing information for TYBOST.

TYBOST® (cobicistat) tablets, for oral use
Initial U.S. Approval: 2012

----------**RECENT MAJOR CHANGES**----------

Contraindications (4)	06/2016
Warnings and Precautions (5.4)	06/2016

----------**INDICATIONS AND USAGE**----------

TYBOST is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection. (1)

Limitations of Use:

- TYBOST is not interchangeable with ritonavir to increase systemic exposure of darunavir 600 mg twice daily, fosamprenavir, saquinavir, or tipranavir due to lack of exposure data. The use of TYBOST is not recommended with darunavir 600 mg twice daily, fosamprenavir, saquinavir, or tipranavir. (5.4).
- 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. (5.3, 7, 12.3).

----------**DOSAGE AND ADMINISTRATION** ----------

- TYBOST must be coadministered with atazanavir or darunavir at the same time, with food, and in combination with other HIV-1 antiretroviral agents. (2.1)
- Recommended dosage: (2.1)

TYBOST Dosage	Coadministered Agent Dosage	Patient Populations
150 mg orally once daily	atazanavir 300 mg orally once daily	Treatment-naïve or experienced
	darunavir 800 mg orally once daily	Treatment-naïve Treatment-experienced with no darunavir resistance associated substitutions

- Prior to starting TYBOST, assess estimated creatinine clearance. (2.2)
- Coadministration with tenofovir DF: assess estimated creatinine clearance, urine glucose, and urine protein at baseline. (2.2)
- TYBOST coadministered with tenofovir DF is not recommended 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. (2.3)

----------**DOSAGE FORMS AND STRENGTHS**----------

Tablets: 150 mg. (3)

----------**CONTRAINDICATIONS**----------

Coadministration with certain drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or loss of therapeutic effect. (4)

----------**WARNINGS AND PRECAUTIONS**----------

- Assess creatinine clearance (CLcr) before initiating treatment. (5.1)
- When TYBOST is used in combination with a tenofovir disoproxil fumarate (tenofovir DF) containing regimen, cases of acute renal failure and Fanconi syndrome have been reported. (5.2)
- Use with tenofovir DF: Assess urine glucose and urine protein at baseline and monitor CLcr, urine glucose, and urine protein. Monitor serum phosphorus in patients with or at risk for renal impairment. (5.2)
- TYBOST in combination with more than one antiretroviral that requires pharmacokinetic enhancement (i.e., two protease inhibitors or elvitegravir in combination with a protease inhibitor) is not recommended. (5.4)
- Use with HIV-1 protease inhibitors other than atazanavir or darunavir administered once daily is not recommended. (5.4)
- Coadministration with drugs or regimens containing ritonavir is not recommended. (5.4)

----------**ADVERSE REACTIONS**----------

The most common adverse drug reactions observed with TYBOST in combination with atazanavir (incidence greater than 5%, Grades 2-4) are jaundice and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------**DRUG INTERACTIONS**----------

TYBOST, in combination with atazanavir or darunavir, can alter the concentration of drugs metabolized by CYP3A or CYP2D6. Drugs that induce CYP3A can alter the concentrations of TYBOST, atazanavir and darunavir. Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.3, 7, 12.3)

----------**USE IN SPECIFIC POPULATIONS**----------

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk. (8.1)
- Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TYBOST is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection *[see Dosage and Administration (2.1)].*

Limitations of Use:

- TYBOST is not interchangeable with ritonavir to increase systemic exposure of darunavir 600 mg twice daily, fosamprenavir, saquinavir, or tipranavir due to lack of exposure data. The use of TYBOST is not recommended with darunavir 600 mg twice daily, fosamprenavir, saquinavir, or tipranavir *[see Warnings and Precautions (5.4)].*

- 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 *[see Warnings and Precautions (5.3), Drug Interactions (7), and Clinical Pharmacology (12.3)].*

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Administer TYBOST in conjunction with atazanavir or darunavir and other antiretroviral agents in the treatment of adults with HIV-1 infection. The recommended dosages of TYBOST and atazanavir or darunavir given with food are presented in Table 1. TYBOST must be coadministered at the same time as atazanavir or darunavir *[see Drug Interactions (7)].* Consult the prescribing information for atazanavir or darunavir.

Table 1 Recommended Dosing Regimens

TYBOST Dosage	Coadministered Agent Dosage	Patient Populations
150 mg orally once daily	atazanavir 300 mg orally once daily	Treatment-naïve or experienced
	darunavir 800 mg orally once daily	Treatment-naïve Treatment-experienced with no darunavir resistance associated substitutions

2.2 Testing Prior to Initiation of TYBOST

Prior to starting TYBOST, assess estimated creatinine clearance because TYBOST decreases estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function *[see Warnings and Precautions (5.1)].* When coadministering TYBOST with tenofovir disoproxil fumarate (tenofovir DF), assess estimated creatinine clearance, urine glucose, and urine protein at baseline *[see Warnings and Precautions 5.2]*.

2.3 Renal Impairment

TYBOST coadministered with tenofovir DF is not recommended 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 *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Orange, round, biconvex, film-coated tablets debossed with “GSI” on one side and plain faced on the other side providing 150 mg of cobicistat.

4 CONTRAINDICATIONS

The concomitant use of TYBOST with atazanavir or darunavir and the following drugs (see Table 2) is contraindicated due to the potential for serious and/or life-threatening events or loss of therapeutic effect *[see Drug Interactions (7.1, 7.2)]*.

Table 2 Drugs that are Contraindicated with Concomitant use with TYBOST and Atazanavir or Darunavir

Drug Class	Drugs within Class that are Contraindicated	Clinical Comment
Alpha 1-Adrenoreceptor Antagonist	alfuzosin	Potential for increased alfuzosin concentrations, which can result in serious or life-threatening reactions such as hypotension.
Antianginal	ranolazine	Potential for serious and/or life-threatening reactions.
Antiarrhythmic	dronedarone	Potential for increased dronedarone concentrations.
Anticonvulsants	carbamazepine, phenobarbital, phenytoin	Potential for decreased atazanavir or darunavir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.
Anti-gout	colchicine	Contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions.
Antimycobacterial	rifampin	Rifampin is a potent inducer of CYP metabolism and coadministration may cause a significant decrease in the plasma concentrations of atazanavir or darunavir and result in loss of therapeutic effect and

		development of resistance.
Antineoplastics	irinotecan	**Contraindicated with TYBOST coadministered with atazanavir only:** Atazanavir inhibits UGT1A1 and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicity.
Antipsychotics	lurasidone pimozide	Potential for serious and/or life-threatening reactions. Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Ergot Derivatives	dihydroergotamine, ergotamine, methylergonovine	Potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products	St. John's wort (*Hypericum perforatum*)	Products containing St. John's wort may result in reduced plasma concentrations of atazanavir or darunavir, which may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis.
Non-nucleoside Reverse Transcriptase Inhibitor	nevirapine	**Contraindicated with TYBOST coadministered with atazanavir only:** Nevirapine substantially decreases atazanavir exposure which may result in loss of therapeutic effect and development of resistance. Potential risk for nevirapine-associated adverse reactions due to increased nevirapine exposures.
Phosphodiesterase-5 (PDE-5) Inhibitor	sildenafil[a] when administered as REVATIO® for the treatment of pulmonary arterial hypertension	Potential for sildenafil-associated adverse reactions (which include visual disturbances, hypotension, priapism, and syncope).
Protease Inhibitor	indinavir	**Contraindicated with TYBOST coadministered with atazanavir only:** Both atazanavir and indinavir are associated with indirect (unconjugated) hyperbilirubinemia.
Sedative/hypnotics	triazolam, orally administered midazolam[b]	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Co-administration of triazolam or orally administered midazolam may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life-threatening benzodiazepine reactions such as prolonged or increased sedation or respiratory depression.

a. See *Drug Interactions (7), Table 6* for sildenafil when dosed as VIAGRA for erectile dysfunction.
b. See *Drug Interactions (7), Table 6* for parenterally administered midazolam.

5 WARNINGS AND PRECAUTIONS

5.1 Effects on Serum Creatinine

TYBOST decreases 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.

Prior to initiating therapy with TYBOST, assess estimated creatinine clearance *[see Dosage and Administration (2.2)]*. Dosage recommendations are not available for drugs that require dosage adjustments in TYBOST-treated patients with renal impairment *[see Adverse Reactions (6.1), Drug Interactions (7.3), and Clinical Pharmacology (12.2)]*. Consider alternative medications that do not require dosage adjustments in patients with renal impairment.

Although TYBOST 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 0.4 mg/dL from baseline should be closely monitored for renal safety.

5.2 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 was used in an antiretroviral regimen that contained tenofovir DF.

- Coadministration of TYBOST and tenofovir DF is not recommended 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 *[see Dosage and Administration (2.2, 2.3)]*.

- Document urine glucose and urine protein at baseline *[see Dosage and Administration (2.2)]* and perform routine monitoring of estimated creatinine clearance, urine glucose, and urine protein during treatment when TYBOST is used with tenofovir DF. Measure serum phosphorus in patients with or at risk for renal impairment when used with tenofovir DF.

- Coadministration of TYBOST and tenofovir DF in combination with concomitant or recent use of a nephrotoxic agent is not recommended.

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