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**----------

Indications and Usage (1.1)	10/2019
Dosage and Administration	
Recommended Dosage in Pediatric Patients (2.2)	10/2019
Warnings and Precautions	
Risk of Serious Adverse Reactions or Loss of Virologic Response Due to Drug Interactions (5.3)	08/2020

----------**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 in adults and in pediatric patients:

- weighing at least 35 kg coadministered with atazanavir or
- weighing at least 40 kg coadministered with darunavir. (1.1)

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. (1.2, 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. (1.2, 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, 2.2)
- Recommended dosage in adults: (2.1)

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

- Recommended dosage in pediatric patients: TYBOST 150 mg orally once daily. For dosage recommendations of the coadministered protease inhibitor atazanavir or darunavir, refer to Table 2 of the full prescribing information. (2.2)
- Prior to starting TYBOST, assess estimated creatinine clearance. (2.3)
- Coadministration with tenofovir disoproxil fumarate (TDF): assess estimated creatinine clearance, urine glucose, and urine protein at baseline. (2.3)
- TYBOST coadministered with TDF is not recommended in patients who have an estimated creatinine clearance below 70 mL/min because dose adjustment of TDF is required below 50 mL/min and such dose adjustments have not been established for coadministration with TYBOST. (2.4)

----------**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 TDF-containing regimen, cases of acute renal failure and Fanconi syndrome have been reported. (5.2)
- Use with TDF: 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: TYBOST coadministered with darunavir or atazanavir is not recommended during pregnancy. TYBOST coadministered with darunavir or atazanavir should not be initiated in pregnant individuals. (2.5, 8.1, 12.3)
- Lactation: Breastfeeding is not recommended due to the potential for HIV transmission. (8.2)
- Pediatrics: Not recommended in combination with atazanavir for patients weighing less than 35 kg. Not recommended in combination with darunavir for patients weighing less than 40 kg. (8.4)

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

Revised: 08/2020

Reference ID: 4660245

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Indications
- 1.2 Limitations of Use

2 DOSAGE AND ADMINISTRATION
- 2.1 Recommended Dosage in Adults
- 2.2 Recommended Dosage in Pediatric Patients
- 2.3 Testing Prior to Initiation of TYBOST
- 2.4 Renal Impairment
- 2.5 Not Recommended During Pregnancy

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Effects on Serum Creatinine
- 5.2 New Onset or Worsening Renal Impairment When Used with Tenofovir Disoproxil Fumarate
- 5.3 Risk of Serious Adverse Reactions or Loss of Virologic Response Due to Drug Interactions
- 5.4 Antiretrovirals that are Not Recommended in Combination with TYBOST

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS
- 7.1 Potential Effect of Cobicistat (Coadministered with Atazanavir or Darunavir) on the Pharmacokinetics of Concomitant Drugs
- 7.2 Potential Effect of Concomitant Drugs on the Pharmacokinetics of Cobicistat (Coadministered with Atazanavir or Darunavir)
- 7.3 Established and Other Potentially Significant Interactions

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
- 14.1 Clinical Trial Results in HIV-1 Infected Treatment-Naïve Adult Subjects – Trial 114
- 14.2 Clinical Trial Results in HIV-1 Infected Virologically Suppressed Pediatric Subjects – Trial 128

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

Reference ID: 4660245

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Indications

Adult Patients:

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 in adults *[see Dosage and Administration (2.1)].*

Pediatric Patients:

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 in pediatric patients *[see Dosage and Administration (2.2)]:*

- weighing at least 35 kg coadministered with atazanavir or
- weighing at least 40 kg coadministered with darunavir.

1.2 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 in Adults

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.

Reference ID: 4660245

Table 1 Recommended Dosing Regimens in Treatment-Naïve or Treatment-Experienced Adults

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

2.2 Recommended Dosage in Pediatric Patients

Administer TYBOST in conjunction with atazanavir or darunavir and other antiretroviral agents in the treatment of pediatric patients with HIV-1 infection. The recommended dosages of TYBOST and atazanavir or darunavir given with food are based on weight and presented in Table 2. 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 2 Recommended Dosing Regimens in Treatment-Naïve or Treatment-Experienced Pediatric Patients

TYBOST Dosage	Coadministered Agent Dosage	Patient Populations and Weight
150 mg orally once daily	atazanavir 300 mg orally once daily	Treatment-naïve or treatment-experienced weighing at least 35 kg
	darunavir 800 mg orally once daily	Treatment-naïve or treatment-experienced with no darunavir resistance-associated substitutions weighing at least 40 kg

2.3 Testing Prior to Initiation of TYBOST

Prior to or when initiating TYBOST and during treatment with TYBOST, on a clinically appropriate schedule, 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 TDF, assess estimated creatinine clearance, urine glucose, and urine protein at baseline. In patients with

Reference ID: 4660245

chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.2)].*

2.4 Renal Impairment

TYBOST coadministered with TDF is not recommended in patients who have an estimated creatinine clearance below 70 mL/min because dose adjustment of TDF 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)]*.

2.5 Not Recommended During Pregnancy

TYBOST coadministered with darunavir is not recommended for use during pregnancy because of substantially lower exposures of darunavir and cobicistat during the second and third trimesters *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

TYBOST coadministered with atazanavir is not recommended for use during pregnancy because of substantially lower exposures of cobicistat during the second and third trimesters *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

TYBOST coadministered with darunavir or atazanavir should not be initiated in pregnant individuals. An alternative regimen is recommended for individuals who become pregnant during therapy with TYBOST coadministered with darunavir or atazanavir.

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 is contraindicated due to the potential for serious and/or life-threatening events or loss of therapeutic effect *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: dronedarone
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Anti-gout: colchicine
- Antimycobacterial: rifampin
- Antineoplastics: irinotecan*

Reference ID: 4660245

- Antipsychotics: lurasidone, pimozide
- Ergot Derivatives: dihydroergotamine, ergotamine, methylergonovine
- GI Motility Agent: cisapride
- Herbal Products: St. John's wort (*Hypericum perforatum*)
- Hormonal Contraceptives: drospirenone/ ethinyl estradiol*
- Lipid-modifying Agents: lomitapide, lovastatin, simvastatin
- Non-nucleoside Reverse Transcriptase Inhibitor: nevirapine*
- Phosphodiesterase-5 (PDE-5) Inhibitor: sildenafil when administered as Revatio® for the treatment of pulmonary arterial hypertension
- Protease Inhibitor: indinavir*
- Sedative/hypnotics triazolam, orally administered midazolam

*These contraindications apply only to TYBOST coadministered with atazanavir

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 (2.3)]*. 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 TDF.

Reference ID: 4660245

- Coadministration of TYBOST and TDF is not recommended in patients who have an estimated creatinine clearance below 70 mL/min because dose adjustment of TDF is required below 50 mL/min and such dose adjustments have not been established for coadministration with TYBOST *[see Dosage and Administration (2.3, 2.4)]*.

- Document urine glucose and urine protein at baseline *[see Dosage and Administration (2.3)]* and perform routine monitoring of estimated creatinine clearance, urine glucose, and urine protein during treatment when TYBOST is used with TDF. Measure serum phosphorus in patients with or at risk for renal impairment when used with TDF.

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

In a clinical trial of TYBOST over 144 weeks (N=692), 10 (2.9%) subjects treated with TYBOST coadministered with atazanavir and TRUVADA® and 11 (3.2%) subjects treated with ritonavir coadministered with atazanavir and TRUVADA discontinued study drug due to a renal adverse event. Seven of the 10 subjects (2.0% overall) in the TYBOST group had laboratory findings consistent with proximal renal tubulopathy leading to study drug discontinuation compared to 7 of 11 subjects (2.0% overall) in the ritonavir group. One subject in the TYBOST group had renal impairment at baseline (i.e., estimated creatinine clearance less than 70 mL/min). The laboratory findings in these 7 subjects with evidence of proximal tubulopathy improved but did not completely resolve in all subjects upon discontinuation of TYBOST coadministered with atazanavir and TRUVADA. Renal replacement therapy was not required in any subject.

5.3 Risk of Serious Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

Initiation of TYBOST, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A, or initiation of medications metabolized by CYP3A in patients already receiving TYBOST, may increase plasma concentrations of medications metabolized by CYP3A and reduce plasma concentrations of active metabolite(s) formed by CYP3A. Initiation of medications that inhibit or induce CYP3A may respectively increase or decrease concentrations of TYBOST with atazanavir or darunavir.

Increased concentrations may lead to:

- clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from higher exposures of concomitant medications.

- clinically significant adverse reactions from higher exposures of TYBOST and atazanavir or darunavir.

Decreased concentrations may lead to:

- loss of therapeutic effect of TYBOST with atazanavir or darunavir and possible development of resistance.

Reference ID: 4660245

- loss of therapeutic effect of the concomitant medications from lower exposures of concomitant drugs or active metabolite(s).

See Table 6 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during TYBOST with atazanavir or darunavir therapy; review concomitant medications during TYBOST with atazanavir or darunavir therapy; and monitor for the adverse reactions associated with concomitant medications *[see Contraindications (4) and Drug Interactions (7)]*.

TYBOST or ritonavir when administered with either atazanavir or darunavir may result in different drug interactions when used with concomitant medications. Complex or unknown mechanisms of drug interactions preclude extrapolation of ritonavir drug interactions to certain TYBOST interactions *[see Drug Interactions (7) and Clinical Pharmacology (12.3)].*

5.4 Antiretrovirals that are Not Recommended in Combination with TYBOST

The following antiretrovirals are not recommended in combination with TYBOST because dosing recommendations for such combinations have not been established and coadministration may result in decreased plasma concentrations of the antiretroviral agents, leading to loss of therapeutic effect and development of resistance:

- More than one antiretroviral that requires pharmacokinetic enhancement (i.e., two protease inhibitors or a protease inhibitor in combination with elvitegravir)
- Darunavir in combination with efavirenz, nevirapine, or etravirine
- Atazanavir in combination with etravirine
- Atazanavir in combination with efavirenz in treatment-experienced patients
- Darunavir 600 mg twice daily
- Other HIV-1 protease inhibitors including fosamprenavir, saquinavir, or tipranavir

TYBOST in combination with fixed-dose combination tablets that contain cobicistat is not recommended.

TYBOST in combination with lopinavir/ritonavir or regimens containing ritonavir is not recommended due to similar effects of TYBOST and ritonavir on CYP3A.

6 ADVERSE REACTIONS

The following adverse reaction is described in greater detail in another section of the labeling:

- New Onset or Worsening Renal Impairment When Used with Tenofovir Disoproxil Fumarate *[see Warnings and Precautions (5.2)].*

Reference ID: 4660245

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions from Clinical Trials Experience in Adults

The safety of TYBOST is based on Week 144 data from a Phase 3 trial, Trial 114, in which 692 HIV-1 infected, antiretroviral treatment-naïve subjects received:

- TYBOST coadministered with atazanavir and TDF/emtricitabine (administered as TRUVADA) (N=344) or
- ritonavir coadministered with atazanavir and TDF/emtricitabine (administered as TRUVADA) (N=348).

The most common adverse reactions (Grades 2–4) and reported in >5% of subjects in the TYBOST group were jaundice (6%) and rash (5%). The proportion of subjects who discontinued study treatment due to adverse events, regardless of severity, was 11% in both the TYBOST and ritonavir groups. Table 3 displays the frequency of adverse reactions (Grades 2–4) occurring in at least 2% of subjects in the TYBOST group in Trial 114.

Table 3 Selected Adverse Reactions[a] (Grades 2–4) Reported in ≥2% of HIV-1 Infected Treatment-Naïve Adults in the TYBOST Coadministered with Atazanavir Group in Trial 114 (Week 144 Analysis)

	TYBOST Coadministered with Atazanavir + TRUVADA N=344	Ritonavir Coadministered with Atazanavir + TRUVADA N=348
Jaundice	6%	3%
Rash[b]	5%	4%
Ocular icterus	4%	2%
Nausea	2%	2%
Diarrhea	2%	1%
Headache	2%	1%

a. Frequencies of adverse reactions are based on Grades 2–4 adverse events attributed to study drugs.

b. Rash events include dermatitis allergic, drug hypersensitivity, pruritus generalized, eosinophilic pustular folliculitis, rash, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash papular, and urticaria.

Less Common Adverse Reactions

Selected adverse reactions of at least moderate severity (≥Grade 2) occurring in less than 2% of subjects receiving TYBOST coadministered with atazanavir and TRUVADA are listed below. These events have been included because of the investigator's

Reference ID: 4660245

assessment of potential causal relationship and were considered serious or have been reported in more than one subject treated with TYBOST and with greater frequency compared with ritonavir.

Gastrointestinal Disorders: vomiting, upper abdominal pain

General Disorders and Administration Site Conditions: fatigue

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis

Psychiatric Disorders: depression, abnormal dreams, insomnia

Renal and Urinary Disorders: nephropathy, Fanconi syndrome acquired, nephrolithiasis

Refer to the prescribing information for atazanavir or darunavir for information regarding adverse reactions with these drugs.

Laboratory Abnormalities: The frequency of laboratory abnormalities (Grades 3−4) occurring in at least 2% of subjects in the TYBOST group in Trial 114 is presented in Table 4.

Table 4 Laboratory Abnormalities (Grades 3−4) in ≥2% of HIV-1 Infected Treatment-Naïve Adults in the TYBOST Coadministered with Atazanavir Group in Trial 114 (Week 144 Analysis)

	TYBOST + Atazanavir + TRUVADA	**Ritonavir + Atazanavir + TRUVADA**
Laboratory Parameter Abnormality	N=344	N=348
Total Bilirubin (>2.5 × ULN)	73%	66%
Creatine Kinase (≥10.0 × ULN)	8%	9%
Urine RBC (Hematuria) (>75 RBC/HPF)	6%	3%
ALT (>5.0 × ULN)	6%	3%
AST (>5.0 × ULN)	4%	3%
GGT (>5.0 × ULN)	4%	2%
Serum Amylase[a] (>2.0 × ULN)	4%	2%
Urine Glucose (Glycosuria) (≥1000 mg/dL)	3%	3%
Neutrophils (<750/mm^3)	3%	2%
Serum Glucose (Hyperglycemia) (>250 mg/dL)	2%	2%

a. For subjects with serum amylase >1.5 × upper limit of normal, lipase test was also performed. The frequency of increased lipase (Grades 3−4) occurring in the TYBOST (N=46) and ritonavir (N=35) groups was 7% and 3%, respectively.

Increase in Serum Creatinine: TYBOST causes increases in serum creatinine and decreases in estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function *[see Warnings and*

Reference ID: 4660245

Precautions (5.1) and Clinical Pharmacology (12.2)]. In Trial 114, increases in serum creatinine and 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 144 weeks of treatment was –15.1 ± 16.5 mL/min in the TYBOST group and –8.0 ± 16.8 mL/min in the ritonavir group.

Serum Lipids: Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides are presented in Table 5. In both groups, mean values for serum lipids remained within the study reference range for each laboratory test. The clinical significance of these changes is unknown.

Table 5 Lipid Values, Mean Change from Baseline, Reported in HIV-1 Infected Treatment-Naïve Adults Receiving TYBOST Coadministered with Atazanavir + TRUVADA or Ritonavir Coadministered with Atazanavir + TRUVADA in Trial 114 (Week 144 Analysis)

	TYBOST + Atazanavir + TRUVADA		**Ritonavir + Atazanavir + TRUVADA**	
	Baseline	**Week 144**	**Baseline**	**Week 144**
	mg/dL	Change from baseline[a]	mg/dL	Change from baseline[a]
Total Cholesterol (fasted)	163 [N=219]	+11 [N=219]	165 [N=227]	+13 [N=227]
HDL-cholesterol (fasted)	43 [N=218]	+7 [N=218]	43 [N=228]	+6 [N=228]
LDL-cholesterol (fasted)	102 [N=218]	+11 [N=218]	104 [N=228]	+16 [N=228]
Triglycerides (fasted)	130 [N=219]	+14 [N=219]	131 [N=227]	+14 [N=227]

a. The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 144 values. Analysis excludes subjects receiving an HMG-CoA reductase inhibitor drug.

Adverse Reactions from Clinical Trials Experience in Pediatric Subjects

The safety of TYBOST was evaluated in HIV-1 infected virologically suppressed pediatric subjects between the ages of 12 to less than 18 years through Week 48 in an open-label clinical trial (Trial 128) of TYBOST coadministered with atazanavir (N=14) or darunavir (N=7) plus two nucleoside reverse transcriptase inhibitors *[see Clinical Studies (14.2)]*. In this trial, the safety profile of TYBOST was similar to that in adults.

Reference ID: 4660245

7 DRUG INTERACTIONS

7.1 Potential Effect of Cobicistat (Coadministered with Atazanavir or Darunavir) on the Pharmacokinetics of Concomitant Drugs

Cobicistat is an inhibitor of CYP3A and CYP2D6. The transporters that cobicistat inhibits include p-glycoprotein (P-gp), BCRP, OATP1B1, and OATP1B3. The plasma concentration of drugs that are primarily metabolized by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1, or OATP1B3 may be increased if those drugs are coadministered with TYBOST.

Based on in vitro data, cobicistat is not expected to induce CYP1A2 or CYP2B6 and based on in vivo data, cobicistat is not expected to induce MDR1 or, in general, CYP3A to a clinically significant extent. The induction effect of cobicistat on CYP2C9, CYP2C19, or UGT1A1 is unknown, but is expected to be low based on CYP3A in vitro induction data.

Coadministration of TYBOST with atazanavir or darunavir 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 drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s). Coadministration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 6.

7.2 Potential Effect of Concomitant Drugs on the Pharmacokinetics of Cobicistat (Coadministered with Atazanavir or Darunavir)

Cobicistat is metabolized by CYP3A, and to a minor extent, by CYP2D6. Atazanavir and darunavir are also metabolized by CYP3A.

Coadministration of TYBOST with atazanavir or darunavir in combination with drugs that induce CYP3A activity have the potential to decrease plasma concentrations of cobicistat, atazanavir, and darunavir, which may lead to loss of therapeutic effect and development of resistance (see Table 6).

Coadministration of TYBOST with atazanavir or darunavir in combination with other drugs that inhibit CYP3A may further increase the plasma concentrations of cobicistat, atazanavir, and darunavir (see Table 6).

7.3 Established and Other Potentially Significant Interactions

Coadministration of TYBOST with fosamprenavir, saquinavir, or tipranavir is not recommended because pharmacokinetic data are not available to provide appropriate dosing recommendations. Use of TYBOST with lopinavir is not recommended because lopinavir is co-formulated with ritonavir.

Table 6 provides dosing recommendations as a result of drug interactions with TYBOST coadministered with atazanavir or darunavir. These recommendations are based on

Reference ID: 4660245

either drug interaction trials or predicted interactions due to the expected magnitude of the interaction and potential for serious adverse events or loss of therapeutic effect *[see Contraindications (4), Warnings and Precautions (5.3, 5.4), and Clinical Pharmacology (12.3)].*

In Table 6, if not specifically stated, the drug interaction information applies to both coadministered agents: TYBOST coadministered with atazanavir or darunavir *[see Clinical Pharmacology (12.3)]*.

In addition to the drug interactions noted in Table 6, TYBOST is not recommended for use in combination with fixed-dose combination tablets that contain cobicistat, lopinavir/ritonavir or regimens containing ritonavir, or in combination with more than one antiretroviral agent that requires pharmacokinetic enhancement *[see Warnings and Precautions (5.4)].*

Evaluate whether dosing adjustments of concomitant medications or coadministered antiretroviral drugs are necessary in:

- Patients on a stable concomitant medication who initiate or switch to a TYBOST-containing regimen
- Patients on a TYBOST-containing regimen who initiate a new concomitant medication
- Patients initiating a TYBOST-containing regimen and a new concomitant medication simultaneously

Under these circumstances, also monitor for adverse events and/or monitor concentrations of concomitant medications if appropriate.

No dose adjustment is required when TDF or rilpivirine are coadministered with TYBOST and atazanavir or darunavir.

Reference ID: 4660245

Table 6 Established and Other Potentially Significant[a] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Potential Effect[b]	Clinical Comment
Antiretroviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
efavirenz	↓ cobicistat ↓ darunavir ↓ atazanavir	**TYBOST coadministered with darunavir:** Coadministration of darunavir and TYBOST with efavirenz is not recommended because it may result in the loss of therapeutic effect and development of resistance to darunavir. **TYBOST coadministered with atazanavir:** ***In treatment-naïve patients:*** Atazanavir 400 mg with TYBOST 150 mg should be coadministered once daily as a single dose with food, and efavirenz 600 mg should be administered once daily on an empty stomach, preferably at bedtime. ***In treatment-experienced patients:*** Coadministration of atazanavir and TYBOST with efavirenz in treatment-experienced patients is not recommended because it may result in the loss of therapeutic effect and development of resistance to atazanavir.
etravirine	↓ cobicistat darunavir: effect unknown ↓ atazanavir	Coadministration with etravirine is not recommended because it may result in the loss of therapeutic effect and development of resistance to atazanavir or darunavir.
nevirapine	↓ atazanavir ↑nevirapine ↓ cobicistat darunavir: effect unknown	**Contraindicated with TYBOST coadministered with atazanavir only:** Coadministration of atazanavir with nevirapine is contraindicated due to potential for loss of atazanavir therapeutic effect and development of resistance, and potential for nevirapine-associated adverse reactions. **TYBOST coadministered with darunavir:** TYBOST coadministration with nevirapine and darunavir is not recommended because it may result in the loss of therapeutic effect and development of resistance to darunavir.
Antiretroviral Agents: CCR5 Antagonists		
maraviroc	↑ maraviroc	Maraviroc is a substrate of CYP3A. When coadministering with maraviroc, patients should receive maraviroc 150 mg twice daily.
Antiretroviral Agents: Protease Inhibitors		
indinavir		**Contraindicated with TYBOST coadministered with atazanavir only:** Both atazanavir and indinavir are associated with indirect (unconjugated) hyperbilirubinemia.

Reference ID: 4660245

Other Agents:		
Alpha 1-adrenoreceptor antagonist: alfuzosin	↑ alfuzosin	Coadministration with alfuzosin is contraindicated due to potential for serious and/or life-threatening reactions such as hypotension.
Antianginal ranolazine	↑ ranolazine	Coadministration with ranolazine is contraindicated due to potential for serious and/or life-threatening reactions.
Antacids: e.g., aluminum and magnesium hydroxide *(please also see H_2-Receptor Antagonists and Proton Pump Inhibitors below)*	↓ atazanavir	**TYBOST coadministered with atazanavir:** With concomitant use, administer a minimum of 2 hours apart.
Antiarrhythmics: dronedarone digoxin Other antiarrhythmics: e.g., amiodarone disopyramide flecainide mexiletine propafenone quinidine	↑ dronedarone ↑ digoxin ↑ antiarrhythmics	Coadministration with dronedarone is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias. When coadministering with digoxin, titrate the digoxin dose and monitor digoxin concentrations. Clinical monitoring is recommended upon coadministration with antiarrhythmics.
Antibacterials (macrolide or ketolide antibiotics): clarithromycin erythromycin telithromycin	↑ clarithromycin ↑ erythromycin ↑ telithromycin ↑ cobicistat ↑ atazanavir ↑ darunavir	Consider alternative antibiotics with concomitant use of TYBOST coadministered with atazanavir or darunavir.
Anticancer Agents: irinotecan dasatinib nilotinib vinblastine vincristine	↑ irinotecan ↑ anticancer agents	**Contraindicated with TYBOST coadministered with atazanavir only:** Coadministration of atazanavir with irinotecan is contraindicated due to potential for increased irinotecan toxicity. A decrease in the dosage or an adjustment of the dosing interval of dasatinib or nilotinib may be necessary upon coadministration with TYBOST coadministered with atazanavir or darunavir. Consult the dasatinib and nilotinib prescribing information for dosing instructions. For vincristine and vinblastine, monitor for hematologic or gastrointestinal side effects.

Reference ID: 4660245

Anticoagulants: Direct Oral Anticoagulants (DOACs) apixaban rivaroxaban betrixaban dabigatran edoxaban	↑ apixaban	**TYBOST coadministered with atazanavir or darunavir:** Due to potentially increased bleeding risk, dosing recommendations for coadministration of apixaban with TYBOST depends on the apixaban dose. Refer to apixaban dosing instructions for coadministration with strong CYP3A and P-gp inhibitors in apixaban prescribing information.
	↑ rivaroxaban	Coadministration of rivaroxaban with TYBOST is not recommended because it may lead to an increased bleeding risk.
	atazanavir: ↑ betrixaban ↑ dabigatran ↑ edoxaban	**TYBOST coadministered with atazanavir:** Due to potentially increased bleeding risk, dosing recommendations for coadministration of betrixaban, dabigatran, or edoxaban with a P-gp inhibitor such as TYBOST coadministered with atazanavir depends on DOAC indication and renal function. Refer to DOAC dosing instructions for coadministration with P-gp inhibitors in DOAC prescribing information.
	darunavir: ↔ betrixaban ↔ dabigatran ↔ edoxaban	**TYBOST coadministered with darunavir:** No dose adjustment.
warfarin	warfarin: effect unknown	Monitor the international normalized ratio (INR) upon coadministration of TYBOST with warfarin.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ atazanavir ↓ darunavir ↓ cobicistat	Coadministration with carbamazepine, phenobarbital, or phenytoin is contraindicated due to potential for loss of therapeutic effect and development of resistance.
Anticonvulsants with CYP3A induction effects that are NOT contraindicated e.g., eslicarbazepine, oxcarbazepine	↓ cobicistat ↓ atazanavir darunavir: effect unknown	Consider alternative anticonvulsant or antiretroviral therapy to avoid potential changes in exposures. If coadministration is necessary, monitor for lack or loss of virologic response.
Anticonvulsants that are metabolized by CYP3A e.g., clonazepam	↑ clonazepam	Clinical monitoring of anticonvulsants is recommended.

Reference ID: 4660245

Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs) e.g., paroxetine Tricyclic Antidepressants (TCAs) e.g., amitriptyline desipramine imipramine nortriptyline Other antidepressants: trazodone	SSRIs: effects unknown ↑ TCAs ↑ trazodone	When coadministering with SSRIs, TCAs, or trazodone, careful dose titration of the antidepressant to the desired effect, including using the lowest feasible initial or maintenance dose, and monitoring for antidepressant response are recommended.
Antifungals: itraconazole ketoconazole voriconazole	↑ itraconazole ↑ ketoconazole Voriconazole: effects unknown ↑ cobicistat ↑ atazanavir ↑ darunavir	Specific dosing recommendations are not available for coadministration with itraconazole or ketoconazole. Coadministration with voriconazole is not recommended unless the benefit/risk assessment justifies the use of voriconazole.
Anti-gout: colchicine	↑ colchicine	Coadministration with colchicine is contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions. <u>Treatment of gout flares – coadministration of colchicine:</u> 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. <u>Prophylaxis of gout flares – coadministration of colchicine:</u> 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. <u>Treatment of familial Mediterranean fever – coadministration of colchicine:</u> Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).

Reference ID: 4660245

Antimycobacterial: rifampin	↓ atazanavir ↓ darunavir ↓ cobicistat	Coadministration with rifampin is contraindicated due to potential for loss of therapeutic effect and development of resistance.
rifabutin	↑ rifabutin cobicistat: effects unknown darunavir: effects unknown atazanavir: effects unknown	The recommended dosage regimen for rifabutin is 150 mg every other day. Monitor for rifabutin associated adverse reactions including neutropenia and uveitis.
Antiplatelets: ticagrelor	↑ ticagrelor	Coadministration with ticagrelor is not recommended.
clopidogrel	↓ clopidogrel active metabolite	Coadministration with clopidogrel is not recommended due to potential reduction of the antiplatelet activity of clopidogrel.
prasugrel	↔ prasugrel active metabolite	No dose adjustment is needed when prasugrel is co-administered with TYBOST.
Antipsychotics: lurasidone	↑ lurasidone	Coadministration with lurasidone is contraindicated due to potential for serious and/or life-threatening reactions.
pimozide	↑ pimozide	Coadministration with pimozide is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
quetiapine	↑ quetiapine	<u>Initiation of TYBOST coadministered with atazanavir or darunavir in patients taking quetiapine:</u> Consider alternative antiretroviral therapy to avoid increases in quetiapine exposure. If coadministration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. <u>Initiation of quetiapine in patients taking TYBOST coadministered with atazanavir or darunavir:</u> Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
Other antipsychotics: e.g., perphenazine risperidone thioridazine	↑ antipsychotic	A decrease in the dose of antipsychotics that are metabolized by CYP3A or CYP2D6 may be needed upon coadministration.

Reference ID: 4660245

Beta-Blockers: e.g., metoprolol carvedilol timolol	↑ beta-blockers	Clinical monitoring is recommended for coadministration with beta-blockers that are metabolized by CYP2D6.
Calcium Channel Blockers: e.g., amlodipine diltiazem felodipine nifedipine verapamil	↑ calcium channel blockers	Clinical monitoring is recommended for coadministration with calcium channel blockers metabolized by CYP3A.
Corticosteroids (all routes, excluding cutaneous): e.g., betamethasone budesonide ciclesonide dexamethasone fluticasone methylprednisolone mometasone triamcinolone	↓ cobicistat ↓ atazanavir ↓ darunavir ↑ corticosteroids	Coadministration with oral dexamethasone or other systemic corticosteroids that induce CYP3A may result in loss of therapeutic effect and development of resistance to atazanavir or darunavir. Consider alternative corticosteroids. Coadministration with corticosteroids whose exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone (whose PK and/or PD are less affected by strong CYP3A inhibitors relative to other studied steroids) should be considered, particularly for long-term use.
Endothelin Receptor Antagonists: bosentan	↑ bosentan ↓ cobicistat ↓ darunavir ↓ atazanavir	<u>Initiation of bosentan in patients taking TYBOST coadministered with atazanavir or darunavir:</u> In patients who have been receiving TYBOST coadministered with atazanavir or darunavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. <u>Initiation of TYBOST coadministered with atazanavir or darunavir in patients taking bosentan:</u> Discontinue use of bosentan at least 36 hours prior to initiation of TYBOST coadministered with atazanavir or darunavir. After at least 10 days following the initiation of TYBOST combined with atazanavir or darunavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability. <u>Switching from ritonavir to TYBOST coadministered with atazanavir or darunavir:</u> Maintain bosentan dose.
Ergot Derivatives: dihydroergotamine, ergotamine, methylergonovine	↑ ergot derivatives	Coadministration is contraindicated due to 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	↑ cisapride	Coadministration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.

Reference ID: 4660245

H_2-Receptor Antagonists: e.g., famotidine	↓ atazanavir	**TYBOST coadministered with atazanavir:** Administer atazanavir/TYBOST either at the same time or a minimum of 10 hours after administering H_2-receptor antagonists. The dose of the H_2-receptor antagonist should not exceed a dose comparable to famotidine 40 mg twice daily in treatment-naïve patients or 20 mg twice daily in treatment-experienced patients. **TYBOST coadministered with atazanavir and TDF:** Treatment-experienced patients: The recommended once daily dosage regimen is TYBOST 150 mg coadministered with atazanavir 400 mg with concomitant use of H_2-receptor antagonists and tenofovir.
HCV Protease Inhibitors: boceprevir simeprevir	darunavir: effects unknown atazanavir: effects unknown boceprevir: effects unknown ↑ simeprevir	No drug interaction data are available. Coadministration with boceprevir or simeprevir is not recommended.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ atazanavir ↓ darunavir ↓ cobicistat	Coadministration is contraindicated due to potential for loss of therapeutic effect and development of resistance.
Hormonal Contraceptives:		Additional or alternative non-hormonal forms of contraception should be considered when estrogen based contraceptives are coadministered with TYBOST and atazanavir or darunavir.
drospirenone/ethinyl estradiol	atazanavir: ↑ drospirenone	**Contraindicated with TYBOST coadministered with atazanavir only:** Coadministration of atazanavir with drospirenone is contraindicated due to potential for drospirenone-associated hyperkalemia.
	darunavir: ↑ drospirenone ↓ ethinyl estradiol	**TYBOST coadministered with darunavir:** For coadministration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia.
Other progestin/estrogen contraceptives	progestin: effects unknown estrogen: effects unknown	No data are available to make recommendations on the coadministration of TYBOST and atazanavir or darunavir with other hormonal contraceptives.
Immuno-suppressants: cyclosporine everolimus sirolimus tacrolimus	↑ immuno-suppressants	These immunosuppressant agents are metabolized by CYP3A. Therapeutic drug monitoring is recommended if coadministered.

Reference ID: 4660245

Inhaled Beta Agonist: salmeterol	↑ salmeterol	Coadministration with salmeterol is not recommended and may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Lipid-modifying Agents: HMG-CoA reductase inhibitors: lovastatin simvastatin	↑ lovastatin ↑ simvastatin	Coadministration with lovastatin or simvastatin is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis.
Other HMG-CoA reductase inhibitors: e.g., atorvastatin rosuvastatin	↑ HMG-CoA reductase inhibitors	Coadministration of atazanavir and TYBOST with atorvastatin is not recommended. For HMG-CoA reductase inhibitors that are not contraindicated with TYBOST coadministered with atazanavir or darunavir, start with the lowest recommended dose and titrate while monitoring for safety (e.g., myopathy). Dosage recommendations with atorvastatin or rosuvastatin are as follows. **TYBOST coadministered with atazanavir:** • Rosuvastatin dosage should not exceed 10 mg **TYBOST coadministered with darunavir:** • Atorvastatin dosage should not exceed 20 mg • Rosuvastatin dosage should not exceed 20 mg
Other lipid-modifying agents: lomitapide	↑ lomitapide	Coadministration with lomitapide is contraindicated due to potential for markedly increased transaminases.
Narcotic Analgesics **For treatment of opioid dependence:** buprenorphine buprenorphine/ naloxone methadone	buprenorphine or buprenorphine/ naloxone: effects unknown methadone: effects unknown	<u>Initiation of buprenorphine, buprenorphine/naloxone, or methadone in patients taking TYBOST coadministered with atazanavir or darunavir:</u> Carefully titrate the dose of buprenorphine, buprenorphine/naloxone, or methadone to the desired effect; use the lowest feasible initial or maintenance dose. <u>Initiation of TYBOST coadministered with atazanavir or darunavir in patients taking buprenorphine, buprenorphine/naloxone, or methadone:</u> A dose adjustment for buprenorphine, buprenorphine/naloxone, or methadone may be needed. Monitor clinical signs and symptoms.

Reference ID: 4660245

fentanyl tramadol	↑ fentanyl ↑ tramadol	Careful monitoring of therapeutic and adverse effects of fentanyl (including potentially fatal respiratory depression) is recommended with coadministration. A dose decrease may be needed for tramadol with concomitant use.
Phosphodiesterase-5 (PDE-5) Inhibitors: avanafil sildenafil tadalafil vardenafil	↑ PDE-5 inhibitors	Coadministration with avanafil is not recommended because a safe and effective avanafil dosage regimen has not been established. Coadministration with TYBOST coadministered with atazanavir or darunavir may result in an increase in PDE-5 inhibitor associated adverse events, including hypotension, syncope, visual disturbances, and priapism. <u>Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH):</u> • Use of sildenafil is contraindicated when used for the treatment of PAH due to potential for sildenafil-associated adverse reactions (which include visual disturbances, hypotension, priapism, and syncope). • The following dose adjustments are recommended for tadalafil concomitant use: *Initiation of tadalafil in patients taking TYBOST coadministered with atazanavir or darunavir:* In patients taking TYBOST coadministered with atazanavir or darunavir for at least 1 week, start tadalafil at 20 mg once daily. Increase tadalafil dose to 40 mg once daily based upon individual tolerability. *Initiation of TYBOST coadministered with atazanavir or darunavir in patients taking tadalafil:* Avoid use of tadalafil during the initiation of TYBOST coadministered with atazanavir or darunavir. Stop tadalafil at least 24 hours prior to starting TYBOST coadministered with atazanavir or darunavir. After at least one week following initiation of TYBOST coadministered with atazanavir or darunavir, resume tadalafil at 20 mg once daily. Increase tadalafil dose to 40 mg once daily based upon individual tolerability. *Patients switching from ritonavir to TYBOST coadministered with atazanavir or darunavir:* Maintain tadalafil dose. <u>Use of PDE-5 inhibitors for erectile dysfunction:</u> Sildenafil at a single dose not exceeding 25 mg in 48 hours, tadalafil at a single dose not exceeding 10 mg in 72 hours, or vardenafil at a single dose not exceeding 2.5 mg in 72 hours can be used with increased

Reference ID: 4660245

		monitoring for PDE-5 inhibitor associated adverse events.
Proton-pump Inhibitors (PPIs) e.g., omeprazole	↓ atazanavir	**TYBOST coadministered with atazanavir:** In treatment-naïve patients, administer TYBOST with atazanavir a minimum of 12 hours after administering PPIs. The dose of the PPI should not exceed a dose comparable to omeprazole 20 mg daily. In treatment-experienced patients, coadministration with PPIs, with or without tenofovir, is not recommended.
Sedative/Hypnotics: midazolam (oral), triazolam	↑ midazolam ↑ triazolam	Coadministration with triazolam or oral administered midazolam is contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. Triazolam and orally administered midazolam are extensively metabolized by CYP3A. Coadministration of triazolam or orally administered midazolam with TYBOST may cause large increases in the concentrations of these benzodiazepines.
Other benzodiazepines: e.g., parenterally administered midazolam clorazepate diazepam estazolam flurazepam	↑ sedatives/hypnotics	Coadministration with parenteral midazolam may increase plasma concentrations of midazolam. Coadministration should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosing reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.
buspirone zolpidem		With other sedatives/hypnotics that are CYP3A metabolized, dose reduction may be necessary and clinical monitoring is recommended.

a. This table is not all inclusive.
b. ↑ = Increase, ↓ = Decrease, ↔ = No change

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors fetal outcomes in individuals exposed to TYBOST during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) 1-800-258-4263.

Reference ID: 4660245

Risk Summary

TYBOST coadministered with darunavir or atazanavir is not recommended during pregnancy *[see Dosage and Administration (2.5)]*. In a clinical trial of individuals taking cobicistat coadministered with darunavir, exposures of cobicistat and darunavir were substantially lower during the second and third trimesters of pregnancy *[see Data and Clinical Pharmacology (12.3)]*.

TYBOST use during pregnancy has been evaluated in a limited number of individuals as reported by the APR, and available data show no significant difference in the rate of overall birth defects for cobicistat compared with the background rate for major defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) (*see Data).* The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15−20%.

In animal reproduction studies in rats and rabbits, no evidence of fetal harm was observed with oral administration of cobicistat during organogenesis at doses that produced exposures up to 1.4 and 3.3 times, respectively, the maximal recommended human dose (MRHD) of 150 mg *(see Data).* Because TYBOST is coadministered with atazanavir or darunavir and other antiretroviral drugs, also refer to the prescribing information of each drug for information about pregnancy.

Data

Human Data

Cobicistat coadministered with darunavir as a fixed dose combination, in combination with a background regimen, was evaluated in a clinical trial of 7 pregnant individuals taking darunavir/cobicistat prior to enrollment and who were willing to remain on darunavir/cobicistat throughout the study. The study period included the second and third trimesters, and through 12 weeks postpartum. Six pregnant individuals completed the trial.

Exposure to darunavir and cobicistat as part of an antiretroviral regimen was substantially lower during the second and third trimesters of pregnancy compared with postpartum *[see Clinical Pharmacology (12.3)]*.

One out of 6 individuals who completed the study experienced virologic failure with HIV-1 RNA >1,000 copies/mL from the third trimester visit through the postpartum period. Five individuals had sustained virologic response (HIV-1 RNA <50 copies/mL) throughout the study period. There are no clinical data on the virologic response when darunavir/cobicistat is initiated during pregnancy.

There were no new clinically relevant safety findings compared with the known safety profile of darunavir/cobicistat in HIV-1-infected adults.

The APR has received prospective reports of live births following exposure to cobicistat-containing regimens during pregnancy, including over 400 exposures in the first trimester and over 80 exposures in the second/third trimester. The prevalence of birth

Reference ID: 4660245

defects in live births was 3.9% (95% CI: 2.2% to 6.3%) and 1.2% (95% CI: 0.0% to 6.5%) following first trimester and second/third trimester exposure, respectively, to cobicistat-containing regimens. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

Animal Data

Cobicistat was administered orally to pregnant rats at doses of 0, 25, 50, and 125 mg/kg/day on gestation day 6 to 17. Maternal toxicity (adverse clinical signs, decreased body weight and food consumption) was noted at 125 mg/kg/day and was associated with increases in postimplantation loss and decreased fetal weights. No malformations were noted at doses up to 125 mg/kg/day. Systemic exposures (AUC) at 50 mg/kg/day in pregnant females were 1.4-fold higher than the exposures at the MRHD.

In pregnant rabbits, cobicistat was administered orally at doses of 0, 20, 50, and 100 mg/kg/day during the gestation days 7 to 20. No maternal or embryo/fetal effects were noted at the highest dose of 100 mg/kg/day. Systemic exposures (AUC) at 100 mg/kg/day were 3.3-fold higher than exposures at the MRHD.

In a pre- and postnatal developmental study, cobicistat was administered orally at doses of 0, 10, 30, and 75 mg/kg from gestation day 6 to postnatal day 20, 21, or 22. At doses of 75 mg/kg/day of cobicistat, neither maternal nor developmental toxicity was noted. Systemic exposures (AUC) at this dose were slightly lower than (0.9-fold) the MRHD.

8.2 Lactation

Risk Summary

There is no information regarding the presence of cobicistat in human milk, the effects on the breastfed infant, or the effects on milk production. The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

8.3 Females and Males of Reproductive Potential

Contraception

TYBOST interacts with certain oral contraceptives *[see Drug Interactions (7.3)].*

8.4 Pediatric Use

The safety and effectiveness of TYBOST coadministered with atazanavir or darunavir and two nucleoside reverse transcriptase inhibitors for the treatment of HIV-1 infection have been established in virologically suppressed pediatric patients *[see Indications and Usage (1.1) and Dosage and Administration (2.2)]*:

- weighing at least 35 kg for TYBOST coadministered with atazanavir or

Reference ID: 4660245

- weighing at least 40 kg for TYBOST coadministered with darunavir.

Use of TYBOST for this indication is supported by evidence from adequate and well-controlled studies in adults, and by pharmacokinetic, safety, and virologic data from an open-label trial (Trial 128) in virologically suppressed, HIV-1 infected pediatric subjects aged 12 years and older. The safety in these subjects through 48 weeks was similar to that in antiretroviral treatment-naïve adults *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*.

Safety and effectiveness of TYBOST in combination with atazanavir in pediatric patients weighing less than 35 kg have not been established. Safety and effectiveness of TYBOST in combination with darunavir in pediatric patients weighing less than 40 kg have not been established.

8.5 Geriatric Use

Clinical trials of TYBOST did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

8.6 Renal Impairment

No dosage adjustment of TYBOST is required in patients with renal impairment, including those with severe renal impairment. No clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects. TYBOST is coadministered with atazanavir or darunavir; therefore, refer to the prescribing information for atazanavir or darunavir for information regarding dosing recommendations of these drugs in patients with renal impairment *[see Clinical Pharmacology (12.3)].*

TYBOST has been shown to decrease estimated creatinine clearance without affecting actual renal glomerular function. Dosing recommendations are not available for drugs that require dosing adjustment for renal impairment when used in combination with TYBOST *[see Dosage and Administration (2), Warnings and Precautions (5.1), Adverse Reactions (6.1), and Clinical Pharmacology (12.2)]*.

8.7 Hepatic Impairment

No dosing adjustment of TYBOST is necessary for patients with mild-to-moderate hepatic impairment. No data are available in patients with severe hepatic impairment. TYBOST is coadministered with atazanavir or darunavir and other antiretroviral drugs; therefore, refer to the prescribing information of these other drugs for information regarding dosing recommendations in patients with hepatic impairment *[see Clinical Pharmacology (12.3)].*

Reference ID: 4660245

10 OVERDOSAGE

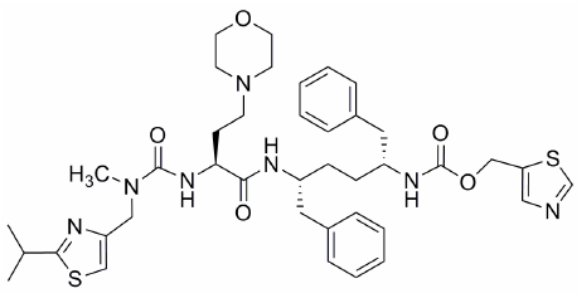
If overdose occurs, the patient must be monitored for evidence of toxicity. Treatment of overdose with TYBOST consists of general supportive measures including monitoring of vital signs, as well as observation of the clinical status of the patient.

As cobicistat is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

11 DESCRIPTION

TYBOST (cobicistat) is a mechanism-based CYP3A inhibitor.

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:



Cobicistat is adsorbed onto silicon dioxide. Cobicistat on silicon dioxide is a white to pale yellow solid with a solubility of 0.1 mg/mL in water at 20 °C.

TYBOST tablets are for oral administration. Each tablet contains 150 mg of cobicistat. The tablets include the following inactive ingredients: silicon dioxide, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The tablets are film-coated with a coating material containing the following inactive ingredients: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, sunset yellow FCF (FD&C Yellow #6) aluminum lake, and iron oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cobicistat is a mechanism-based inhibitor of cytochrome P450 3A (CYP3A). Inhibition of CYP3A-mediated metabolism by cobicistat increases the systemic exposure of CYP3A substrates atazanavir and darunavir.

Reference ID: 4660245

12.2 Pharmacodynamics

Effects on Pharmacokinetic Enhancement

The effect of TYBOST on atazanavir pharmacokinetics was evaluated in the pharmacokinetic substudy (N=48) of Trial 114 in which HIV-1 infected subjects received atazanavir 300 mg coadministered with TYBOST 150 mg or atazanavir 300 mg coadministered with ritonavir 100 mg, both in combination with TRUVADA. The steady-state pharmacokinetic parameters of atazanavir were comparable when coadministered with TYBOST versus ritonavir groups as shown in Table 7 *[see Clinical Studies (14.1)].*

Table 7 Pharmacokinetic Parameters (Mean ± SD) of Atazanavir in HIV-1 Infected Treatment-Naïve Adults (Pharmacokinetic Substudy of Trial 114)

	TYBOST + Atazanavir + TRUVADA Once Daily	**Ritonavir + Atazanavir + TRUVADA Once Daily**
Atazanavir Pharmacokinetic Parameters	N=22	N=26
AUC_{tau} (mcg·hr/mL)	46.13 ± 26.18	47.59 ± 24.38
C_{max} (mcg/mL)	3.91 ± 1.94	4.76 ± 1.94
C_{tau} (mcg/mL)	0.80 ± 0.72	0.85 ± 0.72

The effect of TYBOST on darunavir was evaluated in a clinical study (Trial 115) in 31 healthy subjects who received darunavir 800 mg in combination with TYBOST 150 mg or ritonavir 100 mg, all once daily, for 10 days. With the exception of C_{tau}, the steady-state pharmacokinetic parameters of darunavir were comparable when coadministered with TYBOST versus ritonavir as shown in Table 8, and these results were similar to those reported in previous clinical trials of darunavir 800 mg with ritonavir 100 mg once daily (refer to prescribing information for darunavir).

Table 8 Pharmacokinetic Parameters (Mean ± SD) of Darunavir in Healthy Adults (Trial 115)

	TYBOST + Darunavir Once Daily	**Ritonavir + Darunavir Once Daily**
Darunavir Pharmacokinetic Parameters	N=31	N=31
AUC_{tau} (mcg·hr/mL)	81.08 ± 25.15	79.99 ± 27.20
C_{max} (mcg/mL)	7.74 ± 1.69	7.46 ± 1.52
C_{0h} (mcg/mL)	2.40 ± 1.22	2.48 ± 0.85
C_{tau} (mcg/mL)	1.33 ± 0.89	1.87 ± 1.56

Cardiac Electrophysiology

In a thorough QT/QTc study in 48 healthy subjects, a single dose of cobicistat 250 mg and 400 mg (1.67 and 2.67 times the dose in TYBOST) did not affect the QT/QTc interval. Prolongation of the PR interval was noted in subjects receiving cobicistat. The maximum mean (95% upper confidence bound) difference in PR from placebo after

Reference ID: 4660245

baseline-correction was 9.5 (12.1) msec for the 250 mg cobicistat dose and 20.2 (22.8) for the 400 mg cobicistat dose.

Effects on Serum Creatinine

The effect of TYBOST on serum creatinine was investigated in a trial in subjects with normal renal function (eGFR ≥80 mL/min, N=12) and mild-to-moderate renal impairment (eGFR 50–79 mL/min, N=18). A statistically significant decrease in the 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). No statistically significant changes in $eGFR_{CG}$ were observed compared to baseline for subjects with normal renal function or mild-to-moderate renal impairment 7 days 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 with TYBOST among subjects with normal renal function and mild-to-moderate renal impairment, indicating that cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in $eGFR_{CG}$, without affecting the actual glomerular filtration rate *[see Warnings and Precautions (5.1)]*.

12.3 Pharmacokinetics

Absorption

In a trial where subjects were instructed to take coadministered TYBOST and darunavir with food, median cobicistat peak plasma concentrations were observed approximately 3.5 hours postdose. Steady-state cobicistat C_{max}, AUC_{tau}, and C_{tau} (mean ± SD) values were 0.99 ± 0.3 mcg/mL (n=60), 7.6 ± 3.7 mcg·hr/mL (n=59), and 0.03 ± 0.1 mcg/mL (n=59), respectively.

Effect of Food on Oral Absorption

A food-effect trial was not conducted for TYBOST. In clinical trials, TYBOST was coadministered with other antiretroviral agents *[see Clinical Studies (14.1)]* under fed conditions, in accordance with the prescribing information for these agents. It is recommended that TYBOST coadministered with atazanavir or darunavir be administered with food *[see Dosage and Administration (2.1, 2.2)]*.

Distribution

Cobicistat is 97–98% bound to human plasma proteins and the mean blood-to-plasma ratio was approximately 0.5.

Metabolism

Cobicistat is metabolized by CYP3A and to a minor extent by CYP2D6 enzymes and does not undergo glucuronidation.

Reference ID: 4660245

Elimination

The terminal plasma half-life of cobicistat following administration of TYBOST is approximately 3 to 4 hours. With single dose administration of [^{14}C] cobicistat after multiple dosing of cobicistat for 6 days, the mean percent of the administered dose excreted in feces and urine was 86.2% and 8.2%, respectively.

Specific Populations

Race and Gender

No clinically relevant differences in the pharmacokinetics of cobicistat were observed based on race or gender.

Pediatric Patients

In pediatric subjects aged 12 to less than 18 years who received TYBOST 150 mg coadministered with atazanavir 300 mg (N=12), geometric mean atazanavir C_{max} and AUC_{tau} and cobicistat AUC_{tau} values were approximately 20-30% higher than in adults and geometric mean atazanavir and cobicistat C_{tau} values were approximately 60% to 160% higher than in adults; the increases were not considered clinically significant. In pediatric subjects aged 12 to less than 18 years who received TYBOST 150 mg coadministered with darunavir 800 mg (N=7), geometric mean darunavir C_{max} and AUC_{tau} values were similar between adults and adolescents. Geometric mean darunavir AUC_{tau} and C_{tau} values were 15% and 32% lower, with geometric mean ratios of 0.85 (90% CI: 0.64, 1.13) and 0.68 (90% CI: 0.30, 1.55) in adolescent subjects relative to adults, respectively. This difference was not considered clinically significant based on exposure-response relationships. Geometric mean cobicistat AUC_{tau}, C_{max}, and C_{tau} values were comparable in adolescents and adults (Table 9).

Table 9 Multiple-Dose PK Parameters of Cobicistat, Atazanavir, and Darunavir Following Administration of TYBOST with Atazanavir or Darunavir in HIV-1 Infected Pediatric Subjects Weighing at Least 35 kg[a]

Parameter Geometric Mean (CV%)	Cobicistat		Atazanavir	Darunavir
Treatment Administered	**TYBOST + Atazanavir**	**TYBOST + Darunavir**	**TYBOST + Atazanavir**	**TYBOST + Darunavir**
Pediatric Subjects[a]	N=12	N=7	N=12	N=7
AUC_{tau} (mcg·hr/mL)	12.11 (44.7)	8.33 (34.9)	49.48 (49.1)	77.22 (29.5)
C_{max} (mcg/mL)	1.28 (31.7)	1.10 (20.0)	4.32 (49.9)	7.32 (21.7)
C_{tau} (mcg/mL)	0.09 (156.2)	0.02 (123.9)[b]	0.91 (96.4)	0.68 (91.6)
Adults[c,d]	N=30[c]	N=21[d]	N=30[c]	N=21[d]
AUC_{tau} (mcg·hr/mL)	9.65 (41.8)	7.69 (43.9)	39.96 (52.1)	90.56 (45.3)
C_{max} (mcg/mL)	1.28 (35.6)	1.04 (35.3)	3.54 (45.8)	8.34 (33.3)
C_{tau} (mcg/mL)	0.04 (112.7)	0.02 (135.1)[e]	0.58 (84.7)	1.00 (108.0)

Reference ID: 4660245

CV=Coefficient of Variation

a. From Intensive PK analysis of Trial 128.

b. N=5; Data from two subjects who had undetectable TYBOST C_{tau} concentrations were excluded from summary statistics.

c. From pooled Intensive PK analysis of trials with TYBOST + atazanavir.

d. From Intensive PK analysis of Trial GS-US-299-0102 with TYBOST + darunavir.

e. N=18.

Patients with Renal Impairment

No clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min) and healthy subjects *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

No clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with moderate hepatic impairment (Child-Pugh Class B) and healthy subjects. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of cobicistat has not been studied *[see Use in Specific Populations (8.7)].*

Pregnancy and Postpartum

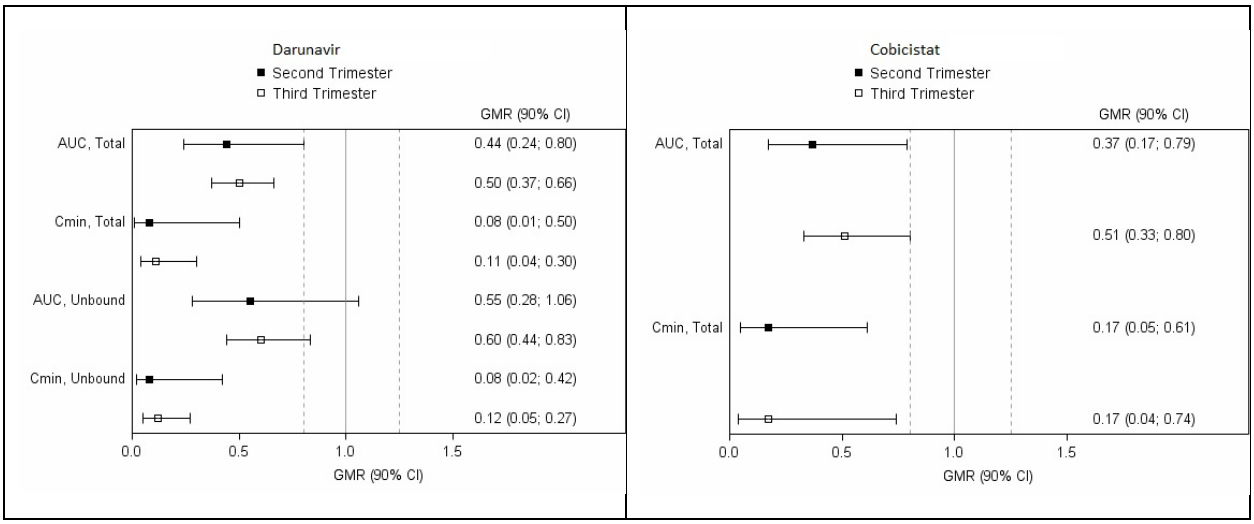
The exposure to total and unbound darunavir boosted with cobicistat after intake of darunavir/cobicistat as part of an antiretroviral regimen was substantially lower during the second and third trimesters of pregnancy compared with 6–12 weeks postpartum (see Table 10 and Figure 1).

Table 10: Pharmacokinetic Results of Total Darunavir after Administration of Darunavir/Cobicistat Once Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy, and Postpartum

Pharmacokinetics of total darunavir (mean ± SD)	2nd Trimester of pregnancy N=7	3rd Trimester of pregnancy N=6	Postpartum (6–12 weeks) N=6
C_{max}, ng/mL	4,340 ± 1,616	4,910 ± 970	7,918 ± 2,199
AUC_{24h}, ng.h/mL	47,293 ± 19,058	47,991 ± 9,879	99,613 ± 34,862
C_{min}, ng/mL	168 ± 149	184 ± 99	1,538 ± 1,344

Reference ID: 4660245

Figure 1: Pharmacokinetic Results (Within-Subject Comparison) of Total and Unbound Darunavir and Total Cobicistat After Administration of Darunavir/Cobicistat at 800/150 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd and 3rd Trimester of Pregnancy Compared to Postpartum



Legend: 90% CI: 90% confidence interval; GMR: geometric mean ratio (i.e. second or third trimester / postpartum). Solid vertical line: ratio of 1.0; dotted vertical lines: reference lines of 0.8 and 1.25.

Assessment of Drug Interactions

Drug interaction trials were conducted with TYBOST (as a single entity) and desipramine, digoxin, and efavirenz. Drug interaction trials of TYBOST coadministered with atazanavir or darunavir included atorvastatin, drospirenone/ethinyl estradiol, and rosuvastatin. Drug interaction trials of TYBOST coadministered with elvitegravir included rosuvastatin and rifabutin.

The effects of cobicistat on the exposure of coadministered drugs are shown in Table 11.

Reference ID: 4660245

Table 11 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Cobicistat[a]

Note: The information listed below is not a comprehensive list of all the available drug interaction data for concomitant medications with cobicistat containing regimens. Please refer to the U.S. prescribing information for antiretroviral medications administered in combination with cobicistat for additional drug interaction information.

Coadministered Drug	Dose of Coadministered Drug (mg)	TYBOST Dose (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00	
				C_{max}	AUC
Atorvastatin	10 single dose	150 once daily	16	18.85[b] (13.53, 26.27)	9.22[b] (7.58, 11.22)
				4.19[c] (3.67, 4.78)	3.90[c] (3.52, 4.32)
Desipramine	50 single dose	150 once daily	8	1.24 (1.08, 1.44)	1.65 (1.36, 2.02)
Digoxin	0.5 single dose	150 once daily	22	1.41 (1.29, 1.55)	1.08 (1.00, 1.17)
Drospirenone/ ethinyl estradiol	3 drospirenone single dose	150 once daily	14	1.12[b] (1.05, 1.19)	2.30[b] (2.00, 2.64)
	0.02 ethinyl estradiol single dose			0.82[b] (0.76, 0.89)	0.78[b] (0.73, 0.85)
	3 drospirenone single dose	150 once daily	15	1.15[c] (1.05, 1.26)	1.58[c] (1.47, 1.71)
	0.02 ethinyl estradiol single dose			0.86[c] (0.77, 0.95)	0.70[c] (0.63, 0.77)
Efavirenz	600 single dose	150 once daily	17	0.87 (0.80, 0.94)	0.93 (0.89, 0.97)
Rosuvastatin	10 single dose	150 once daily	16	10.58[b] (8.72, 12.83)	3.42[b] (2.87, 4.07)
				3.77[c] (3.29, 4.32)	1.93[c] (1.70, 2.20)

a. All interaction studies conducted in healthy subjects.
b. Study conducted in the presence of 300 mg atazanavir.
c. Study conducted in the presence of 800 mg darunavir.

Reference ID: 4660245

12.4 Microbiology

Antiviral Activity

Cobicistat does not inhibit recombinant HIV-1 protease in a biochemical assay and has no detectable antiviral activity in cell culture against HIV-1, HBV, or HCV. The antiviral activity in cell culture of selected HIV-1 antiretroviral drugs was not antagonized by cobicistat.

Resistance

In an analysis of treatment-failure adult subjects who received TYBOST coadministered with atazanavir and TRUVADA in Trial 114 through Week 144, evaluable genotypic data from paired baseline and treatment-failure isolates from subjects who had HIV-1 RNA greater than or equal to 400 copies/mL were available for all 21 virologic failures in the TYBOST group (6%, 21/344). Among the 21 subjects, 3 developed the emtricitabine resistance-associated substitution M184V. No subject developed the tenofovir resistance-associated substitution K65R or K70E, or any primary resistance substitution associated with protease inhibitors. In the ritonavir group, evaluable genotypic data were available for all 19 virologic failures (5%, 19/348). Among the 19 patients, 1 developed the emtricitabine resistance-associated substitution M184V with no tenofovir or protease inhibitor resistance-associated substitutions.

In an as-treated analysis of pediatric subjects between the ages of 12 to less than 18 years who received TYBOST coadministered with atazanavir or darunavir plus two NRTIs in Trial 128, 3 of 20 subjects qualified for resistance analysis through Week 48; all 3 subjects were receiving TYBOST coadministered with atazanavir and 1 had evaluable data and no significant resistance-associated substitutions in protease or reverse transcriptase *[see Clinical Studies (14.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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.

Reference ID: 4660245

Mutagenesis

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

Impairment of 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) of approximately similar human exposures at the recommended 150 mg daily dose.

14 CLINICAL STUDIES

14.1 Clinical Trial Results in HIV-1 Infected Treatment-Naïve Adult Subjects – Trial 114

The activity of TYBOST as a CYP3A inhibitor to increase the systemic exposures of atazanavir or darunavir has been demonstrated in pharmacokinetic trials. In these trials, the exposure of atazanavir or darunavir coadministered with TYBOST 150 mg was consistent with those observed with ritonavir 100 mg *[see Clinical Pharmacology (12.2)]*. For clinical efficacy of darunavir/ritonavir 800/100 mg once daily, refer to the prescribing information for darunavir.

The safety and efficacy of TYBOST coadministered with atazanavir were evaluated in a randomized, double-blind, active-controlled trial (Trial 114) in HIV-1 infected treatment-naïve subjects with baseline estimated creatinine clearance above 70 mL/min (N=692). In Trial 114, subjects were randomized in a 1:1 ratio to receive either atazanavir 300 mg + TYBOST 150 mg once daily or atazanavir 300 mg + ritonavir 100 mg once daily. All subjects received concomitant treatment with 300 mg of TDF and 200 mg of emtricitabine once a day 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 subjects 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). Forty percent of patients had baseline viral loads >100,000 copies/mL. The mean baseline CD4+ cell count was 352 cells/mm^3 (range 1–1455) and 17% had CD4+ cell counts ≤200 cells/mm^3.

Virologic outcomes in Trial 114 through Week 144 are presented in Table 12. In Trial 114, the mean increase from baseline in CD4+ cell count at Week 144 was 281 cells/mm^3 in the TYBOST group and 297 cells/mm^3 in the ritonavir group.

Reference ID: 4660245

Table 12 Virologic Outcome of Randomized Treatment of Trial 114 in HIV-1 Infected Treatment Naïve Adults at Week 144[a]

	TYBOST + Atazanavir + TRUVADA (N=344)	Ritonavir + Atazanavir + TRUVADA (N=348)
HIV-1 RNA <50 copies/mL	72%	74%
Treatment Difference	−2.1% (95% CI = −8.7%, 4.5%)	
HIV RNA ≥50 copies/mL[b]	8%	5%
No Virologic Data at Week 144 Window	20%	21%
Discontinued Study Drug Due to AE or Death[c]	11%	11%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[d]	8%	10%
Missing Data During Window but on Study Drug	<1%	<1%

a. Week 144 window was between Day 967 and 1050 (inclusive).

b. Included subjects who had ≥50 copies/mL in the Week 144 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than an adverse event (AE), death, or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL.

c. Includes subjects who discontinued due to AE 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.

d. Includes subjects who discontinued for reasons other than an AE, death, or lack or loss of efficacy; e.g., withdrew consent, lost to follow-up, etc.

14.2 Clinical Trial Results in HIV-1 Infected Virologically Suppressed Pediatric Subjects – Trial 128

Trial 128 was a Phase 2/3 multicenter, open-label trial to evaluate the pharmacokinetics, safety, and efficacy of TYBOST coadministered with atazanavir or darunavir in HIV-1 infected virologically suppressed pediatric subjects ages 12 years and older with baseline estimated creatinine clearance ≥90 mL/min/1.73 m^2. Subjects were on a stable antiretroviral regimen (for at least 3 months), consisting of atazanavir or darunavir, both administered with ritonavir, combined with 2 nucleotide reverse transcriptase inhibitors (NRTIs). They were switched from ritonavir to TYBOST 150 mg once daily and continued atazanavir (N=14) or darunavir once daily (N=7) and 2 NRTIs.

The mean age of subjects was 14 years (range 12–17 years); median weight was 55 kg; 62% were male, 38% were Asian, 33% were White, 19% were Black, and 67% were not Hispanic or Latino. At baseline, 20/21 subjects had plasma HIV-1 RNA <50 copies/mL and 1 subject had plasma HIV-1 RNA of 50 copies/mL.

In subjects who switched to TYBOST coadministered with atazanavir, 93% (13/14) of subjects remained suppressed (HIV-1 RNA <50 copies/mL), and 1 subject experienced virologic failure at Week 48. From a median baseline CD4+ cell count and CD4+% of 770 cells/mm^3 (range 486 to 1765 cells/mm^3) and 33% (range 23% to 45%), respectively, the median change from baseline in CD4+ cell count and CD4+% at Week 48 was -60 cells/mm^3 (range -500 to 705 cells/mm^3) and -0.3% (range -6% to 8%), respectively.

Reference ID: 4660245

In subjects who switched to TYBOST coadministered with darunavir, 86% (6/7) of subjects remained suppressed (HIV-1 RNA <50 copies/mL), and 1 subject had missing data at Week 48. From a median baseline CD4+ cell count and CD4+% of 1117 cells/mm^3 (range 658 to 2416 cells/mm^3) and 45% (range 28% to 56%), respectively, the median change from baseline in CD4+ cell count and CD4+% at Week 48 was -342 cells/mm^3 (range -1389 to 219 cells/mm^3) and -6% (range -12% to 5%), respectively. All 6 subjects with available data had CD4+ cell counts above 800 cells/mm^3 at Week 48.

16 HOW SUPPLIED/STORAGE AND HANDLING

TYBOST tablets, 150 mg, are orange, round, biconvex, film-coated, and debossed with "GSI" on one side and plain faced on the other side.

Each bottle contains 30 tablets (NDC 61958-1401-1) and a silica gel desiccant, with a child-resistant closure.

Store at 25 °C (77 °F); excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature).

- Keep container tightly closed.
- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interaction

Inform patients that TYBOST coadministered with atazanavir or darunavir may interact with many drugs with potential serious implications and that some drugs are contraindicated with TYBOST coadministered with atazanavir or darunavir. Advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication, including acid-modifying medications or herbal products, including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.3), and Drug Interactions (7)].*

New Onset or Worsening Renal Impairment

Inform patients that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported when TYBOST is used in combination with a TDF containing regimen *[see Warnings and Precautions (5.2)]*.

Pregnancy

Advise patients that TYBOST is not recommended during pregnancy and to alert their healthcare provider if they get pregnant while taking TYBOST *[see Use in Specific Populations (8.1)]*.

Reference ID: 4660245

Inform patients that there is a pregnancy exposure registry that monitors fetal outcomes in pregnant individuals exposed to TYBOST during pregnancy *[see Use in Specific Populations (8.1)].*

Lactation

Instruct mothers with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk *[see Use in Specific Populations (8.2)]*.

Dosing Instructions

Inform patients that TYBOST must be taken at the same time as atazanavir or darunavir and with food once daily as prescribed. It is important to take TYBOST and atazanavir or darunavir together on a regular dosing schedule and to avoid missing doses. Counsel patients about the risks of developing resistance to their HIV-1 medications.

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Patient Information
TYBOST® (TYE-bost)
(cobicistat)
tablets

Important: Ask your healthcare provider or pharmacist about medicines that should not be taken with TYBOST. For more information, see the section **"What should I tell my healthcare provider before taking TYBOST?"**

Read this Patient Information before you start taking TYBOST and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

Also read the Patient Information for atazanavir or darunavir prescribed by your healthcare provider when taking TYBOST.

What is TYBOST?

TYBOST is a prescription medicine used in adults and children:

- 1 time each day with the Human Immunodeficiency Virus-1 (HIV-1) medicines atazanavir **or** darunavir, to increase the amount of those medicines in your blood.
  - When taken with atazanavir, TYBOST is used in adults, and in children who weigh at least 77 pounds (35 kg).
  - When taken with darunavir, TYBOST is used in adults, and in children who weigh at least 88 pounds (40 kg).
- TYBOST is not an antiretroviral medicine and does not treat the HIV-1 virus. You must also take all the antiretroviral HIV-1 medicines prescribed by your healthcare provider even if you take TYBOST and atazanavir or darunavir.
- TYBOST should not be used if you take darunavir when prescribed by your healthcare provider to be taken 2 times each day, or if you take other HIV-1 protease inhibitor medicines, including fosamprenavir, saquinavir, or tipranavir.

It is not known if TYBOST when taken with atazanavir is safe and effective in children who weigh less than 77 pounds (35 kg).

It is not known if TYBOST when taken with darunavir is safe and effective in children who weigh less than 88 pounds (40 kg).

Do not take TYBOST combined with atazanavir or darunavir if you also take a medicine that contains:

- alfuzosin hydrochloride
- carbamazepine
- cisapride
- colchicine, if you have liver or kidney problems
- dronedarone hydrochloride
- ergot-containing medicines:
  - dihydroergotamine mesylate
  - ergotamine tartrate
  - methylergonovine maleate
- lomitapide
- lovastatin
- lurasidone
- midazolam, when taken by mouth
- phenobarbital
- phenytoin
- pimozide
- ranolazine
- rifampin
- sildenafil, when used for treating the lung problem pulmonary arterial hypertension (PAH)
- simvastatin
- St. John's wort (Hypericum perforatum) or a product that contains St. John's wort
- triazolam

Do not take TYBOST with atazanavir if you also take a medicine that contains:

- drospirenone/ethinyl estradiol
- indinavir
- irinotecan
- nevirapine

What should I tell my healthcare provider before taking TYBOST?

Before you take TYBOST, tell your healthcare provider if you:

- have kidney problems
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant
  - It is not known if TYBOST can harm your unborn baby.
  - TYBOST should not be used during pregnancy because you may not have enough TYBOST in your body during pregnancy.
  - Tell your healthcare provider if you become pregnant while taking TYBOST. Your healthcare provider may prescribe different medicines if you become pregnant while taking TYBOST.

Reference ID: 4660245

Pregnancy Registry: There is a pregnancy registry for women who take TYBOST during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. Do not breastfeed if you take TYBOST.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - It is not known if TYBOST can pass to your baby in your breast milk.

  Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TYBOST with atazanavir or darunavir may affect the way other medicines work, and other medicines may affect how TYBOST with atazanavir or darunavir works. **Taking TYBOST with atazanavir or darunavir, along with certain other medicines can lead to severe or life-threatening side effects, or could lead to death. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact when taken with TYBOST with atazanavir or darunavir.
- **Do not start a new medicine without telling your healthcare provider**. Your healthcare provider can tell you if it is safe to take TYBOST with atazanavir or darunavir, along with other medicines.

How should I take TYBOST?

- Take TYBOST exactly as your healthcare provider tells you.
- Do not change your dose or stop taking TYBOST without first talking with your healthcare provider.
- **Stay under the care of your healthcare provider during treatment with TYBOST**. See your healthcare provider regularly while taking TYBOST.
- Take TYBOST 1 time each day at the same time you take atazanavir or darunavir. It is important to take these medicines on a regular dosing schedule.
- Take TYBOST with atazanavir or TYBOST with darunavir, along with food.
- If you take too much TYBOST, call your healthcare provider or go to the nearest hospital emergency room right away.
- Do not run out of TYBOST. The virus in your blood may become resistant to the HIV-1 medicine atazanavir or darunavir if TYBOST is stopped for even a short time. When your supply starts to run low, get more from your healthcare provider or pharmacy.

What are the possible side effects of TYBOST?

TYBOST when taken with certain other medicines can cause new or worse kidney problems, including kidney failure. Your healthcare provider should check your kidneys before you start and while you are taking TYBOST.

The most common side effects of TYBOST with atazanavir include yellowing of the skin and rash.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of TYBOST. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TYBOST?

- Store TYBOST at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
- TYBOST comes in a child-resistant container.
- Do not use TYBOST if the seal over the bottle opening is broken or missing.
- Keep TYBOST in its original container.
- Keep the container tightly closed.

Keep TYBOST and all medicines out of reach of children.

General information about the safe and effective use of TYBOST.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TYBOST for a condition for which it was not prescribed. Do not give TYBOST to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TYBOST that is written for health professionals.

What are the ingredients in TYBOST?

Active ingredient: cobicistat

Inactive ingredients: silicon dioxide, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The tablets are film-coated with a coating material containing polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, sunset yellow FCF (FD&C Yellow #6) aluminum lake, and iron oxide yellow.

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For more information, call 1-800-445-3235 or go to www.GILEAD.com

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 10/2019

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

POONAM MISHRA
08/21/2020 01:36:20 PM
on behalf of Division Director