

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tybost 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of cobicistat.

Excipient(s) with known effect: Each tablet contains 59 micrograms sunset yellow FCF (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Orange, round, biconvex, film-coated tablet of diameter 10.3 mm, debossed with “GSI” on one side of the tablet and plain-faced on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tybost is indicated as a pharmacokinetic enhancer of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected adults. See sections 4.2, 4.4, 5.1 and 5.2.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

Tybost is used in combination with atazanavir or darunavir, therefore the atazanavir or darunavir Summary of Product Characteristics should be consulted.

Tybost must be co-administered with atazanavir or darunavir, taken orally, once daily with food.

The doses of Tybost and the co-administered protease inhibitor, atazanavir or darunavir, are presented in Table 1.

Table 1: Dosing regimens

Dose of Tybost	Dose of HIV-1 protease inhibitor
150 mg once daily	Atazanavir 300 mg once daily
	Darunavir 800 mg once daily

If the patient misses a dose of Tybost within 12 hours of the time it is usually taken, the patient should take Tybost with food as soon as possible and resume their normal dosing schedule in combination

with atazanavir or darunavir. If a patient misses a dose of Tybost by more than 12 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

Special populations

Elderly

No data are available on which to make a dose recommendation for patients over the age of 65 years (see section 5.2).

Renal impairment

No dose adjustment of Tybost is required for patients with renal impairment, including those with severe renal impairment. Cobicistat has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for these patients.

Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine. Tybost should not be initiated in patients with creatinine clearance less than 70 ml/min if any co-administered agent (e.g. emtricitabine, lamivudine, tenofovir disoproxil fumarate, or adefovir) requires dose adjustment based on creatinine clearance. See sections 4.4, 4.8 and 5.2.

Hepatic impairment

No dose adjustment of Tybost is required in patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B). Cobicistat has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, the use of Tybost is not recommended in these patients (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of cobicistat in children aged 0 to less than 18 years have not been established (see section 5.1). No data are available.

Method of administration

Tybost should be taken orally, once daily with food (see section 5.2). The film-coated tablet should not be chewed or crushed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with the following medicinal products due to the potential for serious and/or life-threatening events or loss of therapeutic effect (see sections 4.4 and 4.5):

- alpha 1-adrenoreceptor antagonists: alfuzosin
- antiarrhythmics: amiodarone, quinidine
- anticonvulsants: carbamazepine, phenobarbital, phenytoin
- antimycobacterials: rifampicin
- ergot derivatives: dihydroergotamine, ergometrine, ergotamine
- gastrointestinal motility agents: cisapride
- herbal products: St. John's wort (*Hypericum perforatum*)
- HMG Co-A reductase inhibitors: lovastatin, simvastatin
- neuroleptics: pimozone
- PDE-5 inhibitors: sildenafil for treatment of pulmonary arterial hypertension
- sedatives/hypnotics: orally administered midazolam, triazolam

4.4 Special warnings and precautions for use

Co-administration with other medicinal products

Cobicistat is a strong mechanism-based CYP3A inhibitor and is a CYP3A substrate.

Increased plasma concentrations of medicinal products that are metabolised by CYP3A (including atazanavir and darunavir) are observed on co-administration with cobicistat. Higher plasma concentrations of co-administered medicinal products can result in increased or prolonged therapeutic effects or adverse reactions. For medicinal products metabolised by CYP3A these higher plasma concentrations may potentially lead to severe, life-threatening or fatal events (see section 4.3).

Co-administration of Tybost with medicinal products that induce CYP3A is contraindicated or is not recommended (see sections 4.3 and 4.5) because decreased plasma concentrations of cobicistat could result in plasma levels that are insufficient to achieve adequate pharmacoenhancement of atazanavir or darunavir.

Co-administration of Tybost with medicinal products that inhibit CYP3A may decrease the clearance of cobicistat, resulting in increased cobicistat plasma concentrations (see section 4.5).

Cobicistat is a weak CYP2D6 inhibitor and is metabolised to a minor extent by CYP2D6. Co-administration with cobicistat can increase plasma concentrations of medicinal products that are metabolised by CYP2D6 (see sections 4.3 and 4.5).

Cobicistat inhibits the transporters p-glycoprotein (P-gp), BCRP, MATE1, OATP1B1 and OATP1B3. Co-administration of Tybost in patients receiving medicinal products that are substrates of these transporters may result in increased plasma concentrations of the co-administered medicinal products (see section 4.5).

Unlike ritonavir, cobicistat is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGT1A1. If switching pharmacoenhancer from ritonavir to cobicistat, caution is required during the first two weeks of treatment with Tybost, particularly if doses of any concomitantly administered medicinal products have been titrated or adjusted during use of ritonavir as a pharmacoenhancer (see section 4.5).

Contraception requirements

No dosing recommendations can be made regarding the use of Tybost with oral contraceptives. Alternative forms of contraception should be considered (see section 4.5).

Co-administration of Tybost and antiretroviral medicinal products

Tybost must be co-administered with either atazanavir 300 mg once daily or with darunavir 800 mg once daily (see section 4.2). Safety and efficacy have not been established for use of Tybost with either atazanavir or darunavir when used in any other dosing regimen. Antiviral efficacy data from randomised controlled studies is available for cobicistat-boosted atazanavir, but not for cobicistat-boosted darunavir (see sections 5.1 and 5.2).

Tybost must not be used as a pharmacokinetic enhancer of any other HIV-1 protease inhibitor or any other antiretroviral medicinal product that requires boosting since dosing recommendations for such co-administration have not been established and may result in insufficient plasma level of the antiretroviral medicinal product(s) leading to loss of therapeutic effect and development of resistance (see section 4.2).

Tybost co-administered with atazanavir or darunavir should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 to reach the desired therapeutic plasma concentrations (i.e., another protease inhibitor or elvitegravir). Dosing recommendations for such combinations have not been established and co-administration may result in decreased plasma concentrations of atazanavir, darunavir and/or the other antiretroviral agents that require pharmacoenhancement leading to loss of antiviral activity and development of resistance.

Tybost should not be used concurrently with ritonavir due to similar effects of cobicistat and ritonavir on CYP3A.

Tybost should not be used in combination with other medicinal products containing cobicistat (such as the fixed-dose combination tablet elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil).

Effects on estimated creatinine clearance

Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine. This effect on serum creatinine, leading to a decrease in the estimated creatinine clearance, should be taken into consideration when Tybost is administered to patients in whom the estimated creatinine clearance is used to guide aspects of their clinical management, including adjusting doses of co-administered medicinal products.

Tybost should not be initiated in patients with creatinine clearance less than 70 ml/min if one or more co-administered agent requires dose adjustment based on creatinine clearance (e.g. emtricitabine, lamivudine, tenofovir disoproxil fumarate or adefovir). See sections 4.2, 4.8 and 5.2.

There are currently inadequate data to determine whether co-administration of tenofovir disoproxil fumarate and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil fumarate without cobicistat.

Liver disease

Cobicistat has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, the use of Tybost is not recommended in these patients (see sections 4.2 and 5.2).

Excipients

Tybost contains the azo colouring agent sunset yellow FCF (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Cobicistat is a strong mechanism-based CYP3A inhibitor and is a CYP3A substrate. Increased plasma concentrations of medicinal products that are metabolised by CYP3A (including atazanavir and darunavir) are observed on co-administration with cobicistat.

Cobicistat is a weak CYP2D6 inhibitor and is metabolised to a minor extent by CYP2D6. Co-administration with cobicistat can increase plasma concentrations of medicinal products that are metabolised by CYP2D6 (see sections 4.3 and 4.4).

Cobicistat inhibits the transporters p-glycoprotein (P-gp), BCRP, MATE1, OATP1B1 and OATP1B3. Co-administration of Tybost with medicinal products that are substrates of these transporters can result in increased plasma concentrations of the co-administered medicinal products (see section 4.4).

Cobicistat is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19.

Cobicistat is not expected to induce CYP3A4 or P-gp (MDR1).

Unlike ritonavir, cobicistat is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGT1A1. If switching pharmacoenhancer from ritonavir to cobicistat, caution is required during the first two weeks of treatment with Tybost, particularly if doses of any concomitantly administered medicinal products have been titrated or adjusted during use of ritonavir as a pharmacoenhancer (see section 4.4).

Concomitant use contraindicated

Medicinal products that are extensively metabolised by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in exposure when co-administered with cobicistat. Co-administration of Tybost with medicinal products such as dihydroergotamine, ergotamine, ergometrine, orally administered midazolam, triazolam, amiodarone, quinidine, cisapride, pimozone, alfuzosin, simvastatin, lovastatin, and sildenafil which are highly dependent on CYP3A for clearance

and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (see section 4.3).

Co-administration of Tybost with medicinal products that are strong inducers of CYP3A (such as St. John’s wort (*Hypericum perforatum*), rifampicin, carbamazepine, phenobarbital, phenytoin) may result in decreased plasma concentrations of cobicistat and consequently that of atazanavir or darunavir being boosted, leading to loss of therapeutic effect and possible development of resistance (see section 4.3).

Concomitant use not recommended

Co-administration of Tybost with medicinal products that are moderate to weak inducers of CYP3A may result in decreased plasma concentration of cobicistat and consequently that of atazanavir or darunavir being boosted, leading to loss of therapeutic effect and possible development of resistance. Some examples include, but are not limited to, etravirine, efavirenz, nevirapine, boceprevir, fluticasone, and bosentan (see Table 2).

Co-administration of Tybost with medicinal products that inhibit CYP3A may result in increased plasma concentration of cobicistat. Some examples include, but are not limited to, itraconazole, ketoconazole, and voriconazole (see Table 2).

Tybost co-administered with atazanavir or darunavir should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 to reach the desired therapeutic plasma concentrations (i.e., another protease inhibitor or elvitegravir). Dosing recommendations for such combinations have not been established and may result in decreased plasma concentrations of atazanavir, darunavir and/or the other antiretroviral agents that require pharmacoenhancement leading to loss of antiviral activity and development of resistance.

Other interactions

Interactions of cobicistat and potential co-administered medicinal products are listed in Table 2 below (increase is indicated as “↑”, decrease as “↓”, no change as “↔”). These interactions are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

For additional drug-drug interactions with atazanavir or darunavir, consult their respective Summary of Product Characteristics when using Tybost.

Table 2: Interactions between cobicistat and other medicinal products

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C _{max} , C _{min}	Recommendation concerning co-administration with cobicistat 150 mg and atazanavir or darunavir
ANTIRETROVIRALS		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Tenofovir disoproxil fumarate	Co-administration of tenofovir disoproxil fumarate with cobicistat is expected to increase tenofovir plasma concentration. Tenofovir: AUC: ↑ 23% C _{max} : ↑ 55%	This increase is not considered to be clinically relevant and does not necessitate dose adjustment of tenofovir disoproxil fumarate.

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max} , C_{min}	Recommendation concerning co-administration with cobicistat 150 mg and atazanavir or darunavir
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz (600 mg single dose)	<p>Co-administration of efavirenz and cobicistat is expected to decrease cobicistat plasma concentrations.</p> <p>Efavirenz: AUC: ↔ C_{max}: ↓ 13% C_{min}: ND</p>	Atazanavir or darunavir plasma concentrations may decrease as a consequence of a reduction in cobicistat plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Co-administration is not recommended (see section 4.4).
Etravirine	<p>Interaction not studied.</p> <p>Co-administration of etravirine and cobicistat is expected to decrease cobicistat plasma concentrations.</p>	Atazanavir or darunavir plasma concentrations may decrease as a consequence of a reduction in cobicistat plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Co-administration is not recommended (see section 4.4).
Nevirapine	<p>Interaction not studied.</p> <p>Co-administration of nevirapine and cobicistat is expected to decrease cobicistat plasma concentrations.</p> <p>Nevirapine plasma concentrations may be increased when co-administered with cobicistat.</p>	Atazanavir or darunavir plasma concentrations may decrease as a consequence of a reduction in cobicistat plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Co-administration is not recommended (see section 4.4).
Rilpivirine	<p>Interaction not studied.</p> <p>Co-administration of rilpivirine and cobicistat is expected to increase the plasma concentration of rilpivirine.</p> <p>Rilpivirine is not expected to affect the plasma concentration of cobicistat.</p>	No dose adjustment of rilpivirine is required when atazanavir/cobicistat or darunavir/cobicistat are used concomitantly with rilpivirine.
CCR5 Antagonists		
Maraviroc	<p>Interaction not studied.</p> <p>Maraviroc is a substrate of CYP3A and its plasma concentration increases when co-administered with potent CYP3A inhibitors.</p>	When co-administering maraviroc and Tybost patients should receive maraviroc 150 mg twice daily. For further details, consult the Summary of Product Characteristics for maraviroc.
ANTI-INFECTIVES		
Antifungals		
Ketoconazole	<p>Interaction not studied.</p> <p>Concentrations of ketoconazole and/or cobicistat may increase with co-administration of cobicistat.</p>	When administering ketoconazole with Tybost, the maximum daily dose of ketoconazole should not exceed 200 mg per day. Caution is warranted and clinical monitoring is recommended during co-administration.

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with cobicistat 150 mg and atazanavir or darunavir
Itraconazole Voriconazole Posaconazole Fluconazole	Concentrations of itraconazole, fluconazole and posaconazole may be increased when co-administered with cobicistat. Concentrations of voriconazole may increase or decrease when co-administered with cobicistat.	Clinical monitoring is recommended upon co-administration with Tybost. When administering with Tybost, the maximum daily dose of itraconazole should not exceed 200 mg per day. Voriconazole should not be used unless the possible benefit is considered to outweigh the risks associated with the unpredictable effect on plasma concentrations.
HCV protease inhibitors		
Telaprevir (750 mg three times daily)/ Elvitegravir (150 mg once daily)/Cobicistat (150 mg once daily) ¹	Telaprevir: AUC: ↔ C_{max} : ↔ C_{min} : ↔ Cobicistat: AUC: ↔ C_{max} : ↔ C_{min} : ↑ 232%	No dose adjustment is required when Tybost is co-administered with telaprevir.
Boceprevir	Interaction not studied.	Atazanavir, darunavir or boceprevir plasma concentrations may decrease upon co-administration. Co-administration with Tybost is not recommended.
Antimycobacterials		
Rifabutin (150 mg every other day)/Elvitegravir (150 mg once daily)/Cobicistat (150 mg once daily)	Co-administration of rifabutin, a potent CYP3A inducer, may significantly decrease cobicistat plasma concentrations. Cobicistat: AUC: ↔ C_{max} : ↔ C_{min} : ↓ 66% Rifabutin: AUC: ↔ C_{max} : ↔ C_{min} : ↔ 25-O-desacetyl-rifabutin: AUC: ↑ 525% C_{max} : ↑ 384% C_{min} : ↑ 394%	Co-administration of Tybost and rifabutin is not recommended. If the combination is needed, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to desacetyl-rifabutin. Further dose reduction of rifabutin has not been studied. It should be kept in mind that a twice weekly dose of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifabutin resistance and a treatment failure.

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max} , C_{min}	Recommendation concerning co-administration with cobicistat 150 mg and atazanavir or darunavir
Macrolide antibiotics		
Clarithromycin	Interaction not studied. Concentrations of clarithromycin may be increased upon co-administration with cobicistat.	Concentrations of clarithromycin may be increased upon co-administration of Tybost. Alternative antibiotics should be considered for co-administration with atazanavir/cobicistat. Consult atazanavir Summary of Product Characteristics for dosing recommendations. When clarithromycin is co-administered with darunavir/cobicistat, consult the darunavir Summary of Product Characteristics for dosing recommendations.
ANTI-NEOPLASTICS		
Dasatinib Nilotinib Vinblastine Vincristine	Interaction not studied. Concentrations of these medicinal products may be increased when co-administered with cobicistat.	Concentrations of these medicinal products may be increased when co-administered with Tybost resulting in the potential for increased adverse events usually associated with these anticancer medicinal products.
GLUCOCORTICOIDS		
Inhaled/Nasal corticosteroids		
Fluticasone	Interaction not studied. Concomitant use of inhaled or nasal fluticasone and cobicistat may increase plasma concentrations of fluticasone, resulting in reduced serum cortisol concentrations.	Use of inhaled or nasal fluticasone propionate and Tybost is not recommended unless the potential benefit to the patient outweighs the risks. Alternative inhaled or nasal corticosteroids may be considered.
ORAL ANTI-DIABETICS		
Metformin	Interaction not studied. Cobicistat reversibly inhibits MATE1, and concentrations of metformin may be increased when co-administered with cobicistat.	Careful patient monitoring and dose adjustment of metformin is recommended in patients who are taking Tybost.
NARCOTIC ANALGESICS		
Methadone	Methadone: AUC: ↔ C_{max} : ↔ C_{min} : ↔	No dose adjustment of methadone is required.
Buprenorphine/Naloxone	Buprenorphine: AUC: ↑ 35% C_{max} : ↑ 12% C_{min} : ↑ 66% Naloxone: AUC: ↓ 28% C_{max} : ↓ 28%	No dose adjustment of Tybost is required.
ORAL CONTRACEPTIVES		
Norgestimate/Ethinyl-estradiol	Interaction not studied. Concentrations of contraceptive components may be affected on co-administration with cobicistat.	No data are available to make recommendations on the use of atazanavir/cobicistat or darunavir/cobicistat with combined or progestagen-only oral or implanted contraceptives. Alternative forms of contraception should be used.

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max} , C_{min}	Recommendation concerning co-administration with cobicistat 150 mg and atazanavir or darunavir
ANTIARRHYTHMICS		
Disopyramide Flecainide Systemic lidocaine Mexiletine Propafenone	Interaction not studied. Concentrations of these antiarrhythmic medicinal products may be increased when co-administered with cobicistat.	Caution is warranted and clinical monitoring is recommended upon co-administration of these antiarrhythmic medicinal products with Tybost.
Digoxin (0.5 mg single dose)/Cobicistat (150 mg multiple doses)	Plasma concentrations of digoxin may be increased when co-administered with cobicistat. Digoxin: AUC: ↔ C_{max} : ↑ 41% C_{min} : ND	The peak concentration of digoxin is increased when co-administered with Tybost. The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effects.
ANTI-HYPERTENSIVES		
Metoprolol Timolol	Interaction not studied. Concentrations of beta-blockers may be increased when co-administered with cobicistat.	Clinical monitoring is recommended and a dose reduction may be necessary when these beta-blockers are co-administered with Tybost.
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Interaction not studied. Concentrations of calcium channel blockers may be increased when co-administered with cobicistat.	Clinical monitoring of therapeutic effect and adverse events is recommended when these medicinal products are co-administered with Tybost.
ENDOTHELIN RECEPTOR ANTAGONISTS		
Bosentan	Interaction not studied. Co-administration of bosentan with cobicistat may lead to decreased cobicistat plasma concentrations.	Atazanavir or darunavir plasma concentrations may decrease as a consequence of a reduction in cobicistat plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Co-administration is not recommended (see section 4.4).
ANTICOAGULANTS		
Rivaroxaban	Interaction not studied. Concentrations of rivaroxaban may be affected upon co-administration with cobicistat.	Inhibition of CYP3A and intestinal P-gp may lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Co-administration of rivaroxaban and Tybost is not recommended.
Warfarin	Interaction not studied. Concentrations of warfarin may be affected upon co-administration with cobicistat.	It is recommended that the international normalised ratio (INR) be monitored upon co-administration with Tybost.
Dabigatran	Interaction not studied. Concentrations of dabigatran may be affected upon co-administration with cobicistat.	Clinical monitoring is recommended when dabigatran is co-administered with P-gp inhibitors. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max} , C_{min}	Recommendation concerning co-administration with cobicistat 150 mg and atazanavir or darunavir
INHALED BETA AGONISTS		
Salmeterol	Interaction not studied. Co-administration of salmeterol with cobicistat may result in increased plasma concentrations of salmeterol.	Increased plasma concentrations of salmeterol are associated with the potential for serious and/or life-threatening reactions. Co-administration of salmeterol and Tybost is not recommended (see section 4.4).
HMG Co-A REDUCTASE INHIBITORS		
Atorvastatin Fluvastatin Pitavastatin Pravastatin	Interaction not studied. Plasma concentrations of HMG Co-A reductase inhibitors may be increased when co-administered with cobicistat.	Plasma concentrations of atorvastatin, pitavastatin, fluvastatin, pravastatin or rosuvastatin are expected to increase when co-administered with atazanavir/cobicistat or darunavir/cobicistat.
Rosuvastatin (10 mg single dose)/Elvitegravir (150 mg once daily)/Cobicistat (150 mg once daily)	Rosuvastatin: AUC: ↑ 38% C_{max} : ↑ 89% C_{min} : ↑ 43% Cobicistat: AUC: ↔ C_{max} : ↔ C_{min} : ↔	Co-administration of atorvastatin with Tybost is not recommended. If the use of atorvastatin is considered strictly necessary, the lowest possible dose of atorvastatin should be administered with careful monitoring. Caution should be exercised when co-administering Tybost with pitavastatin. Consult the Summary of Product Characteristics of atazanavir or darunavir for further information on use in combination with these medicinal products.
PHOSPHODIESTERASE TYPE-5 (PDE-5) INHIBITORS		
Sildenafil Tadalafil Vardenafil	Interaction not studied. PDE-5 inhibitors are primarily metabolised by CYP3A. Co-administration with cobicistat may result in increased sildenafil, tadalafil and vardenafil plasma concentrations, which may result in PDE-5 inhibitor-associated adverse reactions.	Co-administration of Tybost with sildenafil for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3). Caution should be exercised, including consideration of dose reduction, when co-administering Tybost with tadalafil for the treatment of pulmonary arterial hypertension. For the treatment of erectile dysfunction, it is recommended that a single dose of sildenafil no more than 25 mg in 48 hours, vardenafil no more than 2.5 mg in 72 hours, or tadalafil no more than 10 mg in 72 hours be co-administered with Tybost.
ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Trazodone	Interaction not studied. Plasma concentrations of trazodone may be increased when co-administered with cobicistat.	Dose titration may be required for most medicinal products of the SSRI class, when co-administered with Tybost.

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max} , C_{min}	Recommendation concerning co-administration with cobicistat 150 mg and atazanavir or darunavir
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus	Interaction not studied. Concentrations of these immunosuppressants may be increased when co-administered with cobicistat.	Therapeutic monitoring is recommended upon co-administration with Tybost.
NEUROLEPTICS		
Perphenazine Risperidone Thioridazine	Interaction not studied. Co-administration of neuroleptics with cobicistat may result in increased plasma concentrations of neuroleptics.	For these neuroleptics, consider reducing the dose of the neuroleptic upon co-administration with Tybost.
SEDATIVES/HYPNOTICS		
Buspirone Clorazepate Diazepam Estazolam Flurazepam Zolpidem	Interaction not studied. Concentrations of these sedatives/hypnotics may be increased when co-administered with cobicistat.	For these sedatives/hypnotics, dose reduction may be necessary and concentration monitoring is recommended.
ANTI-GOUT		
Colchicine	Interaction not studied. Colchicine plasma concentrations may be increased when co-administered with cobicistat.	Dose reductions of colchicine may be required. Tybost should not be co-administered with colchicine to patients with renal or hepatic impairment.

¹ This study was conducted using the fixed-dose combination tablet elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil.

ND = not determined

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited clinical data with cobicistat in pregnant women.

Animal studies do not indicate direct or indirect harmful effects of cobicistat with respect to reproductive toxicity (see section 5.3).

Tybost should not be used during pregnancy unless the clinical condition of the woman requires treatment with cobicistat co-administered with atazanavir or darunavir.

Breast-feeding

It is unknown whether cobicistat/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of cobicistat/metabolites in milk. A risk to the newborns/infants cannot be excluded. Therefore, Tybost should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that HIV infected women do not breast-feed their infants under any circumstances.

Fertility

No human data on the effect of cobicistat on fertility are available. Animal studies do not indicate harmful effects of cobicistat on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions for cobicistat-boosted atazanavir were consistent with the safety profile of ritonavir-boosted atazanavir. The most frequently reported adverse reactions to cobicistat-boosted atazanavir were associated with elevated bilirubin levels (see Table 3).

Tabulated summary of adverse reactions

The safety of cobicistat is based on 144-week data from a phase 3, randomised, active-controlled clinical study (GS-US-216-0114), in which 692 treatment-naïve patients received at least one dose of cobicistat-boosted atazanavir (n = 344) or ritonavir-boosted atazanavir (n = 348) administered with emtricitabine and tenofovir disoproxil fumarate fixed-dose combination. Of these 692 patients, 613 (300 atazanavir/cobicistat and 313 atazanavir/ritonavir) and 496 (250 atazanavir/cobicistat and 246 atazanavir/ritonavir) received at least 48 and 144 weeks of treatment, respectively.

Adverse reactions to cobicistat-boosted atazanavir during 144 weeks of clinical trial experience from study GS-US-216-0114 are listed in Table 3, below, by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$).

Table 3: Tabulated summary of adverse reactions to cobicistat-boosted atazanavir based on experience for 144 weeks from phase 3 study GS-US-216-0114

Frequency	Adverse reaction
<i>Metabolism and nutritional disorders:</i>	
Common:	hyperglycaemia, increased appetite
<i>Psychiatric disorders:</i>	
Common:	insomnia, abnormal dreams
Uncommon:	depression, sleep disorder
<i>Nervous system disorders:</i>	
Common:	headache, dizziness, somnolence, dysgeusia
<i>Eye disorders:</i>	
Very common:	ocular icterus
<i>Gastrointestinal disorders:</i>	
Very common:	nausea
Common:	vomiting, diarrhoea, dyspepsia, abdominal pain, abdominal distension, flatulence, dry mouth
<i>Hepatobiliary disorders:</i>	
Very common:	jaundice
Common:	hyperbilirubinaemia
<i>Skin and subcutaneous tissue disorders:</i>	
Common:	rash
Uncommon:	pruritus
<i>Musculoskeletal and connective tissue disorders:</i>	
Uncommon:	myalgia
<i>Renal and urinary disorders:</i>	
Uncommon:	nephrolithiasis, haematuria, proteinuria
<i>General disorders and administration site conditions:</i>	
Common:	fatigue
Uncommon:	pyrexia, asthenia

Description of selected adverse reactions

Renal impairment

Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine. An increase from baseline in serum creatinine solely due to cobicistat's inhibitory effect generally does not exceed 0.4 mg/dl.

In study GS-US-216-0114, decreases in estimated creatinine clearance occurred early in treatment with cobicistat, after which they stabilised. The mean (\pm 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 cobicistat-boosted atazanavir plus emtricitabine and tenofovir disoproxil fumarate fixed-dose combination group and -8.0 ± 16.8 ml/min in the ritonavir-boosted atazanavir plus emtricitabine and tenofovir disoproxil fumarate fixed-dose combination group.

Effects on the liver

In study GS-US-216-0114, hyperbilirubinaemia ($> 1 \times$ ULN) was common: 97.7% in the cobicistat-boosted atazanavir plus emtricitabine and tenofovir disoproxil fumarate fixed-dose combination group, and 97.4% in the ritonavir-boosted atazanavir plus emtricitabine and tenofovir disoproxil fumarate fixed-dose combination group through 144 weeks of treatment. However, a higher percentage of subjects in the cobicistat-boosted group had increases in total bilirubin $> 2 \times$ ULN than those in the ritonavir-boosted group (88.0% *versus* 80.9%). The rates of study drug discontinuation due to bilirubin-related adverse events were low and similar in both groups (4.9% in the cobicistat-boosted group and 4.0% in the ritonavir-boosted group). An increase of $> 3 \times$ ULN in alanine aminotransferase or aspartate aminotransferase was recorded in 12.8% of subjects in the cobicistat-boosted group and 9.0% in the ritonavir-boosted group.

Paediatric population

No data are available for children below 18 years of age. Tybost is not recommended in this population (see section 4.2).

Other special population(s)

Elderly

Cobicistat has not been studied in patients over the age of 65.

Patients with renal impairment

The safety of Tybost in 73 HIV-1 infected treatment-experienced patients with mild to moderate renal impairment (eGFR by Cockcroft-Gault method 50-89 ml/min) who switched pharmacokinetic enhancer from ritonavir to cobicistat was evaluated in an open-label clinical study (GS-US-236-0118) of cobicistat-boosted atazanavir or darunavir plus two NRTIs. At week 48 the mean change in serum creatinine was 0.04 ± 0.19 mg/dl and the mean change in eGFR by Cockcroft-Gault method was -4.1 ± 9.5 ml/min. The effect of cobicistat on serum creatinine and eGFR in patients switching from ritonavir to cobicistat in study GS-US-236-0118 was consistent with the effect in treatment-naïve patients in study GS-US-216-0114.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system listed in Appendix V**.

4.9 Overdose

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

There is no specific antidote for overdose with cobicistat. As cobicistat is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products, ATC code: V03AX03

Mechanism of action and pharmacodynamic effects

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

The effect of cobicistat on atazanavir pharmacokinetics was demonstrated in the pharmacokinetic sub-study (n = 48) of the phase 3 study GS-US-216-0114 in which HIV-1 infected patients received atazanavir 300 mg + cobicistat 150 mg or atazanavir 300 mg + ritonavir 100 mg, both in combination with emtricitabine and tenofovir disoproxil fumarate fixed-dose combination. The steady-state pharmacokinetic parameters of atazanavir were comparable when boosted with cobicistat *versus* ritonavir (see Table 4).

Table 4: Pharmacokinetic parameters [mean ± SD (%CV)] of atazanavir in the pharmacokinetic sub-study of phase 3 study GS-US-216-0114

Atazanavir pharmacokinetics parameters	Atazanavir + cobicistat^a (n = 22)	Atazanavir + ritonavir^a (n = 26)
AUC _{tau} (µg•h/ml)	46.13 ± 26.18 (56.8)	47.59 ± 24.39 (51.2)
C _{max} (µg/ml)	3.91 ± 1.94 (49.6)	4.76 ± 1.94 (40.8)
C _{tau} (µg/ml)	0.80 ± 0.72 (90.3)	0.85 ± 0.72 (84.7)

^a Plus background regimen of emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg fixed-dose combination

The pharmacokinetic enhancing effect of cobicistat on darunavir was evaluated in a phase 1 clinical study GS-US-216-0115 in 31 healthy subjects that were administered darunavir 800 mg in combination with cobicistat 150 mg or ritonavir 100 mg, all once daily, for 10 days. The steady-state pharmacokinetic parameters of darunavir were comparable when boosted with cobicistat *versus* ritonavir (see Table 5).

Table 5: Pharmacokinetic parameters [mean ± SD (%CV)] of darunavir 800 mg co-administered with cobicistat 150 mg or ritonavir 100 mg once daily

Darunavir pharmacokinetics parameters	Darunavir 800 mg + cobicistat 150 mg once daily (n = 31)	Darunavir 800 mg + ritonavir 100 mg once daily (n = 31)
AUC _{tau} (µg•h/ml)	81.08 ± 25.15 (31.0)	79.99 ± 27.20 (34.0)
C _{max} (µg/ml)	7.74 ± 1.69 (21.8)	7.46 ± 1.52 (20.3)
C _{0h} (µg/ml)	2.40 ± 1.22 (50.7)	2.48 ± 0.85 (34.3)

Antiviral activity *in vitro*

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

Clinical experience

Antiviral efficacy data from randomised controlled studies is available for cobicistat-boosted atazanavir, but not for cobicistat-boosted darunavir (see sections 4.4 and 5.2).

In treatment-naïve HIV-1 infected patients

The safety and efficacy of cobicistat with atazanavir in HIV-1 infected patients were evaluated in the randomised, double-blind, active-controlled phase 3 study GS-US-216-0114 in HIV-1 infected patients with baseline estimated creatinine clearance above 70 ml/min who were treatment-naïve (n = 692).

Patients were randomised in a 1:1 ratio to receive either atazanavir 300 mg + cobicistat 150 mg once daily or atazanavir 300 mg + ritonavir 100 mg once daily, each administered with a fixed background regimen containing tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg administered as a fixed-dose combination tablet. Randomisation was stratified by screening HIV-1 RNA level ($\leq 100,000$ copies/ml or $> 100,000$ copies/ml). Virologic response rate was evaluated in both treatment arms and virologic response was defined as achieving an undetectable viral load (< 50 HIV-1 RNA copies/ml). Viruses were known to be susceptible to atazanavir, emtricitabine and tenofovir disoproxil fumarate at baseline.

Baseline characteristics and treatment outcomes at weeks 48 and 144 for study GS-US-216-0114 are presented in Tables 6 and 7, respectively.

Table 6: Demographic and baseline disease characteristics of antiretroviral treatment-naïve HIV-1 infected adult subjects in study GS-US-216-0114

	Atazanavir + cobicistat^a (n = 344)	Atazanavir + ritonavir^a (n = 348)
Demographic characteristics		
Median age, years (min-max)	36 (19-62)	37 (19-70)
Sex		
Male	83.4%	82.5%
Female	16.6%	17.5%
Ethnicity		
White	57.6%	61.8%
Black or African Heritage	18.9%	18.1%
Asian	12.8%	10.6%
Other	10.8%	9.5%
Baseline disease characteristics		
Median baseline plasma HIV-1 RNA (range) log ₁₀ copies/ml	4.78 (3.22-6.43)	4.84 (3.21-6.44)
Percentage of subjects with viral load > 100,000 copies/ml	38.4%	41.1%
Median baseline CD4+ cell count (range), cells/mm ³	348 (1-1,075)	341 (10-1,455)
Percentage of subjects with CD4+ cell count ≤ 200 cells/mm ³	17.4%	16.4%

^a Plus background regimen of emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg fixed-dose combination

Table 7: Virologic outcome of randomised treatment of study GS-US-216-0114 at weeks 48 and 144

	Week 48 ^a		Week 144 ^b	
	Atazanavir + cobicistat ^f (n = 344)	Atazanavir + ritonavir ^f (n = 348)	Atazanavir + cobicistat ^f (n = 344)	Atazanavir + ritonavir ^f (n = 348)
Virologic success HIV-1 RNA < 50 copies/ml	85%	87%	72%	74%
Treatment difference	-2.2% (95% CI = -7.4%, 3.0%)		-2.1% (95% CI = -8.7%, 4.5%)	
Virologic failure^c	6%	4%	8%	5%
No virologic data in week 48 or 144 window	9%	9%	20%	21%
Discontinued study drug due to AE or death ^d	6%	7%	11%	11%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/ml ^e	3%	2%	8%	10%
Missing data during window but on study drug	0%	0%	< 1%	< 1%

^a Week 48 window is between day 309 and 378 (inclusive)

^b Week 144 window is between day 967 and 1,050 (inclusive)

^c Includes subjects who had ≥ 50 copies/ml in the week 48 or 144 windows; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, and at the time of discontinuation had a viral value of ≥ 50 copies/ml.

^d Includes patients who discontinued due to adverse event (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.

^e Includes subjects who discontinued for reasons other than an adverse event, death, or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up.

^f Plus background regimen of emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg fixed-dose combination

Atazanavir + cobicistat + emtricitabine and tenofovir disoproxil fumarate fixed-dose combination was non-inferior in achieving HIV-1 RNA < 50 copies/ml when compared to atazanavir + ritonavir + emtricitabine and tenofovir disoproxil fumarate fixed-dose combination.

Changes in CD4+ cell counts through 48 and 144 weeks in study GS-US-216-0114 are presented in Table 8.

Table 8: Changes in CD4+ cell counts through weeks 48 and 144 in study GS-US-216-0114

	Week 48		Week 144	
	Atazanavir + cobicistat ^a (n = 344)	Atazanavir + ritonavir ^a (n = 348)	Atazanavir + cobicistat ^a (n = 344)	Atazanavir + ritonavir ^a (n = 348)
Mean increase from baseline in CD4+ T-cell count (cells/mm ³) ^b	213	219	310	332

^a Plus background regimen of emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg fixed-dose combination

^b Missing = excluded analysis

In an analysis of treatment-failure subjects in study GS-US-216-0114 through week 144, evaluable genotypic data from paired baseline and treatment-failure isolates were available for all 21 virologic failures in the cobicistat group. Among the 21 patients, 3 developed the emtricitabine-associated resistance substitution M184V. No subject developed the tenofovir-associated resistance substitutions

K65R or K70E, or any primary resistance substitution associated with protease inhibitors. In the ritonavir group, genotypic data was available for all 19 virologic failures. Among the 19 patients, 1 developed the emtricitabine-associated resistance substitution M184V with no tenofovir- or primary protease inhibitor-associated resistance substitutions.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with cobicistat in one or more subsets of the paediatric population in treatment of HIV-1 infection (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral administration of cobicistat with food in HIV-1 infected subjects, peak plasma concentrations were observed 4 hours post-dose for cobicistat. The steady-state mean C_{max} , AUC_{tau} , and C_{trough} (mean \pm SD) following multiple doses of cobicistat in HIV-1 infected subjects (n = 68), respectively, were 1.2 ± 0.3 $\mu\text{g/ml}$, 10.9 ± 3.8 $\mu\text{g}\cdot\text{h/ml}$, and 0.07 ± 0.07 $\mu\text{g/ml}$.

A food effect study was not conducted for Tybost. In clinical studies, cobicistat was co-administered with atazanavir or darunavir under fed conditions, in accordance with the Summary of Product Characteristics for these agents. It is recommended that Tybost be administered with food.

Distribution

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

Biotransformation

Cobicistat is metabolised via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. Following oral administration of [^{14}C]cobicistat, 99% of circulating radioactivity in plasma was unchanged cobicistat. Low levels of metabolites are observed in urine and faeces and do not contribute to the CYP3A inhibitory activity of cobicistat.

Elimination

Following oral administration of [^{14}C]cobicistat, 86% and 8.2% of the dose were recovered in faeces and urine, respectively. The median terminal plasma half-life of cobicistat following administration of Tybost is approximately 3-4 hours.

Linearity/non-linearity

Cobicistat exposures are non-linear and greater than dose-proportional over the range of 50 mg to 400 mg, consistent with a mechanism-based CYP3A inhibitor.

Elderly

Pharmacokinetics of cobicistat have not been fully evaluated in the elderly (65 years of age and older).

Gender

No clinically relevant pharmacokinetic differences due to gender have been identified for cobicistat.

Ethnicity

No clinically relevant pharmacokinetic differences due to ethnicity have been identified for cobicistat.

Paediatric population

The pharmacokinetics of cobicistat in paediatric subjects have not been established.

Renal impairment

A study of the pharmacokinetics of cobicistat was performed in non-HIV-1 infected subjects with severe renal impairment (estimated creatinine clearance below 30 ml/min). No meaningful differences

in cobicistat pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects, consistent with low renal clearance of cobicistat.

Hepatic impairment

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

Hepatitis B and/or hepatitis C virus co-infection

Pharmacokinetics of cobicistat have not been fully evaluated in hepatitis B and/or C virus co-infected subjects.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. No teratogenic effects were observed in rats and rabbit developmental toxicity studies. In rats, ossification changes in the spinal column and sternebra of fetuses occurred at a dose that produced significant maternal toxicity.

Ex vivo rabbit studies and *in vivo* dog studies suggest that cobicistat has a low potential for QT prolongation, and may slightly prolong the PR interval and decrease left ventricular function at mean concentrations at least 10-fold higher than the human exposure at the recommended 150 mg daily dose.

A long term carcinogenicity study of cobicistat in rats revealed tumourigenic potential specific for this species that is regarded as of no relevance for humans. A long term carcinogenicity study in mice did not show any carcinogenic potential.

The active substance cobicistat is persistent in the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Silicon dioxide
Croscarmellose sodium
Magnesium stearate
Microcrystalline cellulose

Film-coating

Sunset yellow FCF aluminium lake (E110)
Macrogol 3350 (E1521)
Polyvinyl alcohol (partially hydrolysed) (E1203)
Talc (E553B)
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a polypropylene child-resistant closure containing 30 film-coated tablets and a silica gel desiccant.

The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets and outer cartons containing 90 (3 bottles of 30) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences International Limited
Cambridge
CB21 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/872/001
EU/1/13/872/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Gilead Sciences Limited
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE AND CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Tybost 150 mg film-coated tablets
Cobicistat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg of cobicistat.

3. LIST OF EXCIPIENTS

Contains sunset yellow FCF aluminium lake (E110), see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
30 tablets
90 (3 bottles of 30) film-coated tablets
90 (3 bottles of 30) tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Intl Ltd
Cambridge
CB21 6GT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/872/001 30 film-coated tablets
EU/1/13/872/002 90 (3 bottles of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tybost [Outer packaging only]

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tybost 150 mg film-coated tablets Cobicistat

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tybost is and what it is used for
2. What you need to know before you take Tybost
3. How to take Tybost
4. Possible side effects
5. How to store Tybost
6. Contents of the pack and other information

1. What Tybost is and what it is used for

Tybost contains the active substance cobicistat.

Tybost is used in adults aged 18 years and over to treat infection with HIV (human immunodeficiency virus). It is **taken with atazanavir or darunavir** (both protease inhibitors) and acts as a **booster** (*pharmacokinetic enhancer*) to help improve their effect.

Tybost does not directly treat your HIV, but boosts the levels of atazanavir and darunavir in the blood. It does this by slowing down the breakdown of atazanavir and darunavir which will make them stay in the body for longer.

This medicine is not a cure for HIV infection. While taking Tybost you may still develop infections or other illnesses associated with HIV infection. You can also pass on the virus to others, so it is important to take precautions to avoid infecting other people.

2. What you need to know before you take Tybost

Do not take Tybost

- **If you are allergic to cobicistat** or any of the other ingredients of this medicine (listed in section 6 of this leaflet).
- **If you are taking medicines containing any of the following:**
 - **alfuzosin**, used to treat an enlarged prostate gland
 - **amiodarone, quinidine**, used to correct irregular heartbeats
 - **carbamazepine, phenobarbital, phenytoin**, used to prevent seizures
 - **rifampicin**, used to prevent and treat tuberculosis and other infections

- **dihydroergotamine, ergometrine, ergotamine**, used to treat migraine headache
- **cisapride**, used to relieve certain stomach problems
- **St. John's wort (*Hypericum perforatum*)**, a herbal remedy used for depression and anxiety
- **lovastatin, simvastatin**, used to lower blood cholesterol
- **pimozide**, used to treat abnormal thoughts or feelings
- **sildenafil**, used to treat pulmonary arterial hypertension – a lung disease that makes breathing difficult
- orally administered **midazolam, triazolam**, used to help you sleep and/or relieve anxiety

→ **If any of these applies to you, you should not take Tybost and you should tell your doctor immediately.**

Warnings and precautions

You must remain under the care of your doctor while taking Tybost.

You can still pass on HIV when taking this medicine, so it is important to take precautions to avoid infecting other people through sexual contact or blood transfer. This medicine does not directly treat your HIV infection.

Talk to your doctor before taking Tybost:

- **If you are taking another protease inhibitor or elvitegravir.** Tybost taken with atazanavir or darunavir should not be used with another antiviral medicine that requires boosting.
- **Talk to your doctor or pharmacist if you have or have had kidney disease, or if tests have shown problems with your kidneys.** Your doctor will carefully consider whether to treat you with Tybost.
- **Talk to your doctor or pharmacist if you have or have had severe liver disease, or if tests have shown problems with your liver.** Your doctor will carefully consider whether to treat you with Tybost.

→ **If any of these applies to you, talk to your doctor before taking Tybost.**

Children and adolescents

Do not give this medicine to children and adolescents under 18 years of age. The use of Tybost in children and adolescents has not yet been studied.

Other medicines and Tybost

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

This includes medicines and herbal products obtained without a prescription. Tybost may interact with other medicines. As a result, the amounts of Tybost or other medicines in your blood may be affected. This may stop your medicines from working properly, or may make any side effects worse. In some cases, your doctor may need to adjust your dose or check the levels of medicine in your blood.

Medicines that must never be taken with Tybost:

- **alfuzosin**, used to treat an enlarged prostate gland
- **amiodarone, quinidine**, used to correct irregular heartbeats
- **carbamazepine, phenobarbital, phenytoin**, used to prevent seizures
- **rifampicin**, used to prevent and treat tuberculosis and other infections
- **dihydroergotamine, ergometrine, ergotamine**, used to treat migraine headache

- **cisapride**, used to relieve certain stomach problems
 - **St. John's wort** (*Hypericum perforatum*), a herbal remedy used for depression and anxiety
 - **lovastatin, simvastatin**, used to lower blood cholesterol
 - **pimozide**, used to treat abnormal thoughts or feelings
 - **sildenafil**, used to treat pulmonary arterial hypertension – a lung disease that makes breathing difficult
 - orally administered **midazolam, triazolam**, used to help you sleep and/or relieve anxiety
- If you are taking any of these medicines, **do not take Tybost and tell your doctor immediately.**

Medicines used in treating HIV infection:

You should not take Tybost with other medicines containing:

- **ritonavir**
- **cobicistat**

Talk to your doctor if you are taking

- **another protease inhibitor**
- **elvitegravir**
- **efavirenz**
- **etravirine**
- **nevirapine**
- **maraviroc**

→ **Tell your doctor** if you are taking any of these HIV medicines.

Other types of medicine:

- **ketoconazole, itraconazole, voriconazole, posaconazole and fluconazole**, medicines used to treat fungal infections
 - **boceprevir**, a medicine used to treat hepatitis C virus infection
 - **clarithromycin and rifabutin**, medicines used to treat bacterial infections including tuberculosis
 - **dasatinib, nilotinib, vinblastine and vincristine**, medicines used to treat cancer
 - **fluticasone**, a medicine used to treat hay fever and asthma
 - **metformin**, medicine used for the treatment of type 2 diabetes
 - **oral or implanted hormonal contraceptives** used to prevent pregnancy
 - **amlodipine, digoxin, diltiazem, disopyramide, felodipine, flecainide, lidocaine, metoprolol, mexiletine, nifedipine, nifedipine, propafenone, timolol and verapamil**, medicines used to treat heart problems
 - **bosentan**, a medicine used to treat pulmonary arterial hypertension
 - **dabigatran, rivaroxaban and warfarin**, medicines used to thin the blood
 - **salmeterol**, a medicine used to treat asthma
 - **atorvastatin, fluvastatin, pitavastatin, pravastatin and rosuvastatin**, medicines used to lower cholesterol
 - **sildenafil and vardenafil**, medicines used to treat impotence, and **tadalafil**, a medicine used to treat impotence and pulmonary hypertension
 - **trazodone**, a medicine used to treat depression
 - **ciclosporin, sirolimus and tacrolimus**, medicines used to control your body's immune response after a transplant
 - **buspirone, clorazepate, diazepam, estazolam, flurazepam, perphenazine, risperidone, thioridazine, zolpidem**, medicines used to treat nervous system disorders
 - **colchicine**, a medicine used to treat gout
- **Tell your doctor** if you are taking any of these medicines.

→ **Tell your doctor if you are taking these or any other medicines.** Do not stop your treatment without contacting your doctor.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine when pregnant.

- **Tell your doctor immediately if you are pregnant or think you may be pregnant.** In this case you should not take Tybost unless you and your doctor decide it is clearly needed. Your doctor will discuss the potential benefits and risks of taking Tybost to you and your child.
- **Do not breast-feed during treatment with Tybost.** It is not known if the active substance in this medicine can pass into human breast milk. If you are a woman with HIV it is recommended that you do not breast-feed to avoid passing the virus to the baby through your breast milk.

Tybost contains sunset yellow FCF aluminium lake (E110)

Tell your doctor if you have an allergy to sunset yellow FCF aluminium lake (E110). Tybost contains sunset yellow FCF aluminium lake which may cause allergic reactions.

3. How to take Tybost

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Recommended dose for adults:

- **One tablet each day by mouth, with food.** Do not chew, crush or split the tablet.
- **Tybost must be taken with atazanavir (300 mg) or darunavir (800 mg).**

Always take the dose recommended by your doctor. This is to make sure that your medicine is fully effective. Do not change the dose unless your doctor tells you to.

If you take more Tybost than you should

If you accidentally take more than the recommended dose of Tybost you may be at increased risk of experiencing side effects with this medicine (see section 4 of this leaflet).

Contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Tybost

It is important not to miss a dose of Tybost.

If you do miss a dose and notice:

- **within 12 hours** of the time you usually take Tybost, you must take the tablet as soon as possible. Always take the tablet with food. Then take the next dose as usual in combination with atazanavir or darunavir.
- **12 hours or more** after the time you usually take Tybost, then do not take the missed dose. Wait and take the next dose, with food, at your usual time.

Do not stop taking Tybost

Do not stop taking Tybost without talking to your doctor. Stopping Tybost and atazanavir or darunavir may reduce the success of future treatments prescribed by your doctor.

Always keep enough Tybost so you don't run out. When your supply of Tybost starts to run low, get more from your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to tell whether some of the unwanted effects are caused by Tybost or by other medicines that you are taking at the same time, or by the HIV disease itself. The following side effects may occur when taking Tybost with atazanavir.

Very common side effects

(may affect at least 1 in every 10 patients treated)

- feeling sick (*nausea*)
- yellowing of the skin and/or eyes (*jaundice*)

Common side effects

(may affect at least 1 in every 100 patients treated)

- high sugar levels in the blood (*hyperglycaemia*)
- increased appetite, disturbed sense of taste, dry mouth
- headache, dizziness
- vomiting, diarrhoea, stomach pain, problems with digestion resulting in pain after meals (*dyspepsia*), feeling bloated, wind (*flatulence*)
- increased levels of bilirubin in the blood (*hyperbilirubinaemia*)
- rash
- difficulty sleeping, abnormal dreams, drowsiness, tiredness (*fatigue*)

Uncommon side effects

(may affect at least 1 in every 1,000 patients treated)

- blood in the urine (*haematuria*)
- protein in the urine (*proteinuria*)
- feeling depressed
- itchiness
- aching muscles, weakness
- kidney stones
- fever

Reporting of side effects

→ **If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.** You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

For more information on the side effects of atazanavir or darunavir see the package leaflets for these medicines.

5. How to store Tybost

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after {EXP}. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tybost contains

The active substance is cobicistat. Each film-coated tablet contains 150 mg cobicistat.

The other ingredients are

Tablet core

Croscarmellose sodium, magnesium stearate, microcrystalline cellulose, silicon dioxide.

Film-coating

Sunset yellow FCF aluminium lake (E110), macrogol 3350 (E1521), polyvinyl alcohol (partially hydrolysed) (E1203), talc (E553B), titanium dioxide (E171), iron oxide yellow (E172).

What Tybost looks like and contents of the pack

Tybost film-coated tablets are orange, round, biconvex tablets, debossed on one side with “GSI” and plain-faced on the other side of the tablet.

Tybost comes in bottles of 30 tablets (with a silica gel sachet or canister that must be kept in the bottle to help protect your tablets). The silica gel desiccant is contained in a separate sachet or canister and should not be swallowed.

The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets and 90 (3 bottles of 30) film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Gilead Sciences International Limited
Cambridge
CB21 6GT
United Kingdom

Manufacturer

Gilead Sciences Limited
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>