SUMMARY OF PRODUCT CHARACTERISTICS

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 and adolescents aged 12 years and older:

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

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 taken orally, once daily with food.

The doses of Tybost and the co-administered protease inhibitor, atazanavir or darunavir, are presented in Tables 1 and 2.

Table 1: Dosing regimens in adults

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

Table 2: Dosing regimens in adolescents aged 12 years and older, weighing ≥ 35 kg

Body Weight (kg)	**Dose of Tybost**	**Dose of HIV-1 protease inhibitor**
≥ 40	150 mg once daily	Atazanavir 300 mg once daily
		Darunavir 800 mg once daily
35 to < 40	150 mg once daily	Atazanavir 300 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 cobicistat 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. Cobicistat 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, or adefovir) requires dose adjustment based on creatinine clearance. See sections 4.4, 4.8 and 5.2.

Hepatic impairment
No dose adjustment of cobicistat 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 co-administered with atazanavir in children aged 0 to less than 12 years, or weighing less than 35 kg have not been established. The safety and efficacy of cobicistat co-administered with darunavir in children aged 0 to less than 12 years, or weighing less than 40 kg have not been established. 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 is contraindicated with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Therefore, Tybost should not be co-administered with medicinal products that include, but are not limited to, the following (see sections 4.4 and 4.5):

- alpha 1-adrenoreceptor antagonists: alfuzosin
- antiarrhythmics: amiodarone, quinidine
- ergot derivatives: dihydroergotamine, ergometrine, ergotamine
- HMG Co-A reductase inhibitors: lovastatin, simvastatin
- neuroleptics/antipsychotics: pimozide, lurasidone
- PDE-5 inhibitors: sildenafil for treatment of pulmonary arterial hypertension
- sedatives/hypnotics: orally administered midazolam, triazolam

Co-administration is contraindicated with medicinal products that are strong inducers of CYP3A due to the potential for loss of therapeutic effect. Therefore, Tybost should not be co-administered with medicinal products that include, but are not limited to, the following (see sections 4.4 and 4.5):

- anticonvulsants: carbamazepine, phenobarbital, phenytoin
- antimycobacterials: rifampicin

- herbal products: St. John's wort (*Hypericum perforatum*)

Co-administration with dabigatran etexilate, a P-glycoprotein (P-gp) substrate, is contraindicated (see section 4.5).

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 serious and/or life-threatening events (see section 4.3). Co-administration of cobicistat with medicinal products that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of therapeutic effect.

Co-administration of cobicistat 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 cobicistat 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-gp, BCRP, MATE1, OATP1B1 and OATP1B3. Co-administration of cobicistat 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 cobicistat, 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
Plasma concentrations of ethinyloestradiol are decreased following co-administration of drospirenone/ethinyloestradiol with darunavir/cobicistat. Alternative or additional

contraceptive measures are recommended when oestrogen-based contraceptives are co-administered with darunavir/cobicistat.

Plasma concentrations of drospirenone are increased following administration of drospirenone/ethinyloestradiol with atazanavir/cobicistat or with darunavir/cobicistat. If drospirenone/ethinyloestradiol is co-administered with atazanavir/cobicistat or darunavir/cobicistat clinical monitoring is recommended due to the potential for hyperkalemia.

Data are not available to make recommendations on the use of atazanavir/cobicistat or darunavir/cobicistat with other 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 cobicistat 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).

Cobicistat 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). 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 in combination with other medicinal products containing cobicistat or with ritonavir due to similar effects of cobicistat and ritonavir on CYP3A.

<u>Effects on estimated creatinine clearance</u>

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 creatine clearance, should be taken into consideration when cobicistat 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 or adefovir). See sections 4.2, 4.8 and 5.2.

There are currently inadequate data to determine whether co-administration of tenofovir disoproxil and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil 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).

Pregnancy

Treatment with cobicistat and atazanavir or darunavir during the second and third trimesters of pregnancy has been shown to result in lower atazanavir or darunavir exposure compared to postpartum. Cobicistat levels decrease and may not provide sufficient boosting. The substantial reduction in atazanavir or darunavir exposure may result in virological failure and an increased risk of mother-to-child transmission of HIV infection. Therefore, therapy with cobicistat and atazanavir or darunavir should not be initiated during pregnancy, and women who become pregnant during therapy with cobicistat and atazanavir or darunavir should be switched to an alternative regimen (see sections 4.6). Darunavir given with low dose ritonavir may be considered as an alternative regimen.

Excipients

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'**.**

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. Co-administration of cobicistat with medicinal products that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s) (see section 4.4).

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-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 cobicistat with medicinal products such as dihydroergotamine, ergotamine, ergometrine, orally administered midazolam, triazolam, amiodarone, quinidine, pimozide, lurasidone, 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 cobicistat 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 cobicistat 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, and bosentan (see Table 3).

Co-administration of cobicistat 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 3).

Cobicistat 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). 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 3 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 and/or life-threatening 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 3: 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[1]	Co-administration of tenofovir disoproxil 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.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz (600 mg single dose)	Co-administration of efavirenz and cobicistat is expected to decrease cobicistat plasma concentrations. Efavirenz: AUC: ↔ C_{max}: ↓ 13% C_{min}: N/A	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	Interaction not studied. Co-administration of etravirine and cobicistat is expected to decrease 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).
Nevirapine	Interaction not studied. Co-administration of nevirapine and cobicistat is expected to decrease cobicistat plasma concentrations. Nevirapine plasma concentrations may be increased when co-administered with cobicistat.	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).

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
Rilpivirine	Interaction not studied. Co-administration of rilpivirine and cobicistat is expected to increase the plasma concentration of rilpivirine. Rilpivirine is not expected to affect the plasma concentration of cobicistat.	No dose adjustment of rilpivirine is required when atazanavir/cobicistat or darunavir/cobicistat are used concomitantly with rilpivirine.
CCR5 Antagonists		
Maraviroc	Interaction not studied. Maraviroc is a substrate of CYP3A and its plasma concentration increases when co-administered with potent CYP3A inhibitors.	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	Interaction not studied. Concentrations of ketoconazole and/or cobicistat may increase with co-administration of cobicistat.	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.
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 cobicistat, 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.

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
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 cobicistat 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.
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 cobicistat. 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.

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
GLUCOCORTICOIDS		
Corticosteroids		
Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone).	Interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with cobicistat, resulting in reduced serum cortisol concentrations.	Concomitant use of cobicistat and corticosteroids that are metabolised by CYP3A (e.g. fluticasone propionate or other inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone for intranasal or inhalational use should be considered, particularly for long-term use. For coadministration of cutaneously-administered corticosteroids sensitive to CYP3A inhibition, refer to the prescribing information of the corticosteroid for conditions or uses that augment its systemic absorption.
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.

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**
Buprenorphine/Naloxone	Buprenorphine: AUC: ↑ 35% C_{max}: ↔ C_{min}: ↑ 66% Naloxone: AUC: ↓ 28% C_{max}: ↓ 28%	No dose adjustment of cobicistat is required.
ORAL CONTRACEPTIVES		
Drospirenone/Ethinyloestradiol (3 mg/0.02 mg single dose)/ Darunavir (800 mg once daily)/Cobicistat (150 mg once daily)	Drospirenone: AUC: ↑ 58% C_{max}: ↔ C_{min}: N/A Ethinyloestradiol: AUC: ↓ 30% C_{max}: ↔ C_{min}: N/A	Plasma concentrations of ethinyloestradiol are decreased following co-administration of drospirenone/ethinyloestradiol with darunavir/cobicistat. Alternative or additional contraceptive measures are recommended when oestrogen-based contraceptives are co-administered with darunavir/cobicistat. Plasma concentrations of drospirenone are increased following co-administration of drospirenone/ethinyloestradiol with darunavir/cobicistat. If drospirenone/ethinyloestradiol is co-administered with darunavir/cobicistat clinical monitoring is recommended due to the potential for hyperkalemia.
Drospirenone/Ethinyloestradiol (3 mg/0.02 mg single dose)/Atazanavir (300 mg once daily)/Cobicistat (150 mg once daily)	Drospirenone: AUC: ↑ 130% C_{max}: ↔ C_{min}: N/A Ethinyloestradiol: AUC: ↔ C_{max}: ↔ C_{min}: N/A	Plasma concentrations of drospirenone are increased following co-administration of drospirenone/ethinyloestradiol with atazanavir/cobicistat. If drospirenone/ethinyloestradiol is co-administered with atazanavir/cobicistat clinical monitoring is recommended due to the potential for hyperkalemia.
Norgestimate/Ethinyloestradiol	Interaction not studied. Concentrations of norgestimate may be affected on co-administration with cobicistat.	Data are not available to make recommendations on the use of darunavir/cobicistat or atazanavir/cobicistat with other oral contraceptives than drospirenone/ethinyloestradiol. Alternative forms of contraception should be considered.

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}: N/A	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		
Dabigatran	Interaction not studied. Co-administration with Tybost may increase dabigatran plasma concentrations with similar effects as seen with other strong P-gp inhibitors.	Co-administration of cobicistat with dabigatran is contraindicated.

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
Apixaban Rivaroxaban Edoxaban	Interaction not studied. Co-administration with cobicistat may result in increased plasma concentrations of the DOAC, which may lead to an increased bleeding risk.	Co-administration of apixaban, rivaroxaban or edoxaban is not recommended with Tybost.
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.
ANTIPLATELETS		
Clopidogrel	Interaction not studied. Co-administration of clopidogrel with cobicistat is expected to decrease clopidogrel active metabolite plasma concentrations, which may reduce the antiplatelet activity of clopidogrel.	Co-administration of clopidogrel with cobicistat is not recommended.
Prasugrel	Interaction not studied. Cobicistat is not expected to have a clinically relevant effect on plasma concentrations of the active metabolite of prasugrel.	No dose adjustment of prasugrel is required.
ANTICONVULSANTS		
Carbamazepine (200 mg twice daily)/Elvitegravir (150 mg once daily)/Cobicistat (150 mg once daily)	Co-administration of carbamazepine, a potent CYP3A inducer, may significantly decrease cobicistat plasma concentrations. Cobicistat: AUC: ↓ 84% C_{max}: ↓ 72% C_{min}: ↓ 90% Carbamazepine: AUC: ↑ 43% C_{max}: ↑ 40% C_{min}: ↑ 51% Carbamazepine-10,11-epoxide: AUC: ↓ 35% C_{max}: ↓ 27% C_{min}: ↓ 41%	Carbamazepine, a potent CYP3A inducer, decreases cobicistat plasma concentrations and that of atazanavir or darunavir, which may result in loss of therapeutic effect and development of resistance. Co-administration of cobicistat with carbamazepine is contraindicated (see section 4.3).

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		
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, pitavastatin, fluvastatin or pravastatin are expected to increase when co-administered with atazanavir/cobicistat or darunavir/cobicistat. Caution should be exercised when co-administering cobicistat with pitavastatin. Consult the Summary of Product Characteristics of atazanavir or darunavir for further information on use in combination with these medicinal products.
Rosuvastatin (10 mg single dose)/Atazanavir (300 mg once daily)/Cobicistat (150 mg once daily)	Rosuvastatin: AUC: ↑ 242% C_{max}: ↑ 958% C_{min}: N/A Cobicistat: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Plasma concentrations of rosuvastatin are increased when co-administered with atazanavir/cobicistat. When co-administration is necessary, do not exceed 10 mg rosuvastatin daily and clinical monitoring for safety (e.g. myopathy) is recommended.
Rosuvastatin (10 mg single dose)/Darunavir (800 mg once daily)/Cobicistat (150 mg once daily)	Rosuvastatin: AUC: ↑ 93% C_{max}: ↑ 277% C_{min}: N/A Cobicistat: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Plasma concentrations of rosuvastatin are increased when co-administered with darunavir/cobicistat. It is recommended to start with the lowest recommended dose of rosuvastatin and titrate based on clinical response while monitoring for safety (e.g. myopathy).

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
Atorvastatin (10 mg single dose)/Atazanavir (300 mg)/Cobicistat (150 mg once daily)	Atorvastatin: AUC: ↑ 822% C_{max}: ↑ 1785% C_{min}: N/A Cobicistat: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Plasma concentrations of atorvastatin are increased when co-administered with atazanavir/cobicistat. Co-administration is not recommended.
Atorvastatin (10 mg single dose)/Darunavir (800 mg)/Cobicistat (150 mg once daily)	Atorvastatin: AUC: ↑ 290% C_{max}: ↑ 319% C_{min}: N/A Cobicistat: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Plasma concentrations of atorvastatin are increased when co-administered with darunavir/cobicistat. When co-administration is necessary, it is recommended to start with a dose of atorvastatin 10 mg and titrate based on clinical response while monitoring for safety (e.g. myopathy).
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. Cobicistat should not be co-administered with colchicine to patients with renal or hepatic impairment.

N/A = not applicable
DOAC = direct oral anticoagulant
[1] Study was conducted with tenofovir disoproxil fumarate

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).

Treatment with cobicistat and atazanavir or darunavir during pregnancy results in lower atazanavir or darunavir exposure which may be associated with an increased risk of virological failure and an increased risk of mother-to-child transmission of HIV infection. Therapy with cobicistat and atazanavir or darunavir should not be initiated during pregnancy, and women who become pregnant during therapy with cobicistat and atazanavir or darunavir should be switched to an alternative regimen (see sections 4.4).

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 women living with HIV do not breast-feed their infants.

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

Tybost has no or negligible influence on the ability to drive and use machines. However, patients should be informed that dizziness has been reported during treatment with cobicistat-containing regimens.

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 4).

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 4, below, by body system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (frequency cannot be estimated from the available data).

Table 4: Tabulated summary of adverse reactions to cobicistat-boosted atazanavir based on experience of 144 weeks from phase 3 Study GS-US-216-0114

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

The safety of cobicistat was evaluated in 21 HIV-1 infected virologically suppressed paediatric patients between the ages of 12 to < 18 years through 48 weeks in an open-label clinical study (GS-US-216-0128) of cobicistat-boosted atazanavir (n = 14) or darunavir (n = 7) plus two NRTIs. In this study, the safety profile of cobicistat was similar to that in adults.

Other special population(s)

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 96 the mean change in serum creatinine was 0.07 ± 0.15 mg/dl and the mean change in eGFR by Cockcroft-Gault method was -6.2 ± 9.07 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 *Yellow Card Scheme,*
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8). 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 5).

Table 5: 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 6).

Table 6: 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 (≤ 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 7 and 8, respectively.

Table 7: 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 8: 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 9.

Table 9: 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 safety and efficacy of cobicistat with atazanavir or darunavir were evaluated in an open-label phase 2/3 Study GS-US-216-0128 in 21 HIV-1 infected virologically suppressed paediatric patients between the ages of 12 and < 18 years with baseline estimated creatinine clearance ≥90 mL/min. Patients received cobicistat 150 mg once daily with either atazanavir 300 mg once daily (n = 14) or darunavir 800 mg once daily (n = 7), each administered with a background regimen containing two NRTIs.

The mean age of patients was 14 years (range: 12 to 17); 62% were male; 38% were Asian, 33% were White, and 19% were Black. At baseline, 20/21 subjects had plasma HIV-1 RNA < 50 copies/mL and 1 subject had plasma HIV-1 RNA = 50 copies/mL.

In patients treated with cobicistat + atazanavir, the median baseline CD4+ cell count and CD4+% was 770 cells/mm^3 (range: 486 to 1765) and 33% (range: 23% to 45%), respectively. At Week 48, 93% (13/14) of patients retained HIV-1 RNA < 50 copies/mL and the median change from baseline in CD4+ cell count and CD4+% was -60 cells/mm^3 and -0.3%, respectively. In patients treated with cobicistat + darunavir, the median baseline CD4+ cell count and CD4+% was 1117 cells/mm^3 (range: 658 to 2416) and 45% (range: 28% to 56%), respectively. At Week 48, 86% (6/7) of patients retained HIV-1 RNA < 50 copies/mL (1 subject had missing data) and the median change from baseline in CD4+ cell count and CD4+% was -342 cells/mm^3 and -6%, respectively. Overall, 3 of 21 patients qualified for resistance analysis: 1 patient showed no resistance in protease or reverse transcriptase and 2 had missing data due to assay failure.

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 ± SD) following multiple doses of cobicistat in HIV-1 infected subjects (n = 68), respectively, were 1.2 ± 0.3 µg/ml, 10.9 ± 3.8 µg•h/ml, and 0.07 ± 0.07 µg/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

In paediatric patients aged 12 to < 18 years who received cobicistat-boosted atazanavir (n = 14) or darunavir (n = 7) in Study GS-US-216-0128, exposures of atazanavir and cobicistat (AUC_{tau}, C_{max}, and C_{trough}) were higher (24% to 180%) than in adults; however, the increases were not considered clinically significant as the safety profiles were similar in adult and paediatric patients. Mean darunavir C_{trough} was lower (61%) in the paediatric patients relative to adults but was not considered clinically significant based on exposure-response relationships. The pharmacokinetics of cobicistat in paediatric subjects < 12 years of age or < 35 kg 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 cobicistat 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 foetuses 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 (E551)
Croscarmellose sodium
Magnesium stearate
Microcrystalline cellulose (E460)

Film-coating

Sunset yellow FCF (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

4 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.

Pack sizes containing 1 bottle of 30 film-coated tablets or 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 Ltd

280 High Holborn

London

WC1V 7EE

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 11972/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

31/05/2023