

1. NAME OF THE MEDICINAL PRODUCT

Symtuza 800 mg/150 mg/200 mg/10 mg film-coated tablets

Symtuza 675 mg/150 mg/200 mg/10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Symtuza 800 mg/150 mg/200 mg/10 mg film-coated tablets

Each tablet contains 800 mg of darunavir (as ethanolate), 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as fumarate).

Symtuza 675 mg/150 mg/200 mg/10 mg film-coated tablets

Each tablet contains 675 mg of darunavir (as ethanolate), 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as fumarate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Symtuza 800 mg/150 mg/200 mg/10 mg film-coated tablets

Yellow to yellowish-brown capsule shaped tablet of 22 mm x 11 mm, debossed with “8121” on one side and “JG” on the other side.

Symtuza 675 mg/150 mg/200 mg/10 mg film-coated tablets

Bluish grey to grey, oval-shaped, scored tablet of 22 mm x 11mm, debossed with “6121” on one side and “JG” on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symtuza is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and paediatric patients aged 6 years and older with body weight at least 25 kg.

Genotypic testing should guide the use of Symtuza (see sections 4.2, 4.4, and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV-1 infection.

Posology

Adults and paediatric patients weighing at least 40 kg

Antiretroviral Therapy (ART)-naïve patients

The recommended dose regimen is one 800 mg darunavir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir alafenamide tablet once daily taken with food.

ART-experienced patients

One 800 mg darunavir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir alafenamide tablet once daily taken with food may be used in patients with prior exposure to antiretroviral medicinal products but without darunavir resistance associated mutations (DRV-RAMs)* and who have plasma HIV-1 RNA < 100 000 copies/mL and CD4+ cell count ≥ 100 cells $\times 10^6$ /L (see section 5.1).

* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V.

Paediatric patients aged 6 years and older weighing at least 25 kg to less than 40 kg

ART-naïve paediatric patients

The recommended dose regimen is one 675 mg darunavir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir alafenamide tablet once daily taken with food.

ART-experienced paediatric patients

One 675 mg darunavir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir alafenamide tablet once daily taken with food may be used in patients with prior exposure to antiretroviral medicinal products but without DRV-RAMs* and who have plasma HIV-1 RNA < 100 000 copies/mL and CD4+ cell count ≥ 100 cells $\times 10^6/L$ (see section 5.1).

* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V.

Advice on missed doses

If a dose of Symtuza is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose with food as soon as possible. If a missed dose is noticed later than 12 hours of the time it is usually taken, it should not be taken and the patient should resume the usual dosing schedule.

In case a patient vomits within 1 hour of taking Symtuza, another dose should be taken with food as soon as possible. If a patient vomits more than 1 hour after taking the dose, the patient does not need to take another dose until the next regularly scheduled time.

Special populations

Elderly

This medicine should be used with caution in patients above 65 years of age (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, this medicine should be used with caution in these patients, as darunavir and cobicistat are metabolised by the hepatic system (see section 5.2).

This medicine must not be used in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Renal impairment

No dose adjustment is required in patients with estimated glomerular filtration rate (eGFR) ≥ 30 mL/min.

This medicine should not be initiated in patients with eGFR < 30 mL/min, as there are no data available (see sections 5.1 and 5.2).

It should be discontinued in patients with eGFR that declines below 30 mL/min during treatment (see sections 5.1 and 5.2).

Pregnancy and postpartum

Treatment with darunavir/cobicistat (two of the components of Symtuza) during pregnancy results in low darunavir exposure (see sections 4.4 and 5.2). Therefore, therapy with Symtuza should not be initiated during pregnancy, and women who become pregnant during therapy with this fixed-dose combination (FDC) should be switched to an alternative regimen (see sections 4.4 and 4.6).

Paediatric population

The safety and efficacy of darunavir/cobicistat/emtricitabine/tenofovir alafenamide FDC have not been established in children aged 3 to < 6 years, or weighing < 25 kg. No data are available.

Darunavir/cobicistat/emtricitabine/tenofovir alafenamide FDC should not be used in paediatric patients below 3 years of age because of safety concerns related to toxicity and mortality observed in juvenile rats dosed with darunavir up to days 23 to 26 of age (see sections 4.4 and 5.3).

Method of administration

Symtuza should be taken orally, once daily with food (see section 5.2). The tablet should not be crushed.

Adults and paediatric patients weighing at least 40 kg

For patients unable to swallow the 800 mg/150 mg/200 mg/10 mg tablet whole, the tablet may be split into two pieces using a tablet-cutter. Each piece should be consumed immediately after splitting to ensure the entire dose is administered.

Paediatric patients aged 6 years and older weighing at least 25 kg to less than 40 kg

For patients unable to swallow the 675 mg/150 mg/200 mg/10 mg tablet whole, the scored tablet may be split by hand into two pieces. Each piece should be consumed immediately after splitting to ensure the entire dose is administered.

4.3 Contraindications

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

Patients with severe (Child-Pugh Class C) hepatic impairment.

Co-administration with strong CYP3A inducers such as the medicinal products listed below due to the potential for loss of therapeutic effect (see section 4.5):

- carbamazepine, phenobarbital, phenytoin
- rifampicin
- lopinavir/ritonavir
- St. John's Wort (*Hypericum perforatum*)

Co-administration with medicinal products such as those products listed below due to the potential for serious and/or life-threatening adverse reactions (see section 4.5):

- alfuzosin
- amiodarone, dronedarone, ivabradine, quinidine, ranolazine
- colchicine when used in patients with renal and/or hepatic impairment (see section 4.5)
- rifampicin
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- dapoxetine
- domperidone
- naloxegol
- pimozone, quetiapine, sertindole, lurasidone (see section 4.5)
- elbasvir/grazoprevir
- triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5)
- sildenafil - when used for the treatment of pulmonary arterial hypertension, avanafil
- simvastatin, lovastatin and lomitapide (see section 4.5)
- ticagrelor

4.4 Special warnings and precautions for use

ART-experienced patients

Symtuza should not be used in treatment-experienced patients with one or more DRV-RAMs (see section 5.1) or with HIV-1 RNA $\geq 100\,000$ copies/mL or CD4⁺ cell count < 100 cells $\times 10^6/L$.

Pregnancy

Treatment with darunavir/cobicistat 800/150 mg during the second and third trimester has been shown to result in low darunavir exposure, with a reduction of around 90% in C_{min} levels (see section 5.2). Cobicistat levels decrease and may not provide sufficient boosting. The substantial reduction in darunavir exposure may result in virological failure and an increased risk of mother to child transmission of HIV infection. Therefore, therapy with Symtuza should not be initiated during pregnancy, and women who become pregnant during therapy with Symtuza should be switched to an alternative regimen (see sections 4.2 and 4.6).

Patients co-infected with HIV and hepatitis B or C virus

Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

The safety and efficacy of Symtuza in patients co-infected with HIV-1 and hepatitis C virus (HCV) have not been established. Tenofovir alafenamide is active against hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis C, please refer also to the relevant Summary of Product Characteristics for these medicinal products.

Discontinuation of Symtuza therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Symtuza should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Symtuza should not be administered concomitantly with medicinal products containing tenofovir disoproxil (e.g. fumarate, phosphate, or succinate), lamivudine, or adefovir dipivoxil used for the treatment of HBV infection.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Elderly

As limited information is available on the use of Symtuza in patients aged 65 and over, caution should be exercised, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy (see sections 4.2 and 5.2).

Hepatotoxicity

Hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with darunavir/ritonavir. During the darunavir/ritonavir clinical development program (N = 3 063), hepatitis was reported in 0.5% of patients receiving combination antiretroviral therapy with darunavir/ritonavir. Patients with pre-existing liver dysfunction, including chronic hepatitis B or C, have an increased risk for liver function abnormalities including severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

Appropriate laboratory testing should be conducted prior to initiating therapy with Symtuza and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of Symtuza treatment.

If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients using Symtuza, interruption or discontinuation of treatment should be considered promptly (see section 5.3).

Nephrotoxicity

Post-marketing cases of renal impairment, including acute renal failure and proximal renal tubulopathy have been reported with tenofovir alafenamide-containing products. A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded (see section 5.3). It is recommended that renal function is assessed in all patients prior to, or when, initiating therapy with Symtuza and that it is also monitored during therapy in all patients as clinically appropriate. In patients who develop clinically significant decreases in renal function or evidence of proximal renal tubulopathy, discontinuation of Symtuza should be considered.

Renal impairment

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 Symtuza 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. For more information consult the cobicistat Summary of Product Characteristics.

Patients with co-existing conditions

Hepatic impairment

The safety and efficacy of darunavir/cobicistat/emtricitabine/tenofovir alafenamide FDC or its components have not been established in patients with severe underlying liver disorders. Symtuza is, therefore, contraindicated in patients with severe hepatic impairment. Due to an increase in the unbound darunavir plasma concentrations, Symtuza should be used with caution in patients with mild or moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

Haemophiliac patients

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis in patients with haemophilia type A and B treated with HIV PIs. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with HIV PIs was continued or reintroduced if treatment had been discontinued. A causal relationship has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should, therefore, be made aware of the possibility of increased bleeding.

Severe skin reactions

During the darunavir/ritonavir clinical development program (N = 3 063), severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported in 0.4% of patients. DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and Stevens-Johnson syndrome has been rarely (< 0.1%) reported, and during post-marketing experience toxic epidermal necrolysis and acute generalised exanthematous pustulosis have been reported. Symtuza should be discontinued immediately if signs or symptoms of severe skin reactions develop. These can include, but are not limited to, severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Sulphonamide allergy

Darunavir contains a sulphonamide moiety. Symtuza should be used with caution in patients with a known sulphonamide allergy.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Immune reconstitution inflammatory syndrome (IRIS)

In HIV infected patients treated with CART, IRIS has been reported. In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumonia caused by *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. In addition, reactivation of herpes simplex and herpes zoster has been observed in clinical trials with darunavir co-administered with low dose ritonavir.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of IRIS; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.8).

Opportunistic infections

Patients receiving Symtuza or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Interactions with medicinal products

Co-administration of other medicinal products

Symtuza is indicated for use as a complete regimen for the treatment of HIV-1 infection and should not be administered with other antiretroviral products (see section 4.5). Symtuza should not be administered concomitantly with medicinal products requiring pharmacokinetic enhancement with ritonavir or cobicistat. Symtuza should not be administered concomitantly with medicinal products containing tenofovir disoproxil (as fumarate, phosphate or succinate), lamivudine, or adefovir dipivoxil used for the treatment of HBV infection.

Paediatric population

Reductions in bone mineral density (BMD $\geq 4\%$) of the spine and total body less head (TBLH) have been reported in patients aged between 3 to <12 years who received tenofovir alafenamide-containing products for 48 weeks (see section 4.8). The long-term effects of changes in BMD on the growing bone, including the risk of fracture, are uncertain. A multidisciplinary approach is recommended to decide the appropriate monitoring during treatment.

Excipients

This medicinal product 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

No interaction trials have been performed using Symtuza. Interactions that have been identified in studies with individual components of Symtuza, i.e. with darunavir (in combination with low dose ritonavir), cobicistat, emtricitabine or tenofovir alafenamide, determine the interactions that may occur with Symtuza.

Darunavir and cobicistat

Darunavir is an inhibitor of CYP3A, a weak inhibitor of CYP2D6 and an inhibitor of P-gp. Cobicistat is a mechanism based inhibitor of CYP3A, and a weak CYP2D6 inhibitor. Cobicistat inhibits the transporters p-glycoprotein (P-gp), BCRP, MATE1, OATP1B1 and OATP1B3. Cobicistat is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19. Cobicistat is not expected to induce CYP1A2, CYP3A4, CYP2C9, CYP2C19, UGT1A1, or P-gp (MDR1).

Co-administration of Symtuza and medicinal products primarily metabolised by CYP3A or transported by P-gp, BCRP, MATE1, OATP1B1 and OATP1B3 may result in increased systemic exposure to such medicinal products, which could increase or prolong their therapeutic effect and adverse reactions (see section 4.3 or table below).

Symtuza must not be combined with medicinal products that are highly dependent on CYP3A for clearance and for which increased systemic exposure is associated with serious and/or life-threatening events (narrow therapeutic index).

Co-administration of Symtuza and 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 their therapeutic effect. These interactions are described in the interaction table below.

Darunavir and cobicistat are metabolised by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and cobicistat, resulting in lowered plasma concentrations of darunavir and cobicistat (e.g. efavirenz, carbamazepine, phenytoin, phenobarbital, rifampicin, rifapentine, rifabutin, St. John's Wort) (see section 4.3 and interaction table below).

Co-administration of Symtuza and other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and cobicistat and may result in increased plasma concentrations of darunavir and cobicistat (e.g. azole antifungals like clotrimazole). These interactions are described in the interaction table below.

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

Emtricitabine

In vitro and clinical pharmacokinetic interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine with other medicinal products is low.

Emtricitabine did not inhibit the glucuronidation reaction of a non-specific UGT substrate *in vitro*. Co-administration of emtricitabine with medicinal products that are eliminated by active tubular secretion may increase concentrations of emtricitabine, and/or the co-administered medicinal product. Medicinal products that decrease renal function may increase concentrations of emtricitabine.

Tenofovir alafenamide

Tenofovir alafenamide is transported by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Medicinal products that strongly affect P-gp activity and BCRP may lead to changes in tenofovir alafenamide absorption. Medicinal products that induce P-gp activity (e.g., rifampicin, rifabutin, carbamazepine, phenobarbital) are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentration of tenofovir alafenamide, which may lead to

loss of therapeutic effect of tenofovir alafenamide and development of resistance. Co-administration of tenofovir alafenamide with other medicinal products that inhibit P-gp (e.g., cobicistat, ritonavir, ciclosporin) are expected to increase the absorption and plasma concentration of tenofovir alafenamide. It is not known whether the co-administration of tenofovir alafenamide and xanthine oxidase inhibitors (e.g. febuxostat) would increase systemic exposure to tenofovir.

Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro*. It is not an inhibitor of CYP3A4 *in vivo*. Tenofovir alafenamide is a substrate of OATP1B1 and OATP1B3 *in vitro*. The distribution of tenofovir alafenamide in the body may be affected by the activity of OATP1B1 and OATP1B3.

Interaction table

Expected interactions between Symtuza with potential concomitant medicinal products are listed in Table 1 below and are based on the studies conducted with the components of Symtuza, as individual agents or combined, or are potential interactions that may occur.

Interaction trials with the components of Symtuza have only been performed in adults.

The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as a pharmacokinetic enhancer; therefore, there may be different recommendations for the use of darunavir with concomitant medicines. Refer to the prescribing information for darunavir for further information.

The below list of examples of interactions is not comprehensive and therefore the label of each medicinal product that is co-administered with Symtuza should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

Table 1: Interactions between the individual components of Symtuza and other medicinal products		
INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal product examples by therapeutic area	Interaction	Recommendations concerning co-administration
ALPHA ADRENORECEPTOR ANTAGONISTS		
Alfuzozin	Based on theoretical considerations DRV/COBI is expected to increase alfuzozin concentrations (CYP3A4 inhibition)	The concomitant use of Symtuza with alfuzozin is contraindicated (see section 4.3).
ANAESTHETIC		
Alfentanil	Based on theoretical considerations DRV/COBI is expected to increase alfentanil plasma concentrations.	The concomitant use with Symtuza may require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression.
ANTACIDS		
Aluminium/magnesium hydroxide Calcium carbonate	No mechanistic interaction expected based on theoretical considerations.	Symtuza and antacids can be used concomitantly without dose adjustment.

ANTIANGINA/ANTIARRHYTHMIC		
Disopyramide Flecainide Mexiletine Propafenone Lidocaine (systemic) Amiodarone Dronedarone Ivabradine Quinidine Ranolazine	Based on theoretical considerations DRV/COBI is expected to increase these antiarrhythmic plasma concentrations. (CYP3A inhibition)	Caution is warranted and concentration monitoring, if available, is recommended for these antiarrhythmics when co-administered with Symtuza. Co-administration of amiodarone, dronedarone, ivabradine, quinidine, or ranolazine and Symtuza is contraindicated (see section 4.3).
Digoxin	Based on theoretical considerations DRV/COBI is expected to increase digoxin plasma concentrations. (P-glycoprotein inhibition)	It is recommended that the lowest possible dose of digoxin should initially be given to patients on Symtuza. The digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state of the subject.
ANTIBIOTIC		
Clarithromycin	Based on theoretical considerations clarithromycin is expected to increase darunavir and/or cobicistat plasma concentrations. (CYP3A inhibition) Concentrations of clarithromycin may be increased upon co-administration with DRV/COBI. (CYP3A inhibition)	Caution should be exercised when clarithromycin is combined with Symtuza. For patients with renal impairment the Summary of Product Characteristics for clarithromycin should be consulted for the recommended dose.
ANTICOAGULANT/PLATELET AGGREGATION INHIBITOR		
Apixaban Rivaroxaban	Based on theoretical considerations co-administration of Symtuza with these anticoagulants may increase concentrations of the anticoagulant. (CYP3A and/or P-glycoprotein inhibition)	Co-administration of Symtuza with a direct oral anticoagulant (DOAC) that is metabolised by CYP3A4 and transported by P-gp is not recommended as this may lead to an increased bleeding risk.

Dabigatran etexilate Edoxaban	dabigatran etexilate (150 mg): <u>darunavir/cobicistat 800/150 mg single dose:</u> dabigatran AUC ↑ 164% dabigatran C _{max} ↑ 164% <u>darunavir/cobicistat 800/150 mg once daily:</u> dabigatran AUC ↑ 88% dabigatran C _{max} ↑ 99%	Clinical monitoring and dose reduction is required when a DOAC transported by P-gp but not metabolised by CYP3A4, including dabigatran etexilate and edoxaban, is co-administered with Symtuza.
Ticagrelor	Based on theoretical considerations co-administration of DRV/COBI with ticagrelor may increase concentrations of ticagrelor. (CYP3A and/or P-glycoprotein inhibition).	Concomitant administration of Symtuza with ticagrelor is contraindicated (see section 4.3).
Clopidogrel	Based on theoretical considerations co-administration of Symtuza with clopidogrel is expected to decrease clopidogrel active metabolite plasma concentration, which may reduce the antiplatelet activity of clopidogrel.	Co-administration of Symtuza with clopidogrel is not recommended. Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended (see section 4.3).
Warfarin	Based on theoretical considerations DRV/COBI may alter warfarin plasma concentrations.	It is recommended that the international normalised ratio (INR) be monitored when warfarin is co-administered with Symtuza.
ANTICONVULSANTS		
Carbamazepine Phenobarbital Phenytoin Oxcarbazepine	Based on theoretical considerations these anticonvulsants are expected to decrease darunavir and/or cobicistat and/or tenofovir alafenamide plasma concentrations. (CYP3A and/or P-gp induction).	Co-administration of Symtuza and these anticonvulsants is contraindicated (see section 4.3). Co-administration of Symtuza with oxcarbazepine is not recommended. Alternative anticonvulsants should be considered.
Clonazepam	Based on theoretical considerations Symtuza is expected to increase concentrations of clonazepam. (inhibition of CYP3A)	Clinical monitoring is recommended when co-administering Symtuza with clonazepam.
ANTI-DEPRESSANTS		
Herbal supplements St. John's Wort	Based on theoretical considerations St. John's Wort is expected to decrease darunavir and/or cobicistat and/or tenofovir alafenamide plasma concentrations. (CYP3A and/or P-gp induction)	Co-administration of St. John's Wort and Symtuza is contraindicated (see section 4.3).

Paroxetine Sertraline	Based on theoretical considerations DRV/COBI is expected to increase these anti-depressant plasma concentrations. (CYP2D6 and/or CYP3A inhibition) Prior data with ritonavir-boosted darunavir however showed a decrease in these anti-depressant plasma concentrations (unknown mechanism); the latter may be specific to ritonavir.	If these anti-depressants are to be used with Symtuza clinical monitoring is recommended and a dose adjustment of the anti-depressant may be needed.
Amitriptyline Desipramine Imipramine Nortriptyline Trazodone	Based on theoretical considerations DRV/COBI is expected to increase these anti-depressant plasma concentrations. (CYP2D6 and/or CYP3A inhibition)	
ANTI-DIABETICS		
Metformin	Based on theoretical considerations DRV/COBI is expected to increase metformin plasma concentrations. (MATE1 inhibition)	Careful clinical monitoring and dose adjustment of metformin is recommended in patients who are taking Symtuza.
ANTIEMETICS		
Domperidone	Not studied.	Co-administration of domperidone with Symtuza is contraindicated.
ANTIFUNGALS		
Clotrimazole Fluconazole Itraconazole Isavuconazole Posaconazole Voriconazole	Based on theoretical considerations DRV/COBI is expected to increase these antifungal plasma concentrations, and darunavir, cobicistat and/or tenofovir alafenamide plasma concentrations may be increased by the antifungals. (CYP3A and/or P-gp inhibition) Concentrations of voriconazole may increase or decrease when co-administered with DRV/COBI.	Caution is warranted and clinical monitoring is recommended. When co-administration is required, the daily dose of itraconazole should not exceed 200 mg. Voriconazole should not be combined with Symtuza unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
ANTIGOUT MEDICINES		
Colchicine	Based on theoretical considerations DRV/COBI is expected to increase colchicine plasma concentrations. (CYP3A and/or P-glycoprotein inhibition)	A reduction in colchicine dose or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with Symtuza is required. The combination of colchicine and Symtuza is contraindicated in patients with renal or hepatic impairment (see section 4.3).

ANTIMALARIALS		
Artemether/Lumefantrine	Based on theoretical considerations DRV/COBI is expected to increase lumefantrine plasma concentrations. (CYP3A inhibition)	Symtuza and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.
ANTIMYCOBACTERIALS		
Rifampicin	Based on theoretical considerations rifampicin is expected to decrease darunavir and/or cobicistat and/or tenofovir alafenamide plasma concentrations. (CYP3A and/or P-gp induction)	The combination of rifampicin and Symtuza is contraindicated (see section 4.3).
Rifabutin Rifapentine	Based on theoretical considerations these antimycobacterials are expected to decrease darunavir and/or cobicistat and/or tenofovir alafenamide plasma concentrations. (CYP3A and/or P-gp induction)	Co-administration of Symtuza with rifabutin and rifapentine 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 rifabutin. Further dose reduction of rifabutin has not been studied. It should be kept in mind that the twice weekly dose of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients. This recommendation is different from ritonavir-boosted darunavir. Consult the Summary of Product Characteristics for darunavir for further details.
ANTI-NEOPLASTICS		
Dasatinib Nilotinib Vinblastine Vincristine Everolimus Irinotecan	Based on theoretical considerations DRV/COBI is expected to increase these anti-neoplastic plasma concentrations. (CYP3A inhibition)	Concentrations of these medicinal products may be increased when co-administered with Symtuza resulting in the potential for increased adverse events usually associated with these medicinal products. Caution should be exercised when combining one of these anti-neoplastic agents with Symtuza. Concomitant use of everolimus or irinotecan and Symtuza is not recommended.

ANTIPSYCHOTICS/NEUROLEPTICS		
Perphenazine Risperidone Thioridazine Lurasidone Pimozide Quetiapine Sertindole	Based on theoretical considerations DRV/COBI is expected to increase these neuroleptic plasma concentrations. (CYP3A, CYP2D6 and/or P-gp inhibition)	Clinical monitoring is recommended when co-administering Symtuza with perphenazine, risperidone or thioridazine. For these neuroleptics, consider reducing the dose of the neuroleptic upon co-administration with Symtuza. The combination of lurasidone, pimozide, quetiapine or sertindole and Symtuza is contraindicated (see section 4.3).
β-BLOCKERS		
Carvedilol Metoprolol Timolol	Based on theoretical considerations DRV/COBI is expected to increase these beta-blocker plasma concentrations. (CYP2D6 inhibition)	Clinical monitoring is recommended when co-administering Symtuza with beta-blockers and a lower dose of the beta-blocker should be considered.
CALCIUM CHANNEL BLOCKERS		
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Based on theoretical considerations DRV/COBI is expected to increase these calcium channel blocker plasma concentrations. (CYP3A inhibition)	Clinical monitoring is recommended when these medicinal products are co-administered with Symtuza.
CORTICOSTEROIDS		
Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone)	Based on theoretical considerations DRV/COBI is expected to increase these corticosteroid plasma concentrations. (CYP3A inhibition)	Concomitant use of Symtuza and corticosteroids (all routes of administration) that are metabolised by CYP3A may increase the risk for 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 should be considered, particularly for long-term use.
Dexamethasone (systemic)	Based on theoretical considerations (systemic) dexamethasone is expected to decrease darunavir and/or cobicistat plasma concentrations. (CYP3A induction)	Systemic dexamethasone should be used with caution when combined with Symtuza.

ENDOTHELIN RECEPTOR ANTAGONISTS		
Bosentan	Based on theoretical considerations bosentan is expected to decrease darunavir and/or cobicistat plasma concentrations. (CYP3A induction) Symtuza is expected to increase bosentan plasma concentrations. (CYP3A inhibition)	Co-administration of Symtuza and bosentan is not recommended.
ERGOT DERIVATIVES		
e.g. Dihydroergotamine Ergometrine Ergotamine Methylergonovine	Based on theoretical considerations DRV/COBI may increase ergot derivative exposure.	Co-administration of Symtuza and ergot derivatives is contraindicated (see section 4.3).
HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS		
NS3-4A inhibitors		
Elbasvir/grazoprevir	Based on theoretical considerations Symtuza may increase the exposure to grazoprevir. (OATP1B and CYP3A inhibition)	Concomitant use of Symtuza with elbasvir/grazoprevir is contraindicated (see section 4.3).
Glecaprevir/pibrentasvir	Based on theoretical considerations DRV/COBI may increase the exposure to glecaprevir and pibrentasvir. (P-gp, BCRP and/or OATP1B1/3 inhibition)	It is not recommended to co-administer Symtuza with glecaprevir/pibrentasvir.
Daclatasvir Ledipasvir Sofosbuvir	Based on theoretical considerations, no clinically relevant interaction is expected.	Symtuza and sofosbuvir, sofosbuvir/ledipasvir, or daclatasvir can be used concomitantly without dose adjustment
Herbal products		
St. John's Wort (<i>Hypericum perforatum</i>)	Based on theoretical consideration, St. John's Wort may substantially decrease DRV/COBI (CYP3A4 induction) and TAF exposures. (P-gp induction)	The concomitant use of Symtuza with these medicinal products is contraindicated (see section 4.3).
HMG CO-A REDUCTASE INHIBITORS		
Atorvastatin Fluvastatin Pitavastatin Pravastatin Rosuvastatin	Atorvastatin (10 mg once daily): atorvastatin AUC ↑ 290% atorvastatin C _{max} ↑ 319% atorvastatin C _{min} ND Rosuvastatin (10 mg once daily): rosuvastatin AUC ↑ 93% rosuvastatin C _{max} ↑ 277% rosuvastatin C _{min} ND Based on theoretical considerations DRV/COBI is expected to increase the plasma concentrations of fluvastatin, pitavastatin, pravastatin, lovastatin and simvastatin. (CYP3A inhibition and/or transport)	Concomitant use of a HMG CoA reductase inhibitor and Symtuza may increase plasma concentrations of the lipid lowering agent, which may lead to adverse reactions such as myopathy. When administration of HMG CoA reductase inhibitors and Symtuza is desired, it is recommended to start with the lowest dose and titrate up to the desired clinical effect while monitoring for safety.
Lovastatin Simvastatin		Concomitant use of Symtuza with lovastatin and simvastatin is contraindicated (see section 4.3).

OTHER LIPID MODIFYING AGENTS		
Lomitapide	Based on theoretical considerations, Symtuza is expected to increase the exposure of lomitapide when co-administered. (CYP3A inhibition)	Co-administration is contraindicated (see section 4.3).
H₂-RECEPTOR ANTAGONISTS		
Cimetidine Famotidine Nizatidine Ranitidine	Based on theoretical considerations, no mechanistic interaction is expected.	Symtuza can be co-administered with H ₂ -receptor antagonists without dose adjustments.
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus Everolimus	Based on theoretical considerations DRV/COBI is expected to increase these immunosuppressant plasma concentrations. (CYP3A inhibition) Co-administration of ciclosporin is expected to increase plasma concentrations of tenofovir alafenamide. (P-gp inhibition)	Concentration monitoring of the immunosuppressive agent must be done when co-administration with Symtuza occurs. Concomitant use of everolimus and Symtuza is not recommended.
INHALED BETA AGONISTS		
Salmeterol	Based on theoretical considerations DRV/COBI is expected to increase salmeterol plasma concentrations. (CYP3A inhibition)	Concomitant use of salmeterol and Symtuza is not recommended. The combination may result in increased risk of cardiovascular adverse events with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESICS/TREATMENT OF OPIOID DEPENDENCE		
Buprenorphine/naloxone	Based on theoretical considerations DRV/COBI may increase buprenorphine and/or norbuprenorphine plasma concentrations.	Dose adjustment for buprenorphine may not be necessary when co-administered with Symtuza, but a careful clinical monitoring for signs of opiate toxicity is recommended.
Methadone	Based on theoretical considerations DRV/COBI may increase methadone plasma concentrations. With ritonavir-boosted darunavir, a small decrease in methadone plasma concentrations was observed. Consult the Summary of Product Characteristics for darunavir for further details.	No adjustment of methadone dose is expected when initiating co-administration with Symtuza. Clinical monitoring is recommended, as maintenance therapy may need to be adjusted in some patients.
Fentanyl Oxycodone Tramadol	Based on theoretical considerations DRV/COBI may increase plasma concentrations of these analgesics. (CYP2D6 and/or CYP3A inhibition)	Clinical monitoring is recommended when co-administering Symtuza with these analgesics.

OESTROGEN-BASED CONTRACEPTIVES		
Drospirenone Ethinylestradiol (3 mg/0.02 mg once daily)	drospirenone AUC ↑ 58% drospirenone C _{max} ↑ 15% drospirenone C _{min} ND	Alternative or additional contraceptive measures are recommended when oestrogen based contraceptives are co-administered with Symtuza. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency. When Symtuza is co-administered with a drospirenone-containing product, clinical monitoring is recommended due to the potential for hyperkalaemia.
Ethinylestradiol	ethinylestradiol AUC ↓ 30% ethinylestradiol C _{max} ↓ 14% ethinylestradiol C _{min} ND	
Norethindrone	Based on theoretical considerations DRV/COBI may alter norethindrone plasma concentrations.	
OPIOID ANTAGONIST		
Naloxegol	Not studied.	Co-administration of Symtuza and naloxegol is contraindicated.
PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS		
For the treatment of erectile dysfunction Sildenafil Tadalafil Vardenafil	Based on theoretical considerations DRV/COBI is expected to increase these PDE-5 inhibitor plasma concentrations. (CYP3A inhibition)	Concomitant use of PDE-5 inhibitors for the treatment of erectile dysfunction with Symtuza should be done with caution. If concomitant use of Symtuza with sildenafil, vardenafil or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 72 hours or tadalafil at a single dose not exceeding 10 mg in 72 hours is recommended.
Avanafil		The combination of avanafil and Symtuza is contraindicated (see section 4.3).
For the treatment of pulmonary arterial hypertension Sildenafil Tadalafil	Based on theoretical considerations DRV/COBI is expected to increase these PDE-5 inhibitor plasma concentrations. (CYP3A inhibition)	A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension co-administered with Symtuza has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope). Therefore, co-administration of Symtuza and sildenafil when used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3). Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with Symtuza is not recommended.

Treatment with darunavir/cobicistat (two of the components of Symtuza) during pregnancy results in low darunavir exposure (see section 5.2), which may be associated with an increased risk of treatment failure and an increased risk of HIV transmission to the child. Therefore, therapy with Symtuza should not be initiated during pregnancy, and women who become pregnant during therapy with this FDC should be switched to an alternative regimen (see sections 4.2 and 4.4).

Breast-feeding

Emtricitabine is excreted in human milk. Based on published data, tenofovir alafenamide is excreted in human milk at low levels. The relative infant dose (RID) is estimated to be below 0.1% of the maternal weight-adjusted dose. It is unknown whether darunavir or cobicistat are excreted in human milk. Studies in animals have demonstrated that darunavir and cobicistat are excreted in milk. Studies in rats have demonstrated that darunavir is excreted in milk and at high levels (1 000 mg/kg/day) resulted in toxicity of the offspring.

Because of the potential for adverse reactions in breast-fed infants, women should be instructed not to breast-feed if they are receiving Symtuza.

In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed.

Fertility

No human data on the effect of darunavir, cobicistat, emtricitabine, or tenofovir alafenamide on fertility are available. There was no effect on mating or fertility in animals (see section 5.3). Based on animal studies, no effect on reproduction or fertility is expected with Symtuza.

4.7 Effects on ability to drive and use machines

Symtuza has minor influence on the ability to drive and use machines. Patients should be informed that dizziness may occur when treated with Symtuza (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of Symtuza is based on data from a randomised, double-blinded, comparative Phase 2 trial, GS-US-299-0102 (N = 103 on darunavir/cobicistat/emtricitabine/tenofovir alafenamide [D/C/F/TAF]), data from 2 Phase 3 trials TMC114FD2HTX3001 (AMBER, N = 362 on D/C/F/TAF) and TMC114IFD3013 (EMERALD, N = 763 on D/C/F/TAF), and on all available clinical trial and post-marketing data of its components. As Symtuza contains darunavir, cobicistat, emtricitabine, and tenofovir alafenamide, the adverse reactions associated with each of the individual compounds may be expected.

The most frequent (> 5%) adverse reactions reported in treatment-naïve patients in the Phase 2 (GS-US-299-0102) and Phase 3 Study (AMBER, TMC114FD2HTX3001, Week 96 analysis) were diarrhoea (22.6%), headache (13.1%), rash (12.7%), nausea (9.7%), fatigue (8.0%), and abdominal pain (5.8%).

The most frequent (> 5%) adverse reactions reported in suppressed treatment-experienced patients (EMERALD Study TMC114IFD3013, Week 96 analysis) were diarrhoea (10.5%), headache (10.4%), arthralgia (7.7%), abdominal pain (7.5%), fatigue (5.9%), and rash (5.1%).

Tabulated list of adverse reactions

Adverse reactions are listed by system organ class (SOC) and frequency category in Table 2.

Frequency categories are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$) and not known (frequency cannot be estimated from the available data).

Table 2	
MedDRA system organ class Frequency category	Adverse reaction
<i>Blood and lymphatic system disorders</i>	
common	anaemia
<i>Immune system disorders</i>	
common	(drug) hypersensitivity
uncommon	immune reconstitution inflammatory syndrome
<i>Metabolism and nutrition disorders</i>	
common	diabetes mellitus, anorexia, hypercholesterolaemia, low density lipoprotein increased, hypertriglyceridaemia, hyperlipidaemia, dyslipidaemia
uncommon	hyperglycaemia
<i>Psychiatric disorders</i>	
common	abnormal dreams
<i>Nervous system disorders</i>	
very common	headache
common	dizziness
<i>Gastrointestinal disorders</i>	
very common common	diarrhoea vomiting, nausea, abdominal pain, abdominal distension, dyspepsia, flatulence
uncommon	pancreatitis acute, pancreatic enzymes increased
<i>Hepatobiliary disorders</i>	
common	hepatic enzyme increased
uncommon	acute hepatitis ^a , cytolytic hepatitis ^a
<i>Skin and subcutaneous tissue disorders</i>	
very common common uncommon rare not known	rash (including macular, maculopapular, papular, erythematous, pruritic rash, generalised rash, and allergic dermatitis) pruritus, urticaria angioedema drug reaction with eosinophilia and systemic symptoms ^a , Stevens-Johnson syndrome ^a toxic epidermal necrolysis ^a , acute generalised exanthematous pustulosis ^a
<i>Musculoskeletal and connective tissue disorders</i>	
common	arthralgia, myalgia
uncommon	osteonecrosis
<i>Renal and urinary disorders</i>	
rare	crystal nephropathy ^{a§}
<i>Reproductive system and breast disorders</i>	
uncommon	gynaecomastia ^a
<i>General disorders and administration site conditions</i>	
common	asthenia, fatigue

<i>Investigations</i>	
common	increased blood creatinine

^a Additional adverse reactions only seen with darunavir/ritonavir in other trials or post-marketing experience

[§] Adverse reaction identified in the post-marketing setting. Per the guideline on Summary of Product Characteristics (Revision 2, September 2009), the frequency of this adverse reaction in the post-marketing setting was determined using the "Rule of 3".

Description of selected adverse reactions

Rash

Rash is a common adverse reaction in patients treated with darunavir. Rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing (see section 4.4). In the Phase 2/3 trials in treatment-naïve patients, 12.7% (59/465) of patients receiving Symtuza experienced rash (most of which were grade 1), 1.5% (7/465) of patients discontinued treatment due to rash, of whom one for rash and hypersensitivity. In the Phase 3 trial in suppressed treatment-experienced patients (EMERALD Study TMC114IFD3013), 5.1% (39/763) of patients receiving Symtuza experienced rash (most of which were grade 1), none discontinued treatment due to rash.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

In the Phase 3 trial of Symtuza in treatment-naïve patients, increases from baseline were observed in the fasting lipid parameters total cholesterol, direct low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol, and triglycerides at Week 48 and 96 (see Table 3). The median increases from baseline were greater in the D/C/F/TAF group compared with the DRV/cobicistat (COBI)+F/tenofovir disoproxil fumarate (TDF) group at Week 48.

Table 3				
Lipid parameter	Baseline median	Median increase from baseline at		
		Week 48 D/C/F/TAF	Week 48 D/C + F/TDF	Week 96* D/C/F/TAF
Total cholesterol (mmol/L)	4.22	0.74	0.27	0.88
LDL cholesterol (mmol/L)	2.49	0.45	0.13	0.56
HDL cholesterol (mmol/L)	1.08	0.12	0.04	0.13
Triglycerides (mmol/L)	1.09	0.28	0.16	0.33

p < 0.001 for all 4 lipid parameters when comparing D/C/F/TAF versus D/C + F/TDF at Week 48

* No comparator data available beyond Week 48

Musculoskeletal abnormalities

Increased creatine phosphokinase (CPK), myalgia, myositis and rarely, rhabdomyolysis have been reported with the use of HIV protease inhibitors, particularly in combination with NRTIs.

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Immune reconstitution inflammatory syndrome

In HIV infected patients with severe immune deficiency at the time of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to

onset is more variable, and these events can occur many months after initiation of treatment (see section 4.4).

Bleeding in haemophiliac patients

There have been reports of increased spontaneous bleeding in haemophiliac patients receiving antiretroviral protease inhibitors (see section 4.4).

Decrease estimated creatinine clearance

Cobicistat increases serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function as assessed, for instance, by using Cystatin C (Cyst C) as filtration marker.

In the Phase 3 trial of Symtuza in treatment-naïve patients, increases in serum creatinine and decreases in eGFR_{CG} occurred at the first on-treatment assessment (Week 2) and remained stable through 96 weeks. At Week 48 changes from baseline were smaller with D/C/F/TAF than D/C+F/TDF. The median change in eGFR_{CG} was -5.5 mL/min with D/C/F/TAF and -12.0 mL/min with D/C+F/TDF ($p < 0.001$). Using Cyst C as filtration marker, the median changes in estimated glomerular filtration rate calculated using the CKD-EPI (eGFR_{CKD-EPI CystC}) formula were respectively 4.0 mL/min/1.73 m² and 1.6 mL/min/1.73 m² ($p < 0.001$). At Week 96, the median change in eGFR_{CG} was -5.2 mL/min with D/C/F/TAF. Using Cyst C as filtration marker, the median change in estimated glomerular filtration rate calculated using the CKD-EPI (eGFR_{CKD-EPI CystC}) formula (N = 22) was +4.4 mL/min/1.73 m² with D/C/F/TAF.

Paediatric population

The safety of Symtuza (as an FDC formulation) has not been investigated in paediatric patients. However, the safety of its components was evaluated in adolescents aged 12 to less than 18 years and weighing at least 40 kg through the clinical study TMC114-C230 (N = 12) for darunavir with ritonavir and clinical study GS-US-292-0106 (N = 50) for an FDC containing elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide.

The safety of the components of Symtuza was also evaluated in a limited number of children aged 6 to < 12 years, weighing at least 25 kg to < 40 kg through the clinical study GS-US-216-0128 (N = 9, with 24 weeks follow-up) for cobicistat-boosted darunavir (DRV/COBI) with emtricitabine/tenofovir alafenamide (F/TAF). The data from these studies showed that the overall safety profile of the components of Symtuza in paediatric patients aged 6 to < 18 years weighing at least 25 kg was consistent with that observed in the adult population (see section 5.1).

Reductions in BMD of the spine and of the TBLH $\geq 4\%$ have been reported in paediatric patients receiving other tenofovir alafenamide containing products for 48 weeks (see section 4.4).

Other special populations

Patients co-infected with hepatitis B and/or hepatitis C virus

Limited information is available on the use of Symtuza components in patients co-infected with hepatitis B and/or C virus.

Among 1 968 treatment-experienced patients receiving darunavir co-administered with ritonavir 600/100 mg twice daily, 236 patients were co-infected with hepatitis B or C. Co-infected patients were more likely to have baseline and treatment emergent hepatic transaminase elevations than those without chronic viral hepatitis. The safety of emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet was evaluated in approximately 70 HIV/HBV co-infected patients currently receiving treatment for HIV in an open-label clinical trial (GS-US-292-1249). Based on this limited experience, the safety profile of emtricitabine/tenofovir alafenamide in patients with HIV/HBV co-infection appears to be similar to that in patients with HIV-1 mono-infection (see section 4.4).

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:

Ireland

HPRA Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

Human experience of acute overdose with Symtuza is limited.

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

There is no specific antidote for overdose with Symtuza. Treatment of overdose consists of general supportive measures, including monitoring of vital signs as well as observation of the clinical status of the patient.

Since darunavir and cobicistat are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis. Emtricitabine can be removed by haemodialysis, which removes approximately 30% of the emtricitabine dose over a 3 hour dialysis period starting within 1.5 hours of emtricitabine dosing. Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, antivirals for treatment of HIV infection, combinations, ATC code: J05AR22

Mechanism of action

Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (K_D of $4.5 \times 10^{-12}M$). It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles.

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

Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and nucleoside analogue of 2'-deoxycytidine. Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine triphosphate. Emtricitabine triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase (RT), which results in DNA chain-termination.

Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, tenofovir alafenamide is more efficient than tenofovir disoproxil in concentrating tenofovir in peripheral blood mononuclear cells (PBMC) (including lymphocytes and other HIV target cells) and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV

replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination.

Antiviral activity in vitro

Darunavir, emtricitabine and tenofovir alafenamide demonstrated additive to synergistic antiviral effects in two-drug combination studies in cell culture.

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human PBMCs and human monocytes/macrophages with median EC₅₀ values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC₅₀ values ranging from < 0.1 to 4.3 nM. These EC₅₀ values are well below the 50% cellular toxicity concentration range of 87 µM to > 100 µM.

Cobicistat has no detectable antiviral activity against HIV-1 and does not antagonise the antiviral effect of darunavir, emtricitabine, or tenofovir.

The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI CCR5 cell line, and PBMCs. The EC₅₀ values for emtricitabine were in the range of 0.0013 to 0.64 µM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC₅₀ values ranged from 0.007 to 0.075 µM) and showed strain specific activity against HIV-2 (EC₅₀ values ranged from 0.007 to 1.5 µM).

The antiviral activity of tenofovir alafenamide against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4⁺-T lymphocytes. The EC₅₀ values for tenofovir alafenamide were in the range of 2.0 to 14.7 nM. Tenofovir alafenamide displayed antiviral activity in cell culture against all HIV-1 groups (M, N, and O), including subtypes A, B, C, D, E, F, and G (EC₅₀ values ranged from 0.10 to 12.0 nM) and showed strain specific activity against HIV-2 (EC₅₀ values ranged from 0.91 to 2.63 nM).

Resistance

In vitro selection of darunavir-resistant virus from wild type HIV-1 was lengthy (> 3 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 400 nM. Viruses selected in these conditions and showing decreased susceptibility to darunavir (range: 23-50-fold) harboured 2 to 4 amino acid substitutions in the protease gene. The decreased susceptibility to darunavir of the emerging viruses in the selection experiment could not be explained by the emergence of these protease mutations.

In vivo, darunavir resistance-associated mutations (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V and L89V) in HIV-1 protease were derived from clinical trial data of ART-experienced patients, all of whom were protease inhibitor experienced.

Reduced susceptibility to emtricitabine is associated with M184V/I mutations in HIV-1 RT.

HIV-1 isolates with reduced susceptibility to tenofovir alafenamide express a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed. HIV-1 isolates with the K65R mutation have low-level reduced susceptibility to abacavir, emtricitabine, tenofovir, and lamivudine.

Emerging resistance in HIV-1 infected, treatment-naïve and virologically suppressed patients

Over 96 weeks of treatment in the Phase 3 studies TMC114FD2HTX3001 (AMBER) in treatment-naïve patients and TMC114IFD3013 (EMERALD) in virologically suppressed treatment-experienced patients, resistance testing was performed on samples from patients experiencing protocol-defined virologic failure (PDVF) and who had HIV-1 RNA ≥400 copies/mL at failure or at later time points. Emerging resistance in the Symtuza groups is shown in Table 4. No DRV, primary PI, or TDF/TAF resistance-associated mutations were observed.

Table 4: Emerging resistance in AMBER and EMERALD trial (Week 96)

Study	Treatment group	Subjects, n	Subjects with PDVF, n (%)	Subjects with PDVF evaluated for resistance, n (%)	Subjects with ≥1 emergent RAM, n (%)		
					Protease Primary PI/DRV	Reverse transcriptase TDF/ TAF	FTC
TMC114FD2HTX3001	Symtuza	362	15 (4.1)	9 (2.5)	0	0	1 (M184I/V) ^a
TMC114IFD3013	Symtuza	763	24 (3.1)	4 (0.5)	0	0	0
Total Phase 3	Symtuza	1 125	39 (3.5)	13 (1.2)	0	0	1 (0.1)

^a At Week 36 M184M/I/V observed, conferring resistance to FTC. This subject harbored a K103N mutation at screening, indicating transmitted NNRTI resistance.

DRV = darunavir; FTC = emtricitabine; PDVF = protocol-defined virologic failure; PI = protease inhibitor; RAM = resistance-associated mutation; TDF = tenofovir disoproxil fumarate; TAF = tenofovir alafenamide

Cross-resistance in HIV-1 infected, treatment-naïve and virologically suppressed patients

The emtricitabine-resistant virus with the M184M/I/V mutation was cross-resistant to lamivudine, but retained sensitivity to abacavir, stavudine, tenofovir, and zidovudine.

Clinical data

HIV-1 Treatment-naïve patients

In double-blind Phase 3 Trial TMC114FD2HTX3001 (AMBER), treatment-naïve patients were randomised to receive either Symtuza (N = 362) or a combination of fixed-dose combination of darunavir and cobicistat and fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate (F/TDF) (N = 363) once daily. Virologic response was defined as < 50 copies/mL using the snapshot approach (see Table 5).

The 725 patients in total had a median age of 34 years (range 18-71), 88.3% were male, 83.2% White, 11.1% Black, 1.5% Asian. The mean baseline plasma HIV-1 RNA and the median baseline CD4+ cell count were 4.48 log₁₀ copies/mL (SD = 0.61) and 453 x 10⁶ cells/L (range 38 – 1 456 x 10⁶ cells/L), respectively.

Table 5: Virologic outcomes in AMBER at Week 48 and 96 (FDA Snapshot)

	Week 48		Week 96*
	Symtuza N = 362	DRV/COBI +F/TDF N = 363	Symtuza N = 362
Virologic response, %			
HIV-1 RNA < 50 copies/mL	91.4%	88.4%	85.1%
Treatment difference ^a	2.7 (95% CI: -1.6; 7.1)		-
Virologic failure^b	4.4%	3.3%	5.5%
HIV-1 RNA ≥ 50 copies/mL	2.5%	2.5%	1.7%
Virologic failure leading to discontinuation	0.3%	0	1.4% ^d
Discontinued study drug due to other reasons and last available HIV-1 RNA ≥ 50 copies/mL	1.7%	0.8%	2.5%
No virologic data^c	4.1%	8.3%	9.4%
Reasons			
Discontinued trial due to adverse event or death	2.2%	4.4%	2.2%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL	1.1%	2.5%	5.8%
Missing data during window but on trial	0.8%	1.4%	1.4%

Virologic response (HIV-1-RNA < 50 copies/mL; Snapshot analysis) by subgroup, n/N (%)			
Age			
< 50 years	299/326 (91.7%)	293/331 (88.5%)	276/326 (84.7%)
≥ 50 years	32/36 (88.9%)	28/32 (87.5%)	32/36 (88.9%)
Sex			
Male	292/318 (91.8%)	289/322 (89.8%)	270/318 (84.9%)
Female	39/44 (88.6%)	32/41 (78.0%)	38/44 (86.4%)
Race			
Black	34/40 (85.0%)	34/40 (85.0%)	28/40 (70.0%)
Non-black	281/305 (92.1%)	275/309 (89.0%)	266/305 (87.2%)
Baseline viral load			
≤ 100 000 copies/mL	278/303 (91.7%)	265/293 (90.4%)	260/303 (85.8%)
> 100 000 copies/mL	53/59 (89.8%)	56/70 (80.0%)	48/59 (81.4%)
Baseline CD4+ cell count			
< 200 cells/mm ³	16/22 (72.7%)	25/29 (86.2%)	16/22 (72.7%)
≥ 200 cells/mm ³	315/340 (92.6%)	296/334 (88.6%)	292/340 (85.9%)
CD4+ cell count mean change from baseline	188.7	173.8	228.8

^a Based on stratum adjusted MH test where stratification factors are HIV-1 RNA level (≤ 100 000 or > 100 000 copies/mL) and CD4+ cell count (< 200 or ≥ 200 cells/μL).

^b Included subjects who had HIV-1 RNA ≥ 50 copies/mL in the Week 48/96 window; subjects who discontinued early due to lack or loss of efficacy per investigator's assessment; subjects who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a HIV-1 RNA ≥ 50 copies/mL.

^c Week 48 window: Day 295 – Day 378; Week 96 window: Day 631 – Day 714.

^d Five subjects were discontinued from the study due to efficacy related reasons per investigator's assessment (physician decision), of which 3 had last on treatment HIV-1 RNA < 50 copies/mL.

* No comparator data available beyond Week 48.

Changes in measures of bone mineral density

In the Phase 3 study TMC114FD2HTX3001 in treatment-naïve patients, Symtuza was associated with no or smaller reductions in bone mineral density (BMD) compared DRV/COBI+F/TDF as measured by DXA analysis of hip (LS means percent change: 0.17% vs -2.69%, $p < 0.001$) and lumbar spine (LS means percent change: -0.68% vs -2.38%, $p = 0.004$) after 48 weeks of treatment. After 96 weeks of treatment with Symtuza, the (95% CI) percent changes from baseline in BMD at the hip and spine region were respectively: -0.26 (-0.96; 0.45) % and -0.93 (-1.82; -0.05) %.

Changes in measures of renal function

In studies in treatment-naïve patients, Symtuza was associated with a lower impact on the estimated glomerular filtration rate by Cockcroft-Gault method compared to control group (DRV/COBI+F/TDF).

HIV-1 Treatment-experienced patients

Phase 3 trial TMC114IFD3013 (EMERALD) evaluated the efficacy of Symtuza in virologically-suppressed (HIV-1 RNA less than 50 copies/mL) HIV-1 infected patients. Patients were virologically suppressed for at least 2 months and no more than once had a viral load elevation above 50 HIV-1 RNA copies/mL during the year prior to enrolment. Patients were allowed in the study if they had previous failure on any non-darunavir ARV regimen. Patients had no history of virologic failure on darunavir-based regimens, and if historical genotypes were available, absence of darunavir RAMs. Patients were on a stable ARV regimen (for at least 6 months), consisting of a boosted protease inhibitor [either darunavir once daily or atazanavir (both boosted with ritonavir or cobicistat), or lopinavir with ritonavir] combined with emtricitabine and TDF. They either switched to Symtuza (N = 763) or continued their treatment regimen (N = 378) (randomised 2:1).

Patients had a median age of 46 years (range 19-78), 82% were male, 75.5% White, 20.9% Black, and 2.3% Asian. The median baseline CD4+ cell count was 628 x 10⁶ cells/mm³ (range 111-1 921 x 10⁶ cells/mm³). Week 48 and 96 virologic outcomes in the EMERALD trial are provided in Table 6.

Table 6: Week 48 and 96 virologic outcomes in EMERALD trial			
	Week 48		Week 96*
	Symtuza N = 763	bPI+F/TDF N = 378	Symtuza N = 763
Cumulative protocol-defined virologic rebound ^a , %			
Protocol defined rebound rate	2.5%	2.1%	3.1%
(95% CI) ^b	(1.5; 3.9)	(0.9; 4.1)	(2.0; 4.6)
Difference in proportions	0.4 (95% CI: -1.5; 2.2)		-
FDA snapshot outcome			
HIV-1 RNA < 50 copies/mL	94.9%	93.7%	90.7%
Virologic failure ^c	0.8%	0.5%	1.2%
Treatment difference ^d	0.3 (95% CI: -0.7; 1.2)		-
HIV-1 RNA ≥ 50 copies/mL	0.5%	0.5%	0.7% ^f
Virologic failure - leading to discontinuation	0	0	0
Virologic failure - discontinued due to other reason and last available HIV-1 RNA ≥ 50 copies/mL	0.3%	0	0.5%
No virologic data ^e	4.3%	5.8%	8.1%
Reasons			
Discontinued trial due to adverse event or death	1.4%	1.1%	2.4%
Discontinued trial for other reasons	2.5%	4.2%	5.0%
Missing data during window but on trial	0.4%	0.5%	0.8%
Cumulative protocol-defined virologic rebound by subgroup, %			
Age			
< 50 years	13/507 (2.6%)	7/252 (2.8%)	18/507 (3.6%)
≥ 50 years	6/256 (2.3%)	1/126 (0.8%)	6/256 (2.3%)
Sex			
Male	14/623 (2.2%)	7/313 (2.2%)	20/623 (3.2%)
Female	5/140 (3.6%)	1/65 (1.5%)	4/140 (2.9%)
Race			
Black	6/155 (3.9%)	1/82 (1.2%)	7/155 (4.5%)
Non-black	13/597 (2.2%)	7/293 (2.4%)	17/597 (2.8%)
Previous ARV failure			
0	16/647 (2.5%)	8/325 (2.5%)	19/647 (2.9%)
> 1	3/116 (2.6%)	0/53 (0%)	5/116 (4.3%)

^a 2 consecutive HIV-1 RNA ≥ 50 copies/mL, or in case of discontinuation or at Week 48/96 for any reason, (single) HIV-1 RNA ≥ 50 copies/mL as of baseline (included).

^b Two-sided Exact Clopper-Pearson 95% CI.

^c Included subjects who had ≥ 50 copies/mL in the Week 48/96 window; subjects who discontinued early due to lack or loss of efficacy per investigator's assessment; subjects who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value ≥ 50 copies/mL.

^d Based on MH test adjusting for bPI at screening (ATV with rtv or COBI, DRV with rtv or COBI, LPV with rtv).

^e Week 48 window: Day 295 – Day 378; Week 96 window: Day 631 – Day 714.

^f The following viral load values were observed for these subjects at Week 96: 54 copies/mL, 78 copies/mL, 111 copies/mL, 152 copies/mL, and 210 copies/mL.

* No comparator data available beyond Week 48.

Paediatric population

Patients aged 12 years to < 18 years weighing at least 40 kg

The use of Symtuza in ART-naïve adolescent patients from the age of 12 years to < 18 years and weighing at least 40 kg is supported by two trials in HIV-1 infected paediatric patients (TMC114-C230 and GS-US-292-0106). For more details, refer to the prescribing information of darunavir and emtricitabine/tenofovir alafenamide.

An open-label, Phase 2 trial (TMC114-C230) was conducted for evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir with low dose ritonavir in 12 ART-naïve HIV-1 infected paediatric patients aged 12 to less than 18 years and weighing at least 40 kg. These patients received darunavir/ritonavir 800/100 mg once daily in combination with other antiretroviral agents. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 log₁₀ versus baseline (see Table 7).

Table 7: Virologic outcome in ART-naïve adolescents at Week 48 (TLOVR algorithm)	
TMC114-C230	
Outcomes at Week 48	Darunavir/ritonavir (N = 12)
HIV-1 RNA < 50 copies/mL ^a	83.3% (10)
CD4+ percent median change from baseline	14
CD4+ cell count mean change from baseline ^b	221
≥ 1.0 log ₁₀ decrease from baseline in plasma viral load	100%

^a Imputations according to the TLOVR algorithm.

^b Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0.

In the study GS-US-292-0106, the efficacy, safety, and pharmacokinetics of emtricitabine and tenofovir alafenamide were evaluated in an open-label study in which 50 HIV-1 infected, treatment-naïve adolescents received emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir and cobicistat as a fixed-dose combination tablet. Patients had a median age of 15 years (range: 12-17), and 56% were female, 12% were Asian, and 88% were Black. At baseline, median plasma HIV-1 RNA was 4.7 log₁₀ copies/mL, median CD4+ cell count was 456 cells/mm³ (range: 95-1110), and median CD4+ % was 23% (range: 7-45%). Overall, 22% had baseline plasma HIV-1 RNA > 100 000 copies/mL. At 48 weeks, 92% (46/50) achieved HIV-1 RNA < 50 copies/mL, similar to response rates in studies of treatment-naïve HIV-1 infected adults. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells/mm³. No emergent resistance to E/C/F/TAF (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) was detected through Week 48.

Patients aged 6 years to < 12 years weighing at least 25 kg to < 40 kg

The use of Symtuza in children aged 6 years to < 12 years, weighing at least 25 kg to < 40 kg is supported by open-label study GS-US-216-0128 in which the pharmacokinetics, safety, and antiviral activity of darunavir and cobicistat (administered as separate agents) in combination with emtricitabine/tenofovir alafenamide were evaluated in 9 HIV-1 infected treatment-experienced, virologically suppressed paediatric patients (Cohort 2 DRV/COBI+F/TAF FDC Subgroup). All patients had HIV-1 RNA < 50 copies/mL at baseline and median baseline CD4+ cell count was 929 cells/mm³ (range: 584 - 1232 cells/mm³). Virological outcome for children in Cohort 2 is shown in Table 8.

Table 8: Virologic outcome in ART-experienced, virologically suppressed children (Cohort 2 DRV/COBI+F/TAF FDC^a Subgroup) at Week 24 (FDA Snapshot)	
GS-US-216-0128	
Outcomes at Week 24	Cohort 2 DRV/COBI+F/TAF FDC Subgroup (N = 9)
HIV-1 RNA < 50 copies/mL	100% (9)
CD4+ percent median change from baseline	0.60%
CD4+ cell count median change from baseline	72 cells/mm ³

^a DRV (dose 600 mg tablet or 600 mg+75 mg tablets, based on body weight), COBI (150 mg), F/TAF FDC (200/25 mg)

5.2 Pharmacokinetic properties

Following single-dose administration under fed conditions in healthy participants (N = 96), bioequivalence was established for all components of Symtuza 800 mg/150 mg/200 mg/10 mg as compared to darunavir 800 mg, cobicistat 150 mg, and emtricitabine/tenofovir alafenamide 200/10 mg co-administered as separate formulations. Bioequivalence was also observed between Symtuza

675 mg/150 mg/200 mg/10 mg FDC and darunavir 675 mg, cobicistat 150 mg and emtricitabine/tenofovir alafenamide 200 mg/10 mg co-administered as separate formulations under fed conditions in healthy participants (N = 32).

Absorption

The absolute bioavailability of a single 600 mg dose of darunavir alone was approximately 37% and increased to approximately 82% in the presence of 100 mg twice daily ritonavir. The absolute bioavailability of the emtricitabine 200 mg capsule was 93%.

All components were rapidly absorbed following oral administration of Symtuza in healthy participants. Maximum plasma concentrations of darunavir, cobicistat, emtricitabine and tenofovir alafenamide were achieved at 4.00, 4.00, 2.00, and 1.50 hours after dosing, respectively. The bioavailability of the components of Symtuza was not affected when administered orally as a split tablet compared to administration as a tablet swallowed whole.

The exposure to darunavir and cobicistat administered as the Symtuza was 30-45% lower and 16-29% lower, respectively, in fasted compared to fed condition. For emtricitabine, the C_{max} was 1.26-fold higher in a fasted condition, while the area under the curve (AUC) was comparable in fed and fasted condition. For tenofovir alafenamide, the C_{max} was 1.82-fold higher in fasted condition, while the AUC was 20% lower to comparable in a fasted compared to fed condition. Symtuza tablets should be taken with food. The type of food does not affect exposure to Symtuza.

Distribution

Darunavir

Darunavir is approximately 95% bound to plasma protein. Darunavir binds primarily to plasma α_1 -acid glycoprotein.

Following intravenous administration, the volume of distribution of darunavir alone was 88.1 ± 59.0 L (mean $\pm$ SD) and increased to 131 ± 49.9 L (mean $\pm$ SD) in the presence of 100 mg twice-daily ritonavir.

Cobicistat

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

Emtricitabine

In vitro binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02-200 mcg/mL. At peak plasma concentration, the mean plasma to blood concentration ratio was approximately 1.0 and the mean semen to plasma concentration ratio was approximately 4.0.

Tenofovir alafenamide

In vitro binding of tenofovir to human plasma proteins is < 0.7% and is independent of concentration over the range of 0.01-25 mcg/mL. *Ex vivo* binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical trials was approximately 80%.

Biotransformation

Darunavir

In vitro experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolised by the hepatic CYP system and almost exclusively by isozyme CYP3A4. A [14 C]-darunavir trial in healthy participants showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir with ritonavir dose was due to the parent active substance. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 10-fold less than the activity of darunavir against wild type HIV.

Cobicistat

Cobicistat is metabolised via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. Following oral administration of [¹⁴C]-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.

Emtricitabine

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP enzymes. Following administration of [¹⁴C]-emtricitabine, complete recovery of the emtricitabine dose was achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the dose was recovered in the urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). No other metabolites were identifiable.

Tenofovir alafenamide

Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. *In vitro* studies have shown that tenofovir alafenamide is metabolised to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. *In vivo*, tenofovir alafenamide is hydrolysed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite tenofovir diphosphate.

In vitro, tenofovir alafenamide is not metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolised by CYP3A4. Upon co-administration with the moderate CYP3A inducer probe efavirenz, tenofovir alafenamide exposure was not significantly affected. Following administration of tenofovir alafenamide, plasma [¹⁴C]-radioactivity showed a time-dependent profile with tenofovir alafenamide as the most abundant species in the initial few hours and uric acid in the remaining period.

Elimination

Darunavir

After a 400/100 mg [¹⁴C]-darunavir with ritonavir dose, approximately 79.5% and 13.9% of the administered dose of [¹⁴C]-darunavir could be retrieved in faeces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in faeces and urine, respectively.

The intravenous clearance of darunavir alone (150 mg) and in the presence of low dose (100 mg) ritonavir was 32.8 l/h and 5.9 l/h, respectively. The median terminal plasma half-life of darunavir following administration of Symtuza is 5.5 hours.

Cobicistat

Following oral administration of [¹⁴C]-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 Symtuza is 3.6 hours.

Emtricitabine

Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 mL/min. Following oral administration of Symtuza, the median terminal elimination half-life of emtricitabine is 17.2 hours.

Tenofovir alafenamide

Tenofovir alafenamide is mainly eliminated following metabolism to tenofovir. The median terminal elimination half-life of tenofovir alafenamide was 0.3 hours when administered as Symtuza.

Tenofovir is eliminated from the body by the kidneys by both glomerular filtration and active tubular

secretion. Tenofovir has a median plasma half-life of approximately 32 hours. Renal excretion of intact tenofovir alafenamide is a minor pathway with less than 1% of the dose eliminated in urine. The pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

Special populations

Paediatric population

Available pharmacokinetic data for the different components of Symtuza indicate that exposures between adults and paediatric patients aged 6 years and older, weighing at least 25 kg, were comparable.

Elderly

Limited PK information is available in the elderly (age ≥ 65 years of age) for Symtuza as well as its individual components.

Population pharmacokinetic analysis in HIV infected patients showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV infected patients (N = 12, age ≥ 65 years) (see section 4.4).

No clinically relevant pharmacokinetic differences due to age have been identified for cobicistat, emtricitabine or tenofovir alafenamide in the age range ≤ 65 years.

Gender

Population pharmacokinetic analysis showed a slightly higher darunavir exposure (16.8%) in HIV-1 infected females compared to males. This difference is not clinically relevant.

No clinically relevant pharmacokinetic differences due to gender have been identified for cobicistat, emtricitabine or tenofovir alafenamide.

Renal impairment

Symtuza has not been investigated in patients with renal impairment. There are pharmacokinetic data for the (individual) components of Symtuza.

Darunavir

Results from a mass balance study with [^{14}C]-darunavir with ritonavir showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine unchanged.

Although darunavir has not been studied in patients with renal impairment, population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV infected patients with moderate renal impairment (eGFR_{CG} between 30-60 mL/min, N = 20) (see sections 4.2 and 4.4).

Cobicistat

A trial of the pharmacokinetics of cobicistat was performed in non-HIV-1 infected subjects with severe renal impairment (eGFR_{CG} 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.

Emtricitabine

Mean systemic emtricitabine exposure was higher in patients with severe renal impairment (eGFR_{CG} < 30 mL/min) (33.7 mcg•h/mL) than in subjects with normal renal function (11.8 mcg•h/mL).

Tenofovir alafenamide

No clinically relevant differences in tenofovir alafenamide, or tenofovir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (eGFR_{CG} > 15 but

< 30 mL/min) in studies of tenofovir alafenamide. There are no pharmacokinetic data on tenofovir alafenamide in patients with $eGFR_{CG} < 15$ mL/min.

Hepatic impairment

Symtuza has not been investigated in patients with hepatic impairment. There are pharmacokinetic data for the (individual) components of Symtuza.

Darunavir

Darunavir is primarily metabolised and eliminated by the liver. In a multiple dose trial with darunavir/ritonavir (600/100 mg) twice daily, it was demonstrated that the total plasma concentrations of darunavir in subjects with mild (Child-Pugh Class A, N = 8) and moderate (Child-Pugh Class B, N = 8) hepatic impairment were comparable with those in healthy subjects. However, unbound darunavir concentrations were approximately 55% (Child-Pugh Class A) and 100% (Child-Pugh Class B) higher, respectively. The clinical relevance of this increase is unknown. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see sections 4.2, 4.3 and 4.4).

Cobicistat

Cobicistat is primarily metabolised and eliminated by the liver. A trial 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. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of cobicistat has not been studied.

Emtricitabine

The pharmacokinetics of emtricitabine have not been studied in patients with hepatic impairment; however, emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited.

Tenofovir alafenamide

Clinically relevant changes in tenofovir pharmacokinetics in patients with hepatic impairment were not observed in patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of tenofovir alafenamide has not been studied.

Hepatitis B and/or hepatitis C virus co-infection

There were insufficient pharmacokinetic data in the clinical trials to determine the effect of hepatitis B and/or C virus infection on the pharmacokinetics of darunavir, cobicistat, emtricitabine, or tenofovir alafenamide (refer to sections 4.4 and 4.8).

Pregnancy and postpartum

Treatment with darunavir/cobicistat 800/150 mg once daily during pregnancy results in low darunavir exposure (see Table 9). In women receiving darunavir/cobicistat during the second trimester of pregnancy, mean intra-individual values for total darunavir C_{max} , AUC_{24h} and C_{min} were 49%, 56% and 92% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir C_{max} , AUC_{24h} and C_{min} values were 37%, 50% and 89% lower, respectively, as compared with postpartum. The unbound fraction was also substantially reduced, including around 90% reductions of C_{min} levels. The main cause of these low exposures is a marked reduction in cobicistat exposure as a consequence of pregnancy-associated enzyme induction (see below).

Table 9			
Pharmacokinetic results of total darunavir after administration of darunavir/cobicistat 800/150 mg once daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy, and postpartum			
Pharmacokinetics of total darunavir (mean ± SD)	Second trimester of pregnancy N = 7	Third trimester of pregnancy N = 6	Postpartum (6-12 weeks) N = 6
C_{max} , ng/mL	4 340 ± 1 616	4 910 ± 970	7 918 ± 2 199
AUC_{24h} , ng.h/mL	47 293 ± 19 058	47 991 ± 9 879	99 613 ± 34 862
C_{min} , ng/mL	168 ± 149	184 ± 99	1 538 ± 1 344

The exposure to cobicistat was lower during pregnancy, potentially leading to suboptimal boosting of darunavir. During the second trimester of pregnancy, cobicistat C_{max} , AUC_{24h} , and C_{min} were 50%, 63%, and 83% lower, respectively, as compared with postpartum. During the third trimester of pregnancy, cobicistat C_{max} , AUC_{24h} , and C_{min} , were 27%, 49%, and 83% lower, respectively, as compared with postpartum.

No pharmacokinetic data are available for emtricitabine and tenofovir alafenamide during pregnancy.

5.3 Preclinical safety data

Darunavir

Non-clinical data on darunavir reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. Darunavir has no effect on fertility or early embryonic development and DRV shows no teratogenic potential, at exposure levels below those at the recommended clinical dose in humans.

In juvenile rats receiving darunavir up to days 23-26 (equivalent to less than 2 years of age in humans), increased mortality was observed with convulsions in some animals. These findings were attributed to the immaturity of the liver enzymes and of the blood brain barrier. Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes Symtuza should not be used in paediatric patients below 3 years of age.

Cobicistat

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 sternebrae 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.

Emtricitabine

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Emtricitabine had demonstrated low carcinogenic potential in mice and rats.

Tenofovir alafenamide

Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced bone mineral density in rats and dogs at tenofovir exposures at least four times greater than those expected after administration of Symtuza. A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 15 and 40 times greater, respectively, than those expected after administration of Symtuza.

Tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxicity assays.

Because there is a lower tenofovir exposure in rats and mice after the administration of tenofovir alafenamide compared to tenofovir disoproxil, carcinogenicity studies and a rat peri-postnatal study were conducted only with tenofovir disoproxil. No special hazard for humans was revealed in conventional studies of carcinogenic potential and toxicity to reproduction and development. Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Symtuza 800 mg/150 mg/200 mg/10 mg tablets

Tablet core

Cellulose, microcrystalline (E460(i))
Croscarmellose sodium (E468)
Magnesium stearate (E572)
Silica, colloidal anhydrous (E551)

Tablet coating

Macrogol 4 000
Polyvinyl alcohol (partially hydrolysed)
Talc (E553b)
Titanium dioxide (E171)
Iron oxide yellow (E172)

Symtuza 675 mg/150 mg/200 mg/10 mg tablets

Tablet core

Cellulose, microcrystalline (E460(i))
Croscarmellose sodium (E468)
Magnesium stearate (E572)
Silica, colloidal anhydrous (E551)

Tablet coating

Macrogol 3 350 (polyethylene glycol)
Polyvinyl alcohol (partially hydrolysed)
Talc (E553b)
Titanium dioxide (E171)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Symtuza 800 mg/150 mg/200 mg/10 mg film-coated tablets

3 years

After first opening: 6 weeks

Symtuza 675 mg/150 mg/200 mg/10 mg film-coated tablets

3 years

After first opening: 6 weeks

6.4 Special precautions for storage

Symtuza 800 mg/150 mg/200 mg/10 mg film-coated tablets

Store below 30 °C.

Store in the original package with desiccant inside the bottle in order to protect the tablets from moisture. Keep the bottle tightly closed.

Symtuza 675 mg/150 mg/200 mg/10 mg film-coated tablets

Store below 25 °C.

After first opening of the bottle: Store below 25 °C.

Store in the original package with desiccant inside the bottle in order to protect the tablets from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

Symtuza 800 mg/150 mg/200 mg/10 mg film-coated tablets

White, high density polyethylene (HDPE) bottle with a silica gel desiccant (contained in a separate sachet or canister) fitted with polypropylene (PP) child resistant closure with induction seal.

Each bottle contains 30 tablets.

Pack size of one bottle or three bottles per carton.

Not all pack sizes may be marketed.

Symtuza 675 mg/150 mg/200 mg/10 mg film-coated tablets

White, high density polyethylene (HDPE) bottle with a silica gel desiccant (contained in a separate sachet or canister) fitted with polypropylene (PP) child resistant closure with induction seal.

Each bottle contains 30 tablets.

Pack size of one bottle.

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

Janssen-Cilag International NV

Turnhoutseweg 30

B-2340 Beerse

Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Symtuza 800 mg/150 mg/200 mg/10 mg film-coated tablets

EU/1/17/1225/001 - 30 film-coated tablets

EU/1/17/1225/002 - 90 film-coated tablets (3 x 30)

Symtuza 675 mg/150 mg/200 mg/10 mg film-coated tablets

EU/1/17/1225/003 - 30 film-coated tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 September 2017

Date of latest renewal: 24 May 2022

10. DATE OF REVISION OF THE TEXT

04 September 2026

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