ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 800 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.

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.

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 adolescents (aged 12 years and older with body weight at least 40 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
The recommended dose regimen in adults and adolescents aged 12 years and older, weighing at least 40 kg, is one tablet taken once daily with food.

ART-naïve patients
The recommended dose regimen is one film-coated tablet of Symtuza once daily taken with food.

ART-experienced patients
One film-coated tablet of Symtuza 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 x 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 of Symtuza 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 the medicine, another dose of Symtuza should be taken with food as soon as possible. If a patient vomits more than 1 hour after taking the medicine, the patient does not need to take another dose of Symtuza until the next regularly scheduled time.

Special populations

Elderly
Limited information is available in this population, and, therefore, Symtuza should be used with caution in patients above 65 years of age (see sections 4.4 and 5.2).

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

Symtuza has not been studied in patients with severe hepatic impairment (Child-Pugh Class C), therefore, Symtuza must not be used in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Renal impairment
No dose adjustment of Symtuza is required in patients with estimated glomerular filtration rate according to the Cockcroft-Gault formula ($eGFR_{CG}$) ≥ 30 mL/min.

Symtuza should not be initiated in patients with $eGFR_{CG}$ < 30 mL/min, as there are no data available regarding the use of Symtuza in this population (see sections 5.1 and 5.2).
Symtuza should be discontinued in patients with $eGFR_{CG}$ that declines below 30 mL/min during treatment (see sections 5.1 and 5.2).

Paediatric population
The safety and efficacy of Symtuza in children aged 3-11 years, or weighing < 40 kg, have not yet been established. No data are available.

Symtuza should not be used in paediatric patients below 3 years of age because of safety concerns (see sections 4.4 and 5.3).

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 Symtuza should be switched to an alternative regimen (see sections 4.4 and 4.6).

Method of administration

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

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
- pimozide, 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)
- dabigatran, ticagrelor

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy (ART) has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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 ≥ 100,000 copies/mL or CD4+ cell count < 100 cells x 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

Drug-induced 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

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 Symtuza 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 Reactivation Syndrome

In HIV infected patients treated with CART, immune reactivation syndrome 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 immune reactivation; 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

Symtuza should not be used in paediatric patients below 3 years of age (see sections 4.2 and 5.3).

Symtuza 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 drug 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. Co-administration of cobicistat with medicinal products that are substrates of these transporters can result in increased plasma concentrations of the co-administered medicinal products. 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 may result in increased systemic exposure to such medicinal products, which could increase or prolong their therapeutic effect and adverse reactions. Symtuza, therefore, 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) (see section 4.3 or table below).

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 drug-drug 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 drug 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 drug drug interactions is not comprehensive and therefore the label of each drug 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		
Alfusozin	Based on theoretical considerations DRV/COBI is expected to increase alfusozin concentrations (CYP3A4 inhibition)	The concomitant use of Symtuza with alfusozin 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 therapeutic 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 Edoxaban Rivaroxaban	Based on theoretical considerations co-administration of DRV/COBI with these anticoagulants may increase concentrations of the anticoagulant, which may lead to an increased bleeding risk. (CYP3A and/or P-glycoprotein inhibition)	Co-administration of Symtuza and these anticoagulants is not recommended.
Dabigatran Ticagrelor	Based on theoretical considerations co-administration of DRV/COBI with dabigatran or ticagrelor may increase concentrations of the anticoagulant. (CYP3A and/or P-glycoprotein inhibition).	Concomitant administration of Symtuza with dabigatran or ticagrelor is contraindicated (see section 4.3).
Clopidogrel	Based on theoretical considerations co-administration of DRV/COBI 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.
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	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).
Oxcarbazepine		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 patient 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	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)	Caution is warranted and clinical monitoring is recommended. Therapeutic drug monitoring of voriconazole, posaconazole or itraconazole is recommended. When co-administration is required, the daily dose of itraconazole should not exceed 200 mg.
Voriconazole	Concentrations of voriconazole may increase or decrease when co-administered with DRV/COBI.	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 dosage 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 dosage reduction of rifabutin has not been studied. It should be kept in mind that the twice weekly dosage 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	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.
Everolimus Irinotecan		Concomitant use of everolimus or irinotecan and Symtuza is not recommended.
ANTIPSYCHOTICS/NEUROLEPTICS		
Perphenazine Risperidone Thioridazine	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.
Lurasidone Pimozide Quetiapine Sertindole		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 of therapeutic and adverse effects is recommended when these medicines 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 (*Hypericum perforatum*)	Based on theoretical consideration, St. John's Wort may substantially decrease DRV/COBI (CYP3A4 induction) and TAF exposures. (P-gp induction)	The concomitante 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	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	simvastatin. (CYP3A inhibition and/or transport)	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).
H_2-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	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)	Therapeutic drug monitoring of the immunosuppressive agent must be done when co-administration with Symtuza occurs.
Everolimus		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 dosage 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) Ethinyl estradiol Norethindrone	drospirenone AUC ↑ 58% drospirenone C_{max} ↑ 15% drospirenone C_{min} ND ethinylestradiol AUC ↓ 30% ethinylestradiol C_{max} ↓ 14% ethinylestradiol C_{min} ND Based on theoretical considerations DRV/COBI may alter norethindrone plasma concentrations.	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.
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 Avanafil	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. 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.
PROTON PUMP INHIBITORS		
Dexlansoprazole Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole	Based on theoretical considerations, no mechanistic interaction is expected.	Symtuza can be co-administered with proton pump inhibitors without dose adjustments.
SEDATIVES/HYPNOTICS		
Buspirone Clorazepate Diazepam Estazolam Flurazepam Midazolam (parenteral) Zolpidem	Based on theoretical considerations DRV/COBI is expected to increase these sedative/hypnotic plasma concentrations. (CYP3A inhibition)	Clinical monitoring is recommended when co-administering Symtuza with these sedatives/hypnotics and a lower dose of the sedative/hypnotic should be considered. Caution should be used with co-administration of Symtuza and parenteral midazolam. If Symtuza is co-administered with parenteral midazolam, it should be done in an intensive care unit or similar setting, which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
Midazolam (oral) Triazolam		Co-administration of oral midazolam or triazolam and Symtuza is contraindicated (see section 4.3).
TREATMENT FOR PREMATURE EJACULATION		
Dapoxetine	Not studied.	Co-administration of Symtuza with dapoxetine is contraindicated.

UROLOGICAL DRUGS		
Fesoterodine Solifenacin	Not studied.	Use with caution. Monitor for fesoterodine or solifenacin adverse reactions, dose reduction of fesoterodine or solifenacin may be necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well controlled trials with darunavir, cobicistat, emtricitabine, or tenofovir alafenamide, alone or in combination, in pregnant women. Studies in animals do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

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 Symtuza should be switched to an alternative regimen (see sections 4.2 and 4.4).

Breast-feeding

Emtricitabine is excreted in human milk. It is not known whether darunavir, cobicistat, or tenofovir alafenamide are excreted in human milk. Studies in animals have demonstrated that darunavir, cobicistat and tenofovir are excreted in milk.

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

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

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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 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**
Blood and lymphatic system disorders	
common	anaemia
Immune system disorders	
common uncommon	(drug) hypersensitivity immune reconstitution inflammatory syndrome
Metabolism and nutrition disorders	
common uncommon	diabetes mellitus, anorexia, hypercholesterolaemia, low density lipoprotein increased, hypertriglyceridaemia, hyperlipidaemia, dyslipidaemia hyperglycaemia
Psychiatric disorders	
common	abnormal dreams
Nervous system disorders	
very common common	headache dizziness
Gastrointestinal disorders	
very common common uncommon	diarrhoea vomiting, nausea, abdominal pain, abdominal distension, dyspepsia, flatulence pancreatitis acute, pancreatic enzymes increased
Hepatobiliary disorders	
common uncommon	hepatic enzyme increased acute hepatitis[a], cytolytic hepatitis[a]
Skin and subcutaneous tissue disorders	
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]

Musculoskeletal and connective tissue disorders	
common	arthralgia, myalgia
uncommon	osteonecrosis
Reproductive system and breast disorders	
uncommon	gynaecomastia[a]
General disorders and administration site conditions	
common	asthenia, fatigue
Investigations	
common	increased blood creatinine

[a] Additional adverse drug reactions only seen with darunavir/ritonavir in other trials or postmarketing experience

Description of selected adverse reactions

Rash
Rash is a common adverse drug 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 LDL and 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 ($eGFR_{CKD\text{-}EPI\ CystC}$) formula were respectively 4.0 mL/min/1.73 m^2 and 1.6 mL/min/1.73 m^2 ($p<0.001$). 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 ($eGFR_{CKD\text{-}EPI\ Cyst\ C}$) formula (N = 22) was +4.4 mL/min/1.73 m^2 with D/C/F/TAF.

Paediatric population

The safety of Symtuza in paediatric patients has not been investigated. However,the safety of components of Symtuza was evaluated through the clinical study TMC114-C230 (N = 12) for darunavir with ritonavir and GS-US-292-0106 (N = 50) for a fixed dose combination containing elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide. The data from these studies showed that the overall safety profile of components of Symtuza in paediatric patients aged 12 to < 18 years and weighing at least 40 kg was similar to that observed in the adult population (see section 5.1).

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 study (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 monoinfection (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 the national reporting system listed in Appendix V.

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 with Symtuza 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 x 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 EC_{50} 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 EC_{50} values ranging from < 0.1 to 4.3 nM. These EC_{50} 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 EC_{50} 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 (EC_{50} values ranged from 0.007 to 0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} 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 EC_{50} 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 (EC_{50} values ranged from 0.10 to 12.0 nM) and showed strain specific activity against HIV-2 (EC_{50} 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	Subjects with PDVF	Subjects with ≥1 emergent RAM, n (%)	
					Protease	Reverse transcriptase

			PDVF, n (%)	evaluated for resistance, n (%)	Primary PI/DRV	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 $\log_{10}$ copies/mL (SD = 0.61) and 453 x 10^6 cells/L (range 38 – 1,456 x 10^6 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 TMC114FD2HTX3001in 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 enrollment. 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 10^6 cells/mm^3 (range 111-1921 x 10^6 cells/mm^3). 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

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 $\log_{10}$ 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 $\log_{10}$ copies/mL, median CD4+ cell count was 456 cells/mm^3 (range: 95-1,110), 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/mm^3. No emergent resistance to E/C/F/TAF (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) was detected through Week 48.

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

5.2 Pharmacokinetic properties

The bioavailability of all components of Symtuza was comparable to that when darunavir 800 mg, cobicistat 150 mg, and emtricitabine/tenofovir alafenamide 200/10 mg were co-administered as separate formulations; bioequivalence was established following single-dose administration under fed conditions in healthy subjects (N = 96).

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 subjects. 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 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 ± SD) and increased to 131 ± 49.9 L (mean ± 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-drug 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 drug concentration ratio was approximately 1.0 and the mean semen to plasma drug 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 studies 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 volunteers 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 [^{14}C]-cobicistat, 99% of circulating radioactivity in plasma was unchanged cobicistat. Low levels of metabolites are observed in urine and faeces and do not contribute to the CYP3A inhibitory activity of cobicistat.

Emtricitabine
In vitro studies indicate that emtricitabine is not an inhibitor of human CYP enzymes. Following administration of [^{14}C]-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 [^{14}C]-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 [^{14}C]-darunavir with ritonavir dose, approximately 79.5% and 13.9% of the administered dose of [^{14}C]-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 [^{14}C]-cobicistat, 86% and 8.2% of the dose were recovered in faeces and urine, respectively. The median terminal plasma half-life of cobicistat following administration of 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
The pharmacokinetics of Symtuza have not been investigated in paediatric patients. However, there are pharmacokinetic data for the different components of Symtuza, indicating that doses of 800 mg darunavir, 150 mg cobicistat, 200 mg emtricitabine and 10 mg tenofovir alafenamide result in similar exposures in adults and adolescents aged 12 years and older, weighing at least 40 kg.

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 8). 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 8

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

Tablet core
Croscarmellose sodium
Magnesium stearate
Cellulose, microcrystalline
Silica, colloidal anhydrous

Tablet coating
Macrogol 4,000
Poly (vinyl alcohol)– partially hydrolysed
Talc
Titanium dioxide
Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
After first opening: 6 weeks

6.4 Special precautions for storage

Store in the original package with desiccant inside the bottle in order to protect the tablets from moisture. Keep the bottle tightly closed. Tablets may be stored outside of the original container for up to 7 days and should be discarded after that time if not taken. Tablets stored outside of the original container should not be placed back into the container.

6.5 Nature and contents of container

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.

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)

EU/1/17/1225/001 - 30 film-coated tablets
EU/1/17/1225/002 - 90 film-coated tablets (3 x 30)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 September 2017

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release
Janssen-Cilag SpA
Via C. Janssen, Borgo San Michele
04100
Latina
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Symtuza 800 mg/150 mg/200 mg/10 mg film-coated tablets
darunavir/cobicistat/emtricitabine/tenofovir alafenamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets (3 bottles containing 30 tablets each)
The bottles are not to be distributed individually.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Do not use after 6 weeks of first opening the bottle.

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Storage outside of the original container is allowed for up to 7 days.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1225/001 - 30 film-coated tablets
EU/1/17/1225/002 - 90 film-coated tablets (3 x 30)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

symtuza

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Symtuza 800 mg/150 mg/200 mg/10 mg tablets
darunavir/cobicistat/emtricitabine/tenofovir alafenamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
90 film-coated tablets (3 bottles containing 30 tablets each)
The bottles are not to be distributed individually.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Storage outside of the original container is allowed for up to 7 days.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1225/001 - 30 film-coated tablets
EU/1/17/1225/002 - 90 film-coated tablets (3 x 30)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Symtuza 800 mg/150 mg/200 mg/10 mg - film-coated tablets
darunavir/cobicistat/emtricitabine/tenofovir alafenamide

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

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

What is in this leaflet

1. What Symtuza is and what it is used for

Symtuza is an antiretroviral medicine used to treat infection with human immunodeficiency virus 1 (HIV-1). It is used in adults and adolescents aged 12 years and older who weigh at least 40 kg.
Symtuza contains four active substances:
- darunavir, an anti-HIV medicine known as a protease inhibitor
- cobicistat, a booster (enhancer) of darunavir
- emtricitabine, an anti-HIV medicine known as a nucleoside reverse transcriptase inhibitor
- tenofovir alafenamide, an anti-HIV medicine known as a nucleotide reverse transcriptase inhibitor

Symtuza reduces HIV-1 in your body and this will improve your immune system (your body's natural defences) and reduce the risk of developing illnesses linked to HIV infection but Symtuza is not a cure for HIV infection.

2. What you need to know before you take Symtuza

Do not take Symtuza
- if you are **allergic** (hypersensitive) to darunavir, cobicistat, emtricitabine, tenofovir alafenamide, or any of the other ingredients of Symtuza (listed in section 6).
- if you have **severe liver problems**. Ask your doctor if you are unsure about the severity of your liver disease. Some additional tests might be necessary.

Tell your doctor about **all** medicines you take including medicines taken orally, inhaled, injected or applied to the skin.

Do not combine Symtuza with any of the following medicines
If you are taking any of these, ask your doctor about switching to another medicine.

Medicine	Purpose of the medicine
Alfuzosin	to treat enlarged prostate
Amiodarone, dronedarone, ivabradine, quinidine, or ranolazine	to treat certain heart disorders (*e.g*. abnormal heart rhythm)
Carbamazepine, phenobarbital and phenytoin	to prevent seizures
Colchicine (if you have kidney/liver problems)	to treat gout
The combination product lopinavir/ritonavir	anti-HIV medicine
Rifampicin	to treat some infections such as tuberculosis
Pimozide, *lurasidone, quetiapine* or *sertindole*	to treat psychiatric conditions
Ergot alkaloids like *ergotamine*, *dihydroergotamine*, *ergometrine* and *methylergonovine*	to treat migraine headaches
St. John's Wort (Hypericum perforatum)	a herbal product used for depression
Elbasvir/grazoprevir	to treat hepatitis C infection
Lovastatin, simvastatin and lomitapide	to lower cholesterol levels
Triazolam or *midazolam* (taken by mouth)	to help you sleep and/or relieve anxiety
Sildenafil	to treat a heart and lung disorder called pulmonary arterial hypertension. There are other uses for sildenafil. Please see section 'Other medicines and Symtuza'.
Avanafil	to treat erectile dysfunction
Dabigatran, ticagrelor	to help stop the clumping of platelets in the treatment of patients with a history of a heart attack
Naloxegol	to treat opioid induced constipation
Dapoxetine	to treat premature ejaculation
Domperidone	to treat nausea and vomiting

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Symtuza.

You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

People taking Symtuza may still develop infections or other illnesses associated with HIV infection. You must keep in regular contact with your doctor.

People taking Symtuza may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

Although kidney problems have not been observed with Symtuza, there is a possibility that you may experience kidney problems when taking Symtuza over a long period of time.

Talk to your doctor before taking Symtuza. Tell your doctor immediately, if any of these apply to you.
- if you have had **problems with your liver**, including hepatitis B or C infection. Your doctor may evaluate how severe your liver disease is before deciding if you can take Symtuza.
- if you have **hepatitis B** infection, your liver problems may become worse after you stop taking Symtuza. It is important not to stop taking Symtuza without talking to your doctor first.
- if you have had **kidney disease** or if tests have shown **problems with your kidneys**, before or during treatment. Before starting treatment and during treatment with Symtuza, your doctor may order blood tests to monitor how your kidneys work. Your doctor will consider if Symtuza is the right medicine for you.
- if you have **diabetes**. Symtuza might increase sugar levels in the blood.

- if you notice any **symptoms of infection** (e.g. swollen lymph nodes and fever). In some patients with advanced HIV infection and who had unusual infections due to a weakened immune system (opportunistic infection), signs and symptoms of inflammation from previous infections may occur soon after you start HIV treatment. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.
- if you notice symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, tell your doctor immediately. In addition to the opportunistic infections, **autoimmune disorders** (when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection, due to an improvement in the body's immune response. Autoimmune disorders may occur many months after the start of treatment.
- if you have **haemophilia**. Symtuza might increase the risk of bleeding.
- if you are **allergic to sulphonamides** (e.g. used to treat certain infections).
- if you notice any **muscle or bone problems**. Some patients taking anti-HIV medicines may develop a bone disease called osteonecrosis (bone damage caused by loss of blood supply to the bone). This may be more likely with long-term HIV treatment, more severe damage to the immune system, being overweight, or the use of alcohol or medicines called corticosteroids. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms tell your doctor.

Elderly
Symtuza has only been used in limited numbers of patients 65 years or older. If you belong to this age group, please discuss with your doctor if you can use Symtuza.

Children and adolescents
Symtuza is not for use in children younger than 12 years, or weighing less than 40 kg, as it has not been studied in children under 12 years.

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

There are some medicines that **you must not combine** with Symtuza. These are mentioned above under the heading **'Do not combine Symtuza with any of the following medicines'.**

Symtuza must not be used with another antiviral medicine that contains a booster or another antiviral that requires boosting. In some cases dosage of other medicines might need to be changed. Therefore, always tell your doctor if you take other anti-HIV medicines and follow your doctor's instruction carefully on which medicines can be combined.

You should also not take Symtuza with medicines that contain tenofovir disoproxil (e.g. as fumarate, phosphate, or succinate), lamivudine or adefovir dipivoxil, or medicines that require boosting with ritonavir or cobicistat.

The effects of Symtuza might be reduced if you take any of the following products. Tell your doctor if you take:
- *Bosentan* (to treat high blood pressure in the pulmonary circulation)
- *Dexamethasone* (injection) (corticosteroid)
- *Rifapentine, rifabutin* (to treat bacterial infections)
- *Oxcarbazepine* (to prevent seizures).

The effects of other medicines might be influenced if you take Symtuza. Tell your doctor if you take:
- *Amlodipine, diltiazem, disopyramide, felodipine, flecainide, mexiletine, nicardipine, nifedipine, propafenone, lidocaine, verapamil* (for heart disease) as the therapeutic effect or side effects of these medicines may be increased.
- *Bosentan* (to treat high blood pressure in the pulmonary circulation)

- *Apixaban, edoxaban, rivaroxaban, clopidogrel* (to reduce clotting of the blood) as their therapeutic effect or side effects may be altered.
- *Clonazepam* (to prevent seizures).
- *Oestrogen*-based hormonal contraceptives and hormone replacement therapy. Symtuza might reduce its effectiveness. When used for birth control, non-hormonal contraception methods are recommended.
- *Ethinylestradiol/drospirenone*. Symtuza might increase the risk for elevated potassium levels by drospirenone.
- *Corticosteroids including betamethasone,budesonide, fluticasone, mometasone, prednisone, triamcinolone*. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the skin, eyes, joints and muscles and other inflammatory conditions. These medicines are generally taken orally, inhaled, injected or applied to the skin. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.
- *Buprenorphine/naloxone, methadone* (medicines to treat opioid dependence)
- *Salmeterol* (medicine to treat asthma)
- *Artemether/lumefantrine* (a combination medicine to treat malaria)
- *Dasatinib, irinotecan, nilotinib, vinblastine, vincristine* (medicines to treat cancer)
- *Sildenafil, tadalafil, vardenafil* (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension)
- *Glecaprevir/pibrentasvir* (to treat hepatitis C virus infection).
- *Fentanyl, oxycodone, tramadol* (to treat pain).
- *Fesoterodine, solifenacin* (to treat urologic disorders).

The dosage of other medicines might need to be changed since either their own or Symtuza's therapeutic effect or side effects may be influenced when combined.
Tell your doctor if you take:
- *Alfentanil* (injectable, strong and short-acting, painkiller that is used for surgical procedures)
- *Carvedilol, metoprolol, timolol* (for heart disease)
- *Warfarin* (to reduce clotting of the blood) as its therapeutic effect or side effects may be altered; your doctor may have to check your blood.
- *Digoxin* (to treat certain heart disorders)
- *Clarithromycin* (antibiotic)
- *Clotrimazole, fluconazole, isavuconazole, itraconazole, posaconazole* (for treating fungal infections). *Voriconazole* should only be taken after medical evaluation.
- *Atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin* (to lower cholesterol levels). The risk of muscle damage might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation.
- *Rifabutin* (against bacterial infections)
- *Tadalafil, sildenafil, vardenafil* (for erectile dysfunction or high blood pressure in the pulmonary circulation)
- *Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone* (to treat depression and anxiety)
- *Perphenazine, risperidone, thioridazine* (psychiatric medicines)
- *Ciclosporin, everolimus, tacrolimus, sirolimus* (for dampening down your immune system) as the therapeutic effect or side effects of these medicines might be increased. Your doctor might want to do some additional tests.
- *Colchicine* (antigout). If you have kidney or liver problems see section **'Do not combine Symtuza with any of the following medicines'.**
- *Buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem, midazolam* when used as an injection (medicines to treat trouble with sleeping or anxiety)
- *Metformin* (to treat type 2 diabetes)

This is **not** a complete list of medicines. Tell your healthcare provider about ***all*** medicines that you are taking.

Pregnancy and breast-feeding
Tell your doctor immediately if you are pregnant, planning to become pregnant or if you are breast-feeding. Pregnant or breast-feeding mothers should not take Symtuza.

It is recommended that women with HIV do not breast-feed their infants because of the possibility of the baby becoming infected with HIV through breast milk and because the medicine may affect the baby.

Driving and using machines
Symtuza can cause dizziness. Do not operate machines or drive if you feel dizzy after taking Symtuza.

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

3. How to take Symtuza

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

The recommended dose for adults and adolescents 12 years of age and older, who weigh at least 40 kg is one tablet each day with food.

You must take Symtuza every day and always **with food**. You must eat a meal or a snack within 30 minutes before taking your Symtuza. The type of food is not important.

- The tablet should not be crushed, but swallowed whole. The tablet can be taken with a drink such as water, milk or any nutritional drink. Take Symtuza at around the same time each day.

Removing the child resistant cap

The plastic bottle comes with a child resistant cap and must be opened as follows:
- Push the plastic screw cap down while turning it counter clockwise.
- Remove the unscrewed cap.

If you take more Symtuza than you should
Contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can show what you have taken.

If you forget to take Symtuza
It is important not to miss a dose of Symtuza.

If you do miss a dose:
- **If you notice within 12 hours** of the time you usually take Symtuza, you must take the tablet immediately, with food. Then take the next dose at your usual time.
- **If you notice 12 hours or more** after the time you usually take Symtuza, then do not take the missed dose and take the next doses with food at your usual time. Do not take a double dose to make up for a forgotten dose.

If you vomit within 1 hour of taking the medicine, another dose of Symtuza should be taken with food as soon as possible. If you vomit more than 1 hour after taking the medicine, then you do not need to take another dose of Symtuza until the next regularly scheduled time.

Contact your doctor if you are uncertain about what to do if you miss a dose or vomit.

Do not stop taking Symtuza without talking to your doctor first
Anti-HIV medicines may make you feel better. Even when you feel better, do not stop taking Symtuza. Talk to your doctor first.

When your supply of Symtuza starts to run low, get more from your doctor or pharmacist. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The disease may then become harder to treat.

If you have both HIV infection and hepatitis B, it is very important not to stop taking Symtuza without talking to your doctor first. You may require blood tests for several months after stopping treatment with Symtuza. In some patients with advanced liver disease or cirrhosis, stopping treatment may lead to worsening of hepatitis, which may be life-threatening.
Tell your doctor immediately about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor if you develop any of the following side effects.
Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests before you start Symtuza. If you have chronic hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems. Talk to your doctor about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea coloured) urine, pale-coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or pain and discomfort on your right side below your ribs.

Skin rash may affect more than 1 in 10 patients receiving Symtuza. Although most rashes are mild and disappear after a while as treatment is continued, a rash can occasionally be severe or potentially life-threatening. It is important to talk to your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether Symtuza must be stopped.

Other severe side effects, seen up to 1 patient in 10, were diabetes, increased blood fat levels and symptoms of infection. Inflammation of the pancreas (pancreatitis) has been reported in up to 1 patient in 100.

Very common side effects (may affect more than 1 in 10 people)
- headache
- diarrhoea
- rash

Common side effects (may affect up to 1 in 10 people)
- low red blood cell count (anaemia)
- allergic reactions such as nettle rash (urticaria), itching, decreased appetite (anorexia)
- abnormal dreams
- vomiting, pain or swelling of the belly, indigestion, flatulence (wind)
- abnormal blood test results such as some tests for your kidney. Your doctor will explain these to you.
- dizziness
- joint pain
- muscle pain, muscle cramps or weakness

- weakness
- tiredness (fatigue)
- feeling sick (nausea)

Uncommon side effects (may affect up to 1 in 100 people)
- severe swelling of the skin and other tissues (most often the lips or the eyes)
- symptoms of infection or of autoimmune disorders (immune reconstitution inflammatory syndrome)
- enlargement of breasts
- osteonecrosis (bone damage caused by loss of blood supply to the bone)
- abnormal blood test results such as some tests for your pancreas. Your doctor will explain these to you.

Rare side effects (may affect up to 1 in 1,000 people)
- a reaction called DRESS [severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidney or lung].

Some side effects are typical for anti-HIV medicines similar to Symtuza. These are:
- raised blood sugar and worsening of diabetes
- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.
- immune reconstitution inflammatory syndrome. In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection (unusual infections due to a weakened immune system), signs and symptoms of inflammation from previous infections may occur soon after HIV treatment is started, including Symtuza. In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment.

If you notice any of these symptoms tell your doctor.
During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

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

5. How to store Symtuza

Keep Symtuza out of the sight and reach of children.

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

Do not use this medicine after 6 weeks of first opening the bottle.
Store in the original package in order to protect from moisture. **Keep the bottle tightly closed.** Tablets may be stored outside of the original container for up to 7 days and should be discarded after that time if not taken. Tablets stored outside of the original container should not be placed back into the container.

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

6. Contents of the pack and other information

What Symtuza contains

The active substances are darunavir, cobicistat, emtricitabine, and tenofovir alafenamide. Each film-coated tablet contains 800 mg darunavir (as ethanolate), 150 mg cobicistat, 200 mg emtricitabine, and 10 mg tenofovir alafenamide (as fumarate).

The other ingredients are
Tablet core:
The tablet core contains croscarmellose sodium, magnesium stearate, microcrystalline cellulose and colloidal silicon dioxide.

Film coating:
The film-coating contains polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolysed), talc, titanium dioxide and yellow ferric oxide.

What Symtuza looks like and contents of the pack
Yellow to yellowish-brown capsule shaped film-coated tablet, mentioning “8121” on one side and “JG” on the other side.

Symtuza comes in bottles of 30 tablets (with a silica gel desiccant that must be kept in the bottle to help protect your tablets). The silica gel desiccant is contained in a separate sachet or canister and should not be swallowed.
The Symtuza tablets are available in packs containing one bottle or three bottles per carton.
Not all pack sizes may be marketed.

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