DUMMYDrug

75, 150, 300, 400, 600 and 800 mg

Film-Coated Tablets

1.8.2 Safety Risk Management Plan

Active substance(s) (INN or common name):	Dummy Drug
Pharmacotherapeutic group (ATC Code):	Antivirals for systemic use (J05AE11)
Name of Marketing Authorization Holder or Applicant:	Sandoz
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	[Nationally completed name] 75, 150, 300, 400, 600 and 800 mg Film-coated tablets
Version number	1.2
Data lock point for this RMP	29 Aug 2021
Date of final sign off	21 Dec 2022

List of abbreviations

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Treatment
ARV	Anti-RetroViral
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	Area under the curve
CART	Combination Antiretroviral Therapy
C_{max}	Maximum concentration
C_{min}	Minimum concentration
COBI	Cobicistat
CPK	Creatine Phosphokinase
CYP	Cytochrome P450
DCP	Decentralized Procedure
DRESS	Drug Rash with Eosinophilia and Systemic Symptoms
Dr. med.	Doctor medicine
DRV	Darunavir
DRV-RAMs	Darunavir Resistance Associated Mutations
EEA	European Economic Area
EU	European Union
HBV	Hepatitis-B-Virus
HCP	Healthcare Professional
HCV	Hepatitis-C-Virus
HIV	Human Immunodeficiency Virus
INN	International non-proprietary name
MTCT	Mother-to-child transmission
N/A	Not applicable
ND	Not determined
NNRTI	Non-Nucleoside/Nucleotide Reverse Transcriptase Inhibitors
NRTIs	Nucleoside/Nucleotide Reverse Transcriptase Inhibitors
P-gp	P-glycoprotein
PhV	Pharmacovigilance

PI	Protease Inhibitor
PL	Package leaflet
QPPV	Qualified Person for Pharmacovigilance
QT	Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
RBC	Read blood cells
RMP	Risk Management Plan
rtv	Ritonavir

SmPC	Summary of Product Characteristics

1 Part I: Product(s) Overview

1.1 Administrative information on the RMP

Table 1-1 Administrative information on the RMP

Part	Module/ Annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
PART II Safety Specification	SVIII Summary of the safety concerns	21 Dec2016	1.2
PART III Pharmacovigilance Plan		21 Dec 2016	1.2
PART V Risk Minimization Measures		21 Dec2016	1.2
PART VI Summary of RMP		21 Dec 2016	1.2
PART VII Annexes	ANNEX 2 Current or proposed SmPC/PIL	25 Nov 2015	1.0
	ANNEX 3 Worldwide marketing status by country	25 Nov 2015	1.0
	ANNEX 4 Synopsis of ongoing and completed clinical trial programme	None	N/A
		None	N/A
	ANNEX 5 Synopsis of pharmacoepidemiological study program		
	ANNEX 6 Protocols for proposed and on-going studies in Part III	None	N/A
	ANNEX 7 Specific adverse event follow-up forms	None	N/A
	ANNEX 8 Protocols for studies in Part IV	None	N/A

Part	Module/ Annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	None	N/A
	ANNEX 10 Details of proposed additional risk minimization activities	None	N/A
	ANNEX 11 Mock up examples	None	N/A
	ANNEX 12 Other supporting data	25 Nov 2015	1.0

* A new RMP version number should be assigned each time any Parts/modules are update

QPPV name	Dr. med. Sebastian Horn
QPPV signature	21 Dec 2016,
Contact person for this RMP	Dr. med. Sebastian Horn
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Overview of versions:

Version number of last agreed RMP: This is the first version.

Agreed within: N/A

Table 1-2 Current RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
None	N/A	N/A

1.2 For each product in the RMP

Invented name(s) in the European Economic Area (EEA)	[Nationally completed name] 75, 150, 300, 400, 600 and 800 mg Film coated tablets
Authorization procedure	Decentralized Procedure (DCP)
Brief description of the product including: • chemical class • summary of mode of action • important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines	Pharmacotherapeutic group: Cardiac therapy, other cardiac preparations. ATC code: J05AE10. Mechanism of action Darunavir is an inhibitor of the dimerization and of the catalytic activity of the HIV-1 protease (KD of 4.5 x 1012M). It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles.
Indication(s) in the EEA Current (if applicable)	N/A
Proposed (if applicable)	Darunavir 75 mg, 150 mg, 300 mg and 600 mg: Darunavir, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection. Darunavir 75 mg [150 mg] [300 mg] [600 mg] tablets may be used to provide suitable dose regimens: • For the treatment of HIV-1 infection in antiretroviral treatment (ART)-experienced adult patients, including those that have been highly pre-treated. • For the treatment of HIV-1 infection in pediatric patients from the age of 3 years and at least 15 kg body weight. In deciding to initiate treatment with darunavir coadministered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of darunavir. Darunavir 400 mg and 800 mg: Darunavir, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection. Darunavir, co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV1) infection in adult patients. Darunavir 400 mg [800 mg] tablets may be used to provide suitable dose regimens for the treatment of HIV1 infection in adult and pediatric patients from the age of 3 years and at least 40 kg body weight who are:

	• antiretroviral therapy (ART)-naïve.

	• ART-experienced with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106/l. In deciding to initiate treatment with darunavir in such ART-experienced patients, genotypic testing should guide the use of darunavir.
Posology and route of administration in the EEA Current (if applicable)	N/A

Proposed (if applicable):	Darunavir 75 mg, 150 mg, 300 mg and 600 mg: Therapy should be initiated by a health care provider experienced in the management of HIV infection. After therapy with darunavir has been initiated, patients should be advised not to alter the dosage, dose form or discontinue therapy without discussing with their health care provider. Posology Darunavir must always be given orally with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of ritonavir must, therefore, be consulted prior to initiation of therapy with darunavir. ART-experienced adult patients The recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food. Darunavir 75 mg [150 mg] [300 mg] [600 mg] tablets can be used to construct the twice daily 600 mg regimen. The use of 75 mg tablets to achieve the recommended dose is appropriate when there is a possibility of hypersensitivity to specific colouring agents, or difficulty in swallowing the 300 mg or 600 mg tablets. [[150 mg]: The use of 150 mg tablets to achieve the recommended dose is appropriate when there is a possibility of hypersensitivity to specific colouring agents, or difficulty in swallowing the 300 mg or 600 mg tablets.] [[300 mg]: The use of 75 and 150 mg tablets to achieve the recommended dose is appropriate when there is a possibility of hypersensitivity to specific colouring agents, or difficulty in swallowing the 300 mg tablets.] [600 mg]: The use of 75 and 150 mg tablets to achieve the recommended dose is appropriate when there is a possibility of hypersensitivity to specific colouring agents, or difficulty in swallowing the 600 mg tablets.] A dose regimen of 800 mg once daily with cobicistat 150 mg once daily or ritonavir 100 mg 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 106/l the Summary of Product Characteristics for darunavir 400 mg and 800 mg tablets).

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

ART-naïve pediatric patients (3 to 17 years of age and weighing at least 15 kg)

The weight-based dose of darunavir and ritonavir in pediatric patients is provided in the table below.

Recommended dose for treatment-naïve pediatric patients (3 to 17 years) with Darunavir tablets and ritonavir[a]	
Body weight	**Dose (once daily with food)**
(≥ kg 15**)** kg to < 30 kg	600 mg Darunavir /100 mg ritonavir once daily
≥ 30 kg to < 40 kg	675 mg Darunavir /100 mg ritonavir once daily
≥ 40 kg	800 mg Darunavir /100 mg ritonavir once daily

a ritonavir oral solution: 80 mg/ml

ART-experienced pediatric patients (3 to 17 years of age and weighing at least 15 kg)

Darunavir twice daily taken with ritonavir taken with food is usually recommended.

A once daily dose regimen of darunavir taken with ritonavir 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 106/l.

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

The weight-based dose of darunavir and ritonavir in pediatric patients is provided in the table below. The recommended dose of darunavir with low dose ritonavir should not exceed the recommended adult dose (600/100 mg twice daily or 800/100 mg once daily).

[[300 mg]: The recommended dose of darunavir with low dose ritonavir for pediatric patients is based on body weight. The adult dose of darunavir /ritonavir (600/100 mg twice daily or 800/100 mg once daily) may be used

in pediatric patients of 40 kg or more.]

[[600 mg]: The recommended dose of darunavir with low dose ritonavir for pediatric patients is based on body weight and should not exceed the recommended adult dose (600/100 mg twice daily or 800/100 mg once daily).]

Recommended dose for treatment-experienced pediatric patients (3 to 17 years of age) for

Darunavir tablets and ritonavir[a] patients (3 to 17 years) with darunavir tablets and ritonavir[a]

Body weight (kg)	Dose (once daily with food)	Dose (twice daily with food)
≥ 15 kg to < 30 kg	600 mg Darunavir /100 mg ritonavir once daily	375 mg Darunavir /50 mg ritonavir twice daily
≥ 30 kg to < 40 kg	675 mg Darunavir /100 mg ritonavir once daily	450 mg Darunavir /60 mg ritonavir twice daily
≥ 40 kg	800 mg Darunavir /100 mg ritonavir once daily	600 mg Darunavir /100 mg ritonavir twice daily

a with ritonavir oral solution: 80 mg/ml

For ART-experienced pediatric patients HIV genotypic testing is recommended. However, when HIV genotypic testing is not feasible, the darunavir /ritonavir once daily dosing regimen is recommended in HIV protease inhibitor-naïve pediatric patients and the twice daily dosing regimen is recommended in HIV protease inhibitor-experienced patients.

The use of only 75 mg and 150 mg tablets to achieve the recommended dose of darunavir could be appropriate when there is a possibility of hypersensitivity to specific colouring agents.

Advice on missed doses
In case a dose of darunavir and/or ritonavir was missed within 6 hours of the time it is usually taken, patients should be instructed to take the prescribed

	dose of darunavir and ritonavir with food as soon as possible. If this was noticed later than 6 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule. This guidance is based on the 15 hour half-life of darunavir in the presence of ritonavir and the recommended dosing interval of approximately 12 hours. Special populations Elderly Limited information is available in this population, and therefore, darunavir should be used with caution in this age group. Hepatic impairment Darunavir is metabolised by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, darunavir should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir exposure and a worsening of its safety profile. Therefore, darunavir must not be used in patients with severe hepatic impairment (Child-Pugh Class C). Renal impairment No dose adjustment is required in patients with renal impairment. Pediatric population Darunavir /ritonavir should not be used in children with a body weight of less than 15 kg as the dose for this population has not been established in a sufficient number of patients. Darunavir /ritonavir should not be used in children below 3 years of age because of safety concerns. Darunavir exposures in treatment-naïve adolescents 12 to 17 years weighing at least 40 kg receiving darunavir 800 mg once daily have been determined and were found to be within the therapeutic range as has been established in adults receiving darunavir 800 mg once daily. As a consequence, since darunavir once daily has also been registered for use in treatment-experienced adults 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 106/l, the same indication of darunavir once daily applies to

	treatmentexperienced children 3 to 17 years weighing at least

	15 kg. * DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V Pregnancy and postpartum No dose adjustment is required for darunavir/ritonavir during pregnancy and postpartum. Darunavir should be used during pregnancy only if the potential benefit justifies the potential risk. Method of administration Patients should be instructed to take darunavir with low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir. **Darunavir 400 mg and 800 mg:** Therapy should be initiated by a health care provider experienced in the management of HIV infection. After therapy with darunavir has been initiated, patients should be advised not to alter the dosage, dose form or discontinue therapy without discussing with their health care provider. The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as pharmacokinetic enhancer. Darunavir may therefore have different contraindications and recommendations for concomitant medications depending on whether the compound is boosted with ritonavir or cobicistat. Posology Darunavir must always be given orally with cobicistat or low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of cobicistat or ritonavir as appropriate, must therefore be consulted prior to initiation of therapy with darunavir. Cobicistat is not indicated for use in twice daily regimens or for use in the pediatric population. . ART-naïve adult patients The recommended dose regimen is 800 mg once daily with cobicistat 150 mg once daily or ritonavir 100 mg once daily taken with food. Darunavir 400 mg [800 mg] tablets can be used to construct the once daily 800 mg regimen. ART-experienced adult patients The recommended dose regimens are as follows: • In ART-experienced patients with no darunavir resistance associated mutations (DRV-RAMs)* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106/l a regimen of 800 mg once

	daily with cobicistat 150 mg once daily or ritonavir 100 mg once daily taken with food may be used. Darunavir 400 mg [800 mg] tablets can be used to construct the once daily 800 mg regimen. • In all other ART-experienced patients or if HIV1 genotype testing is not available, the recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food. * DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V <u>ART-naïve pediatric patients (3 to 17 years of age and weighing at least 40 kg)</u> The recommended dose regimen is 800 mg once daily with ritonavir 100 mg once daily taken with food. The dose of cobicistat to be used with darunavir in children less than 18 years of age has not been established. <u>ART-experienced pediatric patients (3 to 17 years of age and weighing at least 40 kg)</u> The dose of cobicistat to be used with darunavir in children less than 18 years of age has not been established. The recommended dose regimens are as follows: • In ART-experienced patients without DRV-RAMs* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106/l a regimen of 800 mg once daily with ritonavir 100 mg once daily taken with food may be used. Darunavir 400 mg [800 mg] tablets can be used to construct the once daily 800 mg regimen. • In all other ART-experienced patients or if HIV1 genotype testing is not available, the recommended dose regimen described in the Summary of Product Characteristics for darunavir 100 mg/ml oral suspension,75 mg, 150 mg, 300 mg or 600 mg tablets. * DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V <u>Advice on missed doses</u> If a once daily dose of darunavir and/or cobicistat or ritonavir is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of darunavir and cobicistat or ritonavir with food as soon as possible. If this is noticed later than 12 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule. This guidance is based on the half-life of darunavir in the presence of cobicistat or ritonavir and the recommended dosing interval of approximately 24 hours.

	Special populations Elderly Limited information is available in this population, and therefore, darunavir should be used with caution in this age group. Hepatic impairment Darunavir is metabolised by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, darunavir should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir exposure and a worsening of its safety profile. Therefore, darunavir must not be used in patients with severe hepatic impairment (Child-Pugh Class C). Renal impairment No dose adjustment is required for darunavir/ritonavir in patients with renal impairment. Cobicistat has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients. Cobicistat inhibits the tubular secretion of creatinine and may cause modest increases in serum creatinine and modest declines in creatinine clearance. Hence, the use of creatinine clearance as an estimate of renal elimination capacity may be misleading. Cobicistat as a pharmacokinetic enhancer of darunavir should, therefore, not be initiated in patients with creatine clearance less than 70 ml/min if any co-administered agent requires dose adjustment based on creatinine clearance: e.g. emtricitabine, lamivudine, tenofovir disoproxil fumarate or adefovir dipovoxil. For information on cobicistat, consult the cobicistat Summary of Product Characteristics. Pediatric population Darunavir should not be used in pediatric patients below 3 years of age or less than 15 kg body weight. ART-naïve pediatric patients (less than 3 years of age or less than 15 kg body weight) No recommendations on posology can be made in this population. ART-experienced pediatric patients (3 to 17 years of age and weighing at least 40 kg) Darunavir exposures in treatment-naïve adolescents 12 to 17 years weighing at least 40 kg receiving darunavir

	/ritonavir 800/100 mg once daily have been determined and were found to be within the therapeutic range as has been established in adults receiving darunavir /ritonavir 800/100 mg once daily. As a consequence, since darunavir /ritonavir 800/100 mg once daily has also been registered for use in treatment-experienced adults 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 106/l, the same indication of darunavir 800 mg once daily applies to treatment-experienced children 3 to 17 years weighing at least 40 kg. The dose of darunavir with cobicistat has not been established in this patient population. * DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V Darunavir should not be used in children less than 15 kg body weight as the dose for this population has not been established in a sufficient number of patients. Darunavir should not be used in children below 3 years of age because of safety concerns. Pregnancy and postpartum No dose adjustment is required for darunavir/ritonavir during pregnancy and postpartum. Darunavir should be used during pregnancy only if the potential benefit justifies the potential risk. <u>Method of administration</u> Patients should be instructed to take darunavir with cobicistat or low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir.
Pharmaceutical form(s) and strengths Current (if applicable)	N/A
Proposed (if applicable)	Film coated tablets 75, 150, 300, 400, 600 and 800 mg
Country and date of first authorization worldwide	Not yet authorized.
Country and date of first launch worldwide	Not yet launched.
Country and date of first authorization in the EEA	Not yet authorized.
Is the product subject to additional monitoring in the EU?	No

2 Part II: Module SVIII – Summary of the safety concerns

Table 2-1 Summary of safety concerns

Summary of safety concerns

Important identified risks	Severe skin reactions
	Hepatotoxicity
	Hyperglycemia
	Lipid abnormalities
	Pancreatitis
	Immune Reconstitution Inflammatory Syndrome
	Development of Drug resistance
	Overdose due to Medication Error
	Drug-Drug Interactions
Important potential risks	Coronary Artery Events
	Cardiac Conduction Abnormalities
	Convulsions
	Growth Abnormalities in the Paediatric Population
Important potential risks Darunavir (DRV)/cobicistat (COBI)	Off –Label Use of DRV/COBI in the Paediatric Population and in ARV treatment-experienced patients with HIV-I RNA > 100,000 copies/mL
	Renal toxicity of DRV/COBI
Missing information	Older People (65 years and above)
	Pregnant and breast-feeding women
	Subjects with severe hepatic impairment (ChildPugh C)
	Subjects with renal impairment
Missing information Darunavir (DRV)/ritonavir (rtv)	Long-term safety data in children from 3 to 17 years of age
Missing information Darunavir (DRV)/cobicistat (COBI)	Long-term safety in adults
	Children < 18 years of age
	Subjects coinfected with HIV and HBV and/or HCV

3 Part III: Pharmacovigilance Plan

The Global Pharmacovigilance System ensures the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

3.1 Part III.1 Safety concerns and overview of planned pharmacovigilance actions

Table 3-1 Severe Skin Reactions

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives

Severe skin reactions	Routine PhV	To detect the rates, courses and potential risk factors of the adverse event of interest in patients treated with darunavir.

Table 3-2 Hepatotoxicity

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
Hepatotoxicity	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

Table 3-3 Hyperglycaemia

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
Hyperglycaemia	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

Table 3-4 Lipid Abnormalities

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
Lipid abnormalities	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

Table 3-5 Pancreatitis

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
Pancreatitis	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

Table 3-6 Immune Reconstitution Inflammatory Syndrome

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
Immune Reconstitution Inflammatory Syndrome	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

Table 3-7 Development of drug resistance

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
Development of drug resistance	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

Table 3-8 Overdose due to medication error

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
Overdose due to medication error	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

Table 3-9 Drug-drug interactions

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
Drug-drug interactions	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

Table 3-10 Coronary Artery Events

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
Coronary Artery Events	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

Table 3-11 Cardiac Conduction Abnormalities

Table

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
Cardiac Conduction Abnormalities	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

3-12 Convulsions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Convulsions	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

Table 3-13 Growth Abnormalities in the Paediatric Population

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Growth Abnormalities in the Paediatric Population	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

Table 3-14 Off-Label Use of DRV/COBI in the Paediatric Population and in ARV treatment-experienced patients with HIV-I RNA > 100,000 copies/mL

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
Off-Label Use of DRV/COBI in the paediatric population and in ARV treatment-experienced patients with HIV-I RNA > 100,000 copies/mL	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

Table 3-15 Renal toxicity of DRV/COBI

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
Renal toxicity of DRV/COBI	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

Table 3-16 Older people (65 years and above)

Table

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
None	Routine PhV	N/A

Table 3-17 Pregnant and breast-feeding women

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
Pregnant and breast-feeding women	Routine PhV	To detect the rates, courses and potential risk factors of adverse events of interest in patients treated with darunavir.

3-18 Subjects with severe hepatic impairment (Child-Pugh C)

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine PhV	N/A

Table 3-19 Subjects with renal impairment

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine PhV	N/A

Table 3-20 DRV/rtv: Long-term safety data in children from 3 to 17 years of age

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
None	Routine PhV	N/A

Table 3-21 DRV/COBI: Long-term safety in adults

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
None	Routine PhV	N/A

Table 3-22 DRV/COBI: Children < 18 years of age

Areas requiring confirmation or additional further investigation	Proposed routine and PhV activities	Objectives
None	Routine PhV	N/A

Table 3-23 DRV/COBI: Subjects coinfected with HIV and HBV and/or HCV

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine PhV	N/A

Table

3.2 Part III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimization measures

None

3.3 Part III.3 Studies and other activities completed since last update of Pharmacovigilance Plan

N/A

3.4 Part III.4 Details of outstanding additional pharmacovigilance activities

3.4.1 Part III.4.1 Imposed mandatory additional pharmacovigilance activity (key to benefit risk)

None

3.4.2 Part III.4.2 Mandatory additional PhV Activity (being a Specific Obligation)

None

3.4.3 Part III.4.3 Required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimization measures

None

3.4.4 Part III.4.4 Stated additional pharmacovigilance activities

None

3.5 Part III.5 Summary of the Pharmacovigilance Plan

N/A

4 Part V: Risk minimization measures

4.1 Part V.1 Risk minimization measures by safety concern

Table 4-1 Risk minimization measures by safety concern

Safety concern	**Severe skin reactions**
Objective(s) of the risk minimization measures	To reduce the risk of severe skin reactions in patients treated with darunavir.
Routine risk minimization measures	Appropriate warnings and information in the Summary of Product Characteristics (SmPC) as follows: Section 4.4 Special warnings and precautions for use: <u>Severe skin reactions</u> 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 generalized exanthematous pustulosis have been reported. Darunavir 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 by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia. Rash occurred more commonly in treatment-experienced patients receiving regimens containing darunavir /ritonavir + raltegravir compared to patients receiving darunavir /ritonavir without raltegravir or raltegravir without darunavir. Darunavir contains a sulphonamide moiety. Darunavir should be used with caution in patients with a known sulphonamide allergy. Section 4.8 Undesirable effects: <u>Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing</u> Common - rash (including macular, maculopapular, papular, erythematous and pruritic rash) Uncommon - angioedema, urticaria, erythema Rare - DRESS, Stevens-Johnson syndrome, erythema multiforme, skin lesion, xeroderma Not known - toxic epidermal necrolysis, acute generalized exanthematous pustulosis <u>Adverse reactions with darunavir/cobicistat in adult patients</u> Very common - rash (including macular, maculopapular, papular, erythematous, pruritic rash, generalized rash, and allergic dermatitis)

Safety concern	**Severe skin reactions**
	Common - angioedema, urticaria Rare - drug reaction with eosinophilia and systemic symptoms, StevensJohnson syndrome Not known - toxic epidermal necrolysis, acute generalized exanthematous pustulosis
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None. The risk of severe skin reactions has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to severe skin reactions. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Hepatotoxicity**
Objective(s) of the risk minimization measures	To reduce the risk of hepatotoxicity in patients treated with darunavir.

Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.2 Posology and method of administration: Hepatic impairment Darunavir is metabolised by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, darunavir should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir exposure and a worsening of its safety

Safety concern	**Hepatotoxicity**

	profile. Therefore, darunavir must not be used in patients with severe hepatic impairment (Child-Pugh Class C). Section 4.3 Contraindications: Patients with severe (Child-Pugh Class C) hepatic impairment. Section 4.4 Special warnings and precautions for use: <u>Hepatotoxicity</u> Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with darunavir. 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 active hepatitis B or C, have an increased risk for liver function abnormalities including severe and potentially fatal hepatic adverse reactions. Appropriate laboratory testing should be conducted prior to initiating therapy with darunavir used in combination with cobicistat or low dose ritonavir 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 darunavir used in combination with cobicistat or low dose ritonavir 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 darunavir used in combination with cobicistat or low dose ritonavir, interruption or discontinuation of treatment should be considered promptly. <u>Patients with coexisting conditions</u> <u>Hepatic impairment</u> The safety and efficacy of darunavir have not been established in patients with severe underlying liver disorders and darunavir is therefore contraindicated in patients with severe hepatic impairment. Due to an increase in the unbound darunavir plasma concentrations, darunavir should be used with caution in patients with mild or moderate hepatic impairment. Section 4.5 Interaction with other medicinal products and other forms of interaction: Rifapentine and rifampicin are strong CYP3A inducers and have been shown to cause profound decreases in concentrations of other protease inhibitors, which can result in virological failure and resistance development (CYP450 enzyme induction). During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with low dose ritonavir, a high frequency of liver reactions was seen with rifampicin. Section 4.8 Undesirable effects:

Safety concern	**Hepatotoxicity**
	Summary of the safety profile The most frequent serious reactions with darunavir /ritonavir 600/100 mg twice daily) are … hepatitis …. Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing Common - increased alanine aminotransferase Uncommon - hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased gammaglutamyltransferase Description of selected adverse reactions Other special populations Patients co-infected with hepatitis B and/or hepatitis C virus Among 1,968 treatment-experienced patients receiving darunavir coadministered with ritonavir 600/100 mg twice daily, 236 patients were coinfected 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 Adverse reactions with darunavir/cobicistat in adult patients Common - hepatic enzyme increased Uncommon - hepatitis, cytolytic hepatitis (these adverse drug reactions have not been reported in clinical trial experience with darunavir/cobicistat but have been noted with darunavir/ritonavir treatment and could be expected with darunavir/cobicistat too) Section 5.3 Preclinical safety data: In repeated-dose toxicology studies in mice, rats and dogs, there were only limited effects of treatment with darunavir. In rodents the target organs identified were the hematopoietic system, the blood coagulation system, liver and thyroid. Changes were observed in liver (hepatocyte hypertrophy, vacuolation, increased liver enzymes) and thyroid (follicular hypertrophy). In the rat, the combination of darunavir with ritonavir lead to a small increase in effect on RBC parameters, liver and thyroid and increased incidence of islet fibrosis in the pancreas (in male rats only) compared to treatment with darunavir alone. In juvenile rats receiving darunavir up to days 23-26, increased mortality was observed with convulsions in some animals. Exposure in plasma, liver and brain was considerably higher than in adult rats after comparable doses in mg/kg between days 5 and 11 of age. After day 23 of life, the exposure was comparable to that in adult rats. The increased exposure was likely at least partly due to immaturity of the drug-metabolising enzymes in juvenile animals.
Other routine risk minimization measures	None

Safety concern	**Hepatotoxicity**
Additional risk minimization measure(s) (repeat as necessary)	None. The risk of hepatotoxicity has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to hepatotoxicity. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Hyperglycemia**
Objective(s) of the risk minimization measures	To reduce the risk of hyperglycemia in patients treated with darunavir.

Routine risk minimization measures	Appropriate warnings and information in SmPC as follows: Section 4.4 Special warnings and precautions for use: 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. Section 4.8 Undesirable effects <u>Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing</u> Uncommon – hyperglycemia, insulin resistance, polydipsia <u>Description of selected adverse reactions</u> *Metabolic parameters*
Safety concern	**Hyperglycemia**
	Weight and levels of blood lipids and glucose may increase during antiretroviral therapy.
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None. The risk of hyperglycemia has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to hyperglycemia. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A

Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Lipid abnormalities**
Objective(s) of the risk minimization measures	To reduce the risk of lipid abnormalities in patients treated with darunavir.
Routine risk minimization measures	Appropriate warnings and information in SmPC as follows: Section 4.4 Special warnings and precautions for use: 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. Section 4.8 Undesirable effects: <u>Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing</u>
Safety concern	**Lipid abnormalities**
	Common - hypertriglyceridemia, hypercholesterolemia, hyperlipidemia Uncommon - decreased high density lipoprotein <u>Adverse reactions with darunavir/cobicistat in adult patients</u> Common - hypercholesterolemia, hypertriglyceridemia, hyperlipidemia <u>Description of selected adverse reactions</u> *Metabolic parameters* Weight and levels of blood lipids and glucose may increase during antiretroviral therapy.
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None. The risk of lipid abnormalities has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	

How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to lipid abnormalities. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Pancreatitis**
Objective(s) of the risk minimization measures	To reduce the risk of pancreatitis in patients treated with darunavir.
Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.8 Undesirable effects: <u>Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing</u> Rare - pancreatitis
Safety concern	**Pancreatitis**
	<u>Adverse reactions with darunavir/cobicistat in adult patients</u> Common – pancreatic enzymes increased Uncommon - pancreatitis acute
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None. The risk of pancreatitis has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.

Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to pancreatitis. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Immune reconstitution inflammatory syndrome**
Objective(s) of the risk minimization measures	To reduce the risk of immune reconstitution inflammatory syndrome in patients treated with darunavir.
Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.4 Special warnings and precautions for use: <u>Immune reconstitution inflammatory syndrome</u> In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (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 are 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

Safety concern	**Immune reconstitution inflammatory syndrome**

	necessary. In addition, reactivation of herpes simplex and herpes zoster has been observed in clinical studies with darunavir co-administered with low dose ritonavir. Autoimmune disorders (such as Graves' disease) 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. Section 4.8 Undesirable effects: <u>Summary of the safety profile</u> During the clinical development program (N=2,613 treatment-experienced subjects who initiated therapy with darunavir /ritonavir 600/100 mg twice daily), 51.3% of subjects experienced at least one adverse reaction. The most frequent serious reactions are … immune reconstitution inflammatory syndrome …. During the Phase III clinical trial GS-US-216-130 with darunavir/cobicistat (N=313 treatment-naïve and treatment-experienced subjects), 66.5% of subjects experienced at least one adverse reaction. Serious adverse reactions are … immune reconstitution inflammatory syndrome …. Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing Uncommon - immune reconstitution inflammatory syndrome <u>Adverse reactions with darunavir/cobicistat in adult patients</u> Uncommon - immune reconstitution inflammatory syndrome <u>Description of selected adverse reactions</u> <u>Immune reconstitution inflammatory syndrome</u> In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None. The risk of immune reconstitution inflammatory syndrome has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Safety concern	**Immune reconstitution inflammatory syndrome**

Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to immune reconstitution inflammatory syndrome. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Development of drug resistance**
Objective(s) of the risk minimization measures	To reduce the risk of development of drug resistance in patients treated with darunavir.
Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.3 Contraindications: Concomitant treatment with any of the following medicinal products is contraindicated given the expected decrease in plasma concentrations of darunavir, ritonavir and cobicistat and the potential for loss of therapeutic effect. Applicable to darunavir boosted with either ritonavir or cobicistat: - The strong CYP3A inducers rifampicin and herbal preparations containing St John's wort (Hypericum perforatum). Co-administration is expected to reduce plasma concentrations of darunavir, ritonavir and cobicistat, which could lead to loss of therapeutic effect and possible development of resistance. Section 4.4 Special warnings and precautions for use: Regular assessment of virological response is advised. In the setting of lack or loss of virological response, resistance testing should be performed. Section 4.5 Interaction with other medicinal products and other forms of interaction: Darunavir and ritonavir are metabolized by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of these compounds and consequently that of darunavir, leading to loss of therapeutic effect and possible development of resistance. CYP3A inducers that are contraindicated include rifampicin, St John's wort and lopinavir. Rifapentine and rifampicin are strong CYP3A inducers and have been shown to cause profound decreases in concentrations of other protease inhibitors, which can result in virological failure and resistance development (CYP450 enzyme induction).

Safety concern	**Development of drug resistance**

Section 5.1 Pharmacodynamic properties:

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.

The clinical trial data from ART-experienced patients (TITAN trial and the pooled analysis of the POWER 1, 2 and 3 and DUET 1 and 2 trials) showed that virologic response to darunavir co-administered with low dose ritonavir was decreased when 3 or more darunavir RAMs (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V and L89V) were present at baseline or when these mutations developed during treatment.

Increasing baseline darunavir fold change in EC50 (FC) was associated with decreasing virologic response. A lower and upper clinical cut-off of 10 and 40 were identified. Isolates with baseline FC ≤ 10 are susceptible; isolates with FC > 10 to 40 have decreased susceptibility; isolates with FC > 40 are resistant.

Viruses isolated from patients on darunavir/ritonavir 600/100 mg twice daily experiencing virologic failure by rebound that were susceptible to tipranavir at baseline remained susceptible to tipranavir after treatment in the vast majority of cases.

The lowest rates of developing resistant HIV virus are observed in ART-naïve patients who are treated for the first time with darunavir in combination with other ART.

The table below shows the development of HIV-1 protease mutations and loss of susceptibility to PIs in virologic failures at endpoint in the ARTEMIS, ODIN and TITAN trials.

	ARTEMIS Week 192	ODIN Week 48		TITAN Week 48
	Darunavir / ritonavir 800/100 mg once daily N=343	Darunavir / ritonavir 800/100 mg once	Darunavir / ritonavir 600/100 mg twice daily N=298	Darunavir / ritonavir 600/100 mg twice daily N=298
Total number of virologic failures[a], n (%)	55 (16.0%)	6daily 5 (22.1%)	54daily (18.2%)	31 (10.4%)
Rebounders	39 (11.4%)			16 (5.4%)
Never suppressed subjects	16 (4.7%)	11 (3.7%) 54 (18.4%)	11 (3.7%) 43 (14.5%)	15 (5.0%)

	Number of subjects with virologic failure and paired baseline/endpoint genotypes, developing mutations[b] at endpoint, n/N

Safety concern	**Development of drug resistance**				
	Primary (major) PI mutations PI RAMs	0/43 4/43	1/60 7/60	0/42 4/42	6/28 10/28
	Number of subjects with virologic failure and paired				
	baseline/endpointPI phenoty darunavir amprenavir atazanavir indinavir lopinavir saquinavir tipranavir	›es, showing 0/39 0/39 0/39 0/39 0/39 0/39 0/39	loss of sus 1/58 1/58 2/56 2/57 1/58 0/56 0/58	ceptibilit to y 0/41 0/40 0/40 0/40 0/40 0/40 0/41	3/26 0/22 0/22 1/24 0/23 0/22 1/25

	a TLOVR non-VF censored algorithm based on HIV-1 RNA < 50 copies/ml, except for TITAN (HIV-1 RNA < 400 copies/ml) b AS-USA lists Low rates of developing resistant HIV-1 virus were observed in ART-naïve patients who are treated for the first time with darunavir/cobicistat once daily in combination with other ART, and in ART-experienced patients with no darunavir RAMs receiving darunavir/cobicistat in combination with other ART. The table below shows the development of HIV-1 protease mutations and resistance to PIs in virologic failures at endpoint in the GS-US-216-130 trial.

	GS-US-216130	
	Week 48 Treatment-naïve darunavir/cobicistat 800/150 mg once daily	Treatment-experienced darunavir/cobicistat 800/150 mg once
	N=29	
Number of subjects with virologic failure[a] and genotype data that develop mutations at endpoint[b], n/N	0/8	1/7
Primary (major) PI mutations	2/8	1/7
PI RAMs		
Number of subjects with virologic failure[a] and phenotype data that show resistance to PIs at endpoint[c], n/N		
HIV PI		
darunavir	0/8	0/7
amprenavir	0/8	0/7
atazanavir	0/8	0/7
indinavir	0/8	0/7
lopinavir	0/8	0/7
saquinavir	0/8	0/7
tipranavir	0/8	0/7

a Virogic failures were defined as: never suppressed: confirmed HIV-1 RNA < 1 log reduction from baseline and ≥ 50 copies/ml at the week-8;

Safety concern	**Development of drug resistance**

	rebound: HIV-1 RNA < 50 copies/ml followed by confirmed HIV-1 RNA to ≥ 400 copies/ml or confirmed > 1 log10 HIV-1 RNA increase from the nadir; discontinuations with HIV-1 RNA ≥ 400 copies/ml at last visit b IAS-USA lists c In GS-US216-130 baseline phenotype was not available <u>Cross-resistance</u> Darunavir FC was less than 10 for 90% of 3,309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to most PIs remain susceptible to darunavir. In the virologic failures of the ARTEMIS trial no cross-resistance with other PIs was observed. In the virologic failures of the GS-US-216-130 trial no crossresistance with other HIV PIs was observed.
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None. The risk of development of drug resistance has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to development of drug resistance. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Overdose due to medication error**
Objective(s) of the risk minimization measures	To reduce the risk of overdose due to medication error in patients treated with darunavir.
Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.9 Overdose: Human experience of acute overdose with darunavir co-administered with cobicistat or low dose ritonavir is limited. Single doses up to 3,200 mg of darunavir as oral solution alone and up to 1,600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

Safety concern	**Overdose due to medication error**
	There is no specific antidote for overdose with darunavir. Treatment of overdose with darunavir consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to overdose due to medication error. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Drug-drug interactions**
Objective(s) of the risk minimization measures	To reduce the risk of drug-drug interactions with darunavir.

Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.4 Special warnings and precautions for use: Darunavir boosted with either ritonavir or cobicistat inhibits the elimination of active substances that are highly dependent on CYP3A for clearance, which results in increased exposure to the co-administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or

Safety concern	**Drug-drug interactions**

	life-threatening events is contraindicated (applies to darunavir boosted with either ritonavir or cobicistat). These active substances include e.g.: - alfuzosin (alpha 1-adrenoreceptor antagonist) - amiodarone, bepridil, dronedarone, quinidine, ranolazine, systemic lidocaine (antiarrhythmics/antianginals) - astemizole, terfenadine (antihistamines) - colchicine when used in patients with renal and/or hepatic impairment (antigout) - ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine) - cisapride (gastrointestinal motility agents) - pimozide, quetiapine, sertindole (antipsychotics/neuroleptics) - triazolam, midazolam administered orally (sedatives/hypnotics) (for caution on parenterally administered midazolam,) - sildenafil - when used for the treatment of pulmonary arterial hypertension, avanafil(PDE-5 inhibitors) - simvastatin and lovastatin (HMG-CoA reductase inhibitors) - ticagrelor (antiplatelets) <u>Only applicable for 400 mg tablets:</u> Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A and P-glycoprotein. Section 4.5 Interaction with other medicinal products and other forms of interaction: The interaction profile of darunavir may differ depending on whether ritonavir or cobicistat is used as pharmacoenhancer. The recommendations given for concomitant use of darunavir and other medicinal products may therefore differ depending on whether darunavir is boosted with ritonavir or cobicistat and caution is also required during the first time of treatment if switching the pharmacoenhancer from ritonavir to cobicistat. <u>Medicinal products that affect darunavir exposure (ritonavir as pharmacoenhancer)</u> Co-administration of darunavir and ritonavir with other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir, which may result in increased plasma concentrations of darunavir and ritonavir. Co-administration with strong CYP3A4 inhibitors is not recommended and caution is warranted (e.g. indinavir, systemic azoles like ketoconazole and clotrimazole). <u>Medicinal products that may be affected by darunavir boosted with ritonavir</u> Darunavir and ritonavir are inhibitors of CYP3A, CYP2D6 and P-gp. Coadministration of darunavir/ritonavir with medicinal products primarily metabolised by CYP3A and/or CYP2D6 or transported by P-gp may result in increased systemic exposure to such medicinal products, which could increase or prolong their therapeutic effect and adverse reactions. Darunavir co-administered with low dose ritonavir must not be combined with medicinal products that are highly dependent on CYP3A for clearance

Safety concern	**Drug-drug interactions**

and for which increased systemic exposure is associated with serious and/or life-threatening events (narrow therapeutic index).

A clinical study utilising a cocktail of medicinal products that are metabolised by cytochromes CYP2C9, CYP2C19 and CYP2D6 demonstrated an increase in CYP2C9 and CYP2C19 activity and inhibition of CYP2D6 activity in the presence of darunavir/ritonavir, which may be attributed to the presence of low dose ritonavir. Co-administration of darunavir and ritonavir with medicinal products which are primarily metabolised by CYP2D6 (such as flecainide, propafenone, metoprolol) may result in increased plasma concentrations of these medicinal products, which could increase or prolong their therapeutic effect and adverse reactions.

Ritonavir inhibits the transporters P-glycoprotein, OATP1B1 and OATP1B3, and co-administration with substrates of these transporters can result in increased plasma concentrations of these compounds (e.g. dabigatran etexilate, digoxin, statins and bosentan).

Medicinal products that may be affected by darunavir boosted with cobicistat

The recommendations for darunavir boosted with ritonavir are adequate also for darunavir boosted with cobicistat with regard to substrates of CYP3A4, CYP2D6, P-glycoprotein, OATP1B1 and OATP1B3. Unlike ritonavir, cobicistat does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGT1A1. **INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS**

Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
HIV ANTIRETROVIRALS		
Nucleo(s/t)ide reverse transcriptase inhibitors (NRTIs)		
Tenofovir disoproxil fumarate 300 mg once daily	tenofovir AUC ↑ 22% tenofovir Cmin ↑ 37% tenofovir Cmax ↑ 24% #darunavir AUC ↑ 21% # darunavir Cmin ↑ 24% # darunavir Cmax ↑ 16% (↑ tenofovir from effect on MDR-1 transport in	Monitoring of renal function may be indicated when boosted darunavir is given in combination with tenofovir, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents. Darunavir co-administered with cobicistat lowers the creatinine clearance.
Non-nucleo(s/t)ide reverse transcriptase inhibitors (NNRTIs)		

Safety concern	**Drug-drug interactions**

Efavirenz 600 mg once daily	efavirenz AUC ↑ 21% efavirenz Cmin ↑ 17% efavirenz Cmax ↑ 15% #darunavir AUC ↓ 13% # darunavir Cmin ↓ 31% # darunavir Cmax ↓ 15% (↑ efavirenz from CYP3A inhibition)	Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated when darunavir coadministered with low dose ritonavir is given in combination with efavirenz.
ANESTHETIC	(↓ darunavir from	
Alfentanil	Not studied. The metabolism of alfentanil is mediated via CYP3A, and may as such be inhibited by boosted darunavir .	The concomitant use with boosted darunavir may require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression.
ANTIANGINA/ANTIARRHYTHMIC		
Disopyramide Flecainide Mexiletine Propafenone Amiodarone Bepridil Dronedarone Lidocaine (systemic) Quinidine Ranolazine	Not studied. Boosted darunavir 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 coadministered with boosted darunavir.
Digoxin 0.4 mg single dose	digoxin AUC ↑ 61% digoxin Cmin ND digoxin Cmax ↑ 29% (↑ digoxin from probable inhibition of P-gp)	Given that digoxin has a narrow therapeutic index, it is recommended that the lowest possible dose of digoxin should initially be prescribed in case digoxin is given to patients on boosted darunavir therapy. The digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state of the subject.
ANTICOAGULANTS		

Safety concern	**Drug-drug interactions**		
	Apixaban Dabigatran etexilate Rivaroxaban	Not studied. Coadministration of boosted darunavir with these anticoagulants may increase concentrations of the anticoagulant. (CYP3A and/or P-gp inhibition)	The use of boosted darunavir and these anticoagulants is not recommended.
	Warfarin	Not studied. Warfarin concentrations may be affected when coadministered with boosted darunavir.	It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with boosted darunavir.
	ANTIGOUT MEDICINES		
	Colchicine	Not studied. Concomitant use of colchicine and boosted darunavir may increase the exposure to colchicine. (CYP3A and/ or Pglycoprotein 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 boosted darunavir is required. For patients with renal or hepatic impairment colchicine with boosted Darunavir is
	ANTIMYCOBACTERIALS		contraindicated
	Rifampicin Rifapentine	Not studied. Rifapentine and rifampicin are strong CYP3A inducers and have been shown to cause profound decreases in concentrations of other protease inhibitors, which can result in virological failure and resistance development (CYP450 enzyme induction). During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with low dose	The combination of rifapentine and boosted darunavir is not recommended. The combination of rifampicin and boosted darunavir is contraindicated.
	ANTIPSYCHOTICSritonavir,/**NEUROLEPTICS** a high		

Safety concern	**Drug-drug interactions**		
	Quetiapine	Not studied. Boosted darunavir is expected to increase these antipsychotic plasma concentrations. (CYP3A inhibition)	Concomitant administration of boosted darunavir and quetiapine is contraindicated as it may increase quetiapinerelated toxicity. Increased concentrations of quetiapine may lead to coma.
	CORTICOSTEROIDS		
	Prednisone	Not studied. Boosted darunavir may increase plasma concentrations of prednisone. (CYP3A inhibition)	Concomitant use of boosted darunavir with low dose ritonavir and prednisone may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Clinical monitoring is recommended when co-administering boosted darunavir with corticosteroids.
	HMG CO-A REDUCTASE INHIBITORS		
	Lovastatin Simvastatin	Not studied. Lovastatin and simvastatin are expected to have markedly increased plasma concentrations when co-administered with boosted darunavir. (CYP3A inhibition)	Increased plasma concentrations of lovastatin or simvastatin may cause myopathy, including rhabdomyolysis. Concomitant use of boosted darunavir with lovastatin and simvastatin is therefore contraindicated.
	INHALED BETA AGONISTS		
	Salmeterol	Not studied. Concomitant use of salmeterol and boosted darunavir may increase plasma concentrations of salmeterol.	Concomitant use of salmeterol and boosted darunavir is not recommended. The combination may result in increased risk of cardiovascular adverse event with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
	NARCOTIC ANALGESICS / TREATMENT OF OPIOID DEPENDENCE		

Safety concern	**Drug-drug interactions**

	Buprenorphine /naloxone 8/2 mg–16/4 mg once daily	buprenorphine AUC ↓ 11% buprenorphine Cmin ↔ buprenorphine Cmax ↓ 8% norbuprenorphine AUC ↑ 46% norbuprenorphine Cmin ↑ 71% norbuprenorphine Cmax ↑ 36%	The clinical relevance of the increase in norbuprenorphine pharmacokinetic parameters has not been established. Dose adjustment for buprenorphine may not be necessary when coadministered with boosted darunavir but a careful clinical monitoring for signs of opiate toxicity is recommended.
	PHOSPHODIESTERASE, TYPE 5 (PD naloxone AUC E-5) INHIBITORS		
	For the treatment of pulmonary arterial hypertension Sildenafil Tadalafil	Not studied. Concomitant use of sildenafil or tadalafil for the treatment of pulmonary arterial hypertension and boosted darunavir may increase plasma concentrations of sildenafil or tadalafil. (CYP3A inhibition)	A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension co-administered with boosted darunavir has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope). Therefore, coadministration of boosted darunavir and sildenafil when used for the treatment of pulmonary arterial hypertension is contraindicated. Co-administration of tadalafil for the treatment of pulmonary arterial hypertension with boosted
	SEDATIVES/HYPNOTICS		Darunavir is not
Safety concern	**Drug-drug interactions**		

	Buspirone Clorazepate Diazepam Estazolam Flurazepam Midazolam (parenteral) Zoldipem Midazolam (oral) Triazolam	Not studied. Sedative/hypnotics are extensively metabolised by CYP3A. Co-administration with boosted darunavir may cause a large increase in the concentration of these medicines. If parenteral midazolam is coadministered with boosted darunavir it may cause a large increase in the concentration of this benzodiazepine. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma	Clinical monitoring is recommended when coadministering boosted darunavir with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. If parenteral midazolam is coadministered with boosted darunavir, it should be done in an intensive care unit (ICU) 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. Boosted darunavir with triazolam or oral midazolam is Contraindicated.
Other routine risk minimization measures	None levels.		
Additional risk minimization measure(s) (repeat as necessary)	None. The risk of drug-drug interactions with darunavir has been included in the SmPC and there is no need for additional risk minimization measures.		
Effectiveness of risk minimization measures			
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.		
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to drug-drug interactions with darunavir. Compare post-marketing AE profile with expected AE profile.		
Planned dates for assessment	Periodic assessments		
Results of effectiveness measurement	N/A		
Impact of risk minimization	N/A		
Comment	N/A		

Safety concern	**Coronary Artery Events**
Objective(s) of the risk minimization measures	To reduce the risk of coronary artery events in patients treated with darunavir.
Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.8 Undesirable effects: The most frequent serious reactions are acute renal failure, myocardial infarction… Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing Uncommon - myocardial infarction, angina pectoris Rare - acute myocardial infarction
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None. The risk of coronary artery events has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to coronary artery events. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Cardiac Conduction Abnormalities**

Objective(s) of the risk minimization measures	To reduce the risk of cardiac conduction abnormalities in patients treated with darunavir.
Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows:
Safety concern	**Cardiac Conduction Abnormalities**
	Section 4.5 Interaction with other medicinal products and other forms of interaction: Concomitant use of salmeterol and boosted darunavir is not recommended. The combination may result in increased risk of cardiovascular adverse event with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Section 4.8 Undesirable effects: <u>Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing</u> Uncommon - prolonged electrocardiogram QT, tachycardia Rare - sinus bradycardia, palpitations
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None. The risk of cardiac conduction abnormalities has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to risk of cardiac conduction abnormalities. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Convulsions**
Objective(s) of the risk minimization measures	To reduce the risk of convulsions in patients treated with darunavir.
Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.8 Undesirable effects: Adverse reactions observed with darunavir/ritonavir in clinical trials and
Safety concern	**Convulsions**
	post-marketing Rare - Convulsion
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None. The risk of convulsions has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to convulsions. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Growth Abnormalities in the Paediatric population**
Objective(s) of the risk minimization measures	To reduce the risk of Growth Abnormalities in the Paediatric population treated with darunavir.
Routine risk minimization measures	Currently available data do not support the need for risk minimization.
Other routine risk minimization measures	None

Additional risk minimization measure(s) (repeat as necessary)	None
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Safety concern	**Growth Abnormalities in the Paediatric population**
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to Growth Abnormalities in the Paediatric population. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Off-Label Use of DRV/COBI in the paediatric population and in ARV treatment-experienced patients with HIV-I RNA > 100,000 copies/mL**
Objective(s) of the risk minimization measures	To reduce the risk of Off-Label Use of DRV/COBI in the paediatric population and in ARV treatment-experienced patients with HIV-I RNA > 100,000 copies/mL.
Routine risk minimization measures	Clear instructions in the SmPC as follows: Section 4.1 Indications and 4.2 Posology and method of administration: Darunavir, co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients. Darunavir tablets may be used to provide suitable dose regimens for the treatment of HIV-1 infection in adult and paediatric patients from the age of 3 years and at least 40 kg body weight who are ART-experienced with no 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. In deciding to initiate treatment with darunavir in such ARTexperienced patients, genotypic testing should guide the use of darunavir.
Other routine risk minimization measures	None

Additional risk minimization measure(s) (repeat as necessary)	None. Indications and posology is clearly stated in the SmPC.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk	Primary indicator: Frequency and severity of AE related to Off-Label Use of DRV/COBI in the paediatric population and in ARV treatment-experienced patients with HIV-I RNA > 100,000 copies/mL. Compare post-marketing AE profile with expected AE profile.
Safety concern	**Off-Label Use of DRV/COBI in the paediatric population and in ARV treatment-experienced patients with HIV-I RNA > 100,000 copies/mL**
minimization measures	
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Renal toxicity of DRV/COBI**
Objective(s) of the risk minimization measures	To reduce the risk of renal toxicity of DRV/COBI in patients treated with darunavir.
Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.4 Special warnings and precautions for use: Cobicistat has not been studied in patients receiving dialysis, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients. Cobicistat decreases the estimated creatinine clearance due to inhibition of tubular secretion of creatinine. This should be taken into consideration if darunavir with cobicistat is administered to patients in whom the estimated creatinine clearance is used to adjust doses of co-administered medicinal products. There are currently inadequate data to determine whether co-administration of tenofovir disoproxil fumarate and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil fumarate without cobicistat.

Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None. The risk of renal toxicity of DRV/COBI has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk	Primary indicator: Frequency and severity of AE related to renal toxicity of DRV/COBI. Compare post-marketing AE profile with expected AE profile.
Safety concern	**Renal toxicity of DRV/COBI**
minimization measures	
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Older people (65 years and above)**
Objective(s) of the risk minimization measures	To inform the HCPs and the patients on the missing information of use of darunavir in elderly population.

Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.2 Posology and method of administration: Special populations Elderly Limited information is available in this population, and therefore, darunavir should be used with caution in this age group. Section 4.4 Special warnings and precautions for use: Elderly As limited information is available on the use of darunavir in patients aged 65 and over, caution should be exercised in the administration of darunavir in elderly patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy. Section 5.2 Pharmacokinetic properties: Special populations Elderly 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). However, only limited data were available in patients above the age of 65 year.
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None. The missing information of use of darunavir in elderly population has been included in the SmPC and there is no need for additional risk minimization measures.
Safety concern	**Older people (65 years and above)**
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to use of darunavir in elderly population. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments

Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Pregnant and breast feeding women**
Objective(s) of the risk minimization measures	To inform the HCPs and the patients on the missing information of use of darunavir in pregnant and breast feeding women.
Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.6 Fertility, pregnancy and lactation: <u>Pregnancy</u> As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account. There are no adequate and well controlled studies with darunavir in pregnant women. Studies in animals do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Darunavir co-administered with cobicistat or low dose ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk. <u>Breast-feeding</u> It is not known whether darunavir is excreted in human milk. Studies in rats have demonstrated that darunavir is excreted in milk and at high levels (1,000 mg/kg/day) resulted in toxicity. 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 under any circumstances if they are receiving darunavir. Section 5.2 Preclinical safety data:
Safety concern	**Pregnant and breast feeding women**
	Darunavir in combination with ritonavir caused a reduction in the number of pups that exhibited the startle response on day 15 of lactation and a reduced pup survival during lactation. These effects may be secondary to pup exposure to the active substance via the milk and/or maternal toxicity. No post weaning functions were affected with darunavir alone or in combination with ritonavir.
Other routine risk minimization measures	None

Additional risk minimization measure(s) (repeat as necessary)	None. The missing information of use of darunavir in pregnant and breast feeding women has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to use in pregnant and breast feeding women. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Subjects with severe hepatic impairment (Child-Pugh C)**
Objective(s) of the risk minimization measures	To inform the healthcare professionals (HCPs) and the patients on the missing information of use of darunavir in patients with severe hepatic impairment.
Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.2 Posology and method of administration: <u>Special populations</u> <u>Hepatic impairment</u> Darunavir is metabolized by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, darunavir should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir exposure and a worsening of its

Safety concern	**Subjects with severe hepatic impairment (Child-Pugh C)**

	safety profile. Therefore, darunavir must not be used in patients with severe hepatic impairment (Child-Pugh Class C). Section 4.3 Contraindications: Use of darunavir is contraindicated in patients with severe (Child-Pugh Class C) hepatic impairment. Darunavir boosted with either ritonavir or cobicistat inhibits the elimination of active substances that are highly dependent on CYP3A for clearance, which results in increased exposure to the co-administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (applies to darunavir boosted with either ritonavir or cobicistat). These active substances include colchicine when used in patients with renal and/or hepatic impairment (antigout). Section 4.4 Special warnings and precautions for use: <u>Elderly</u> As limited information is available on the use of darunavir in patients aged 65 and over, caution should be exercised in the administration of darunavir in elderly patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy. <u>Patients with coexisting conditions</u> <u>Hepatic impairment</u> The safety and efficacy of darunavir have not been established in patients with severe underlying liver disorders and darunavir is therefore contraindicated in patients with severe hepatic impairment. Due to an increase in the unbound darunavir plasma concentrations, darunavir should be used with caution in patients with mild or moderate hepatic impairment. Section 4.5 Interaction with other medicinal products and other forms of interaction: A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with boosted darunavir is required. For patients with renal or hepatic impairment colchicine with boosted darunavir is contraindicated. Section 4.8 Undesirable effects: <u>Patients co-infected with hepatitis B and/or hepatitis C virus</u> Among 1,968 treatment-experienced patients receiving darunavir coadministered with ritonavir 600/100 mg twice daily, 236 patients were coinfected 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.

Safety concern	**Subjects with severe hepatic impairment (Child-Pugh C)**
	Section 5.2 Pharmacokinetic properties: Special populations Hepatic impairment Darunavir is primarily metabolised and eliminated by the liver. In a multiple dose study with darunavir co-administered with 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 therefore, darunavir should be used with caution. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied.
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None. The missing information of use of darunavir in patients with severe hepatic impairment has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to use of darunavir in patients with severe hepatic impairment. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Subjects with renal impairment**
Objective(s) of the risk minimization measures	To inform the HCPs and the patients on the missing information of administration of darunavir in patients with renal impairment.

Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.2 Posology and method of administration:

Safety concern	**Subjects with renal impairment**

	Special populations Renal impairment No dose adjustment is required for darunavir/ritonavir in patients with renal impairment. Cobicistat has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients. Cobicistat inhibits the tubular secretion of creatinine and may cause modest increases in serum creatinine and modest declines in creatinine clearance. Hence, the use of creatinine clearance as an estimate of renal elimination capacity may be misleading. Cobicistat as a pharmacokinetic enhancer of darunavir should, therefore, not be initiated in patients with creatine clearance less than 70 ml/min if any co-administered agent requires dose adjustment based on creatinine clearance: e.g. emtricitabine, lamivudine, tenofovir disoproxil fumarate or adefovir dipovoxil. Section 4.4 Special warnings and precautions for use: Patients with coexisting conditions Renal impairment No special precautions or dose adjustments for darunavir/ritonavir are required in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis. Therefore, no special precautions or dose adjustments are required in these patients. Cobicistat has not been studied in patients receiving dialysis; therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients. Cobicistat decreases the estimated creatinine clearance due to inhibition of tubular secretion of creatinine. This should be taken into consideration if darunavir with cobicistat is administered to patients in whom the estimated creatinine clearance is used to adjust doses of co-administered medicinal products. There are currently inadequate data to determine whether co-administration of tenofovir disoproxil fumarate and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil fumarate without cobicistat. Section 4.5 Interaction with other medicinal products and other forms of interaction: Medicinal products that may be affected by darunavir boosted with cobicistat Darunavir co-administered with cobicistat lowers the creatinine clearance.
Other routine risk minimization measures	None
Additional risk minimization measure(s)	None. The missing information of administration of darunavir in patients with renal impairment has been included in the SmPC and there is no need for additional risk minimization measures.

Safety concern	**Subjects with renal impairment**
(repeat as necessary)	
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to administration of darunavir in patients with renal impairment. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Darunavir/ritonavir: Long-term safety data in children from 3 to 17 years of age**
Objective(s) of the risk minimization measures	To inform the HCPs and the patients on the missing information of coadministration of ritonavir with darunavir in children from 3 to 17 years of age.
Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.2 Posology and method of administration: Darunavir/ritonavir should not be used in children with a body weight of less than 15 kg as the dose for this population has not been established in a sufficient number of patients. Darunavir/ritonavir should not be used in children below 3 years of age because of safety concerns. Darunavir exposures in treatment-naïve adolescents 12 to 17 years weighing at least 40 kg receiving darunavir 800 mg once daily have been determined and were found to be within the therapeutic range as has been established in adults receiving darunavir 800 mg once daily. As a consequence, since darunavir once daily has also been registered for use in treatment-experienced adults 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, the same indication of darunavir once daily applies to treatment-experienced children 3 to 17 years weighing at least 15 kg.
Other routine risk minimization measures	None

Additional risk minimization measure(s) (repeat as necessary)	None.
Safety concern	**Darunavir/ritonavir: Long-term safety data in children from 3 to 17 years of age**
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to co-administration of ritonavir with darunavir in children from 3 to 17 years of age. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Darunavir/cobicistat: Long-term safety in adults**
Objective(s) of the risk minimization measures	To inform the HCPs and the patients on the missing information of longterm safety in adults of co-administration of cobicistat with darunavir.
Routine risk minimization measures	Currently available data do not support the need for risk minimization.
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.

Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to long-term safety in adults of co-administration of cobicistat with darunavir. Compare postmarketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Darunavir/cobicistat: Children < 18 years of age**
Objective(s) of the risk minimization measures	To inform the HCPs and the patients on the missing information of coadministration of cobicistat with darunavir in children < 18 years of age.
Routine risk minimization measures	Appropriate warnings and information in the SmPC as follows: Section 4.2 Posology and method of administration: <u>ART-experienced pediatric patients (3 to 17 years of age and weighing at least 40 kg)</u> The dose of cobicistat to be used with darunavir in children less than 18 years of age has not been established. <u>Special populations</u> <u>ART-experienced pediatric patients (3 to 17 years of age and weighing at least 40 kg)</u> The dose of darunavir with cobicistat has not been established in this patient population.
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None. The missing information of co-administration of cobicistat with darunavir in children < 18 years of age has been included in the SmPC and there is no need for additional risk minimization measures.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.

Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to co-administration of cobicistat with darunavir in children < 18 years of age. Compare postmarketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

Safety concern	**Darunavir/cobicistat: Subjects coinfected with HIV and HBV and/or HCV**
Objective(s) of the risk minimization measures	To inform the HCPs and the patients on the missing information of coadministration of cobicistat with darunavir in subjects coinfected with HIV and HBV and/or HCV.
Routine risk minimization measures	Currently available data do not support the need for risk minimization.
Other routine risk minimization measures	None
Additional risk minimization measure(s) (repeat as necessary)	None.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Routine pharmacovigilance AE reports will be reviewed on an on-going basis and appropriate action taken as needed.
Criteria for judging the success of the proposed risk minimization measures	Primary indicator: Frequency and severity of AE related to co-administration of cobicistat with darunavir in subjects coinfected with HIV and HBV and/or HCV. Compare post-marketing AE profile with expected AE profile.
Planned dates for assessment	Periodic assessments
Results of effectiveness measurement	N/A
Impact of risk minimization	N/A
Comment	N/A

4.2 Part V.2 Risk minimization measure failure (if applicable)

N/A

4.3 Part V.3. Summary table of risk minimization measures

Table 4-2 Summary table of Risk Minimization Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Severe skin reactions	Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None
Hepatotoxicity	Guidance is provided in section 4.2 Posology and method of administration, section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction, section 4.8 Undesirable effects and section 5.3 Preclinical safety data of the SmPC.	None
Hyperglycemia	Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None
Lipid abnormalities	Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None
Pancreatitis	Guidance is provided in section 4.8 Undesirable effects of the SmPC.	None
Immune reconstitution inflammatory syndrome	Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None
Development of drug resistance	Guidance is provided in section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction, and section 5.1 Pharmacodynamic properties of the SmPC.	None
Overdose due to medication error	Guidance is provided in section 4.9 Overdose of the SmPC.	None
Drug-drug interactions	Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.5 Interaction with other medicinal products and other forms of interaction of the SmPC.	None
Coronary Artery Events	Guidance is provided in section 4.8 Undesirable effects of the SmPC.	None
Cardiac conduction abnormalities	Guidance is provided in section 4.5 Interaction with other medicinal products and other forms of interaction and section 4.8 Undesirable effects of the SmPC.	None
Convulsions	Guidance is provided in section 4.8 Undesirable effects of the SmPC.	None
Growth Abnormalities in the paediatric population	Currently available data do not support the need for risk minimization.	None

Off-Label use of DRV/COBI in the paediatric population and in ARV treatmentexperienced patients with	Guidance is provided in section 4.1 Indications of the SmPC.	None
Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
HIV-I RNA > 100,000 copies/mL		
Renal toxicity of DRV/COBI	Guidance is provided in section 4.4 Special warnings and precautions for use of the SmPC.	None
Older people (65 years and above)	Guidance is provided in section 4.2 Posology and method of administration, section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties of the SmPC.	None
Pregnant and breast feeding women	Guidance is provided in section 4.6 Fertility, pregnancy and lactation of the SmPC.	None
Subjects with severe hepatic impairment (ChildPugh C)	Guidance is provided in section 4.2 Posology and method of administration, section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction, section 4.8 Undesirable effects and section 5.2 Pharmacokinetic properties of the SmPC.	None
Subjects with renal impairment	Guidance is provided in section 4.2 Posology and method of administration, section 4.4 Special warnings and precautions for use and 4.5 Interaction with other medicinal products of the SmPC.	None
Darunavir/ritonavir: Long-term safety data in children from 3 to 17 years of age	Guidance is provided in section 4.2 Posology and method of administration of the SmPC.	None
Darunavir/cobicistat: Long-term safety in adults	Currently available data do not support the need for risk minimization.	None
Darunavir/cobicistat: Children < 18 years of age	Guidance is provided in section 4.2 Posology and method of administration of the SmPC.	None
Darunavir/cobicistat: Subjects coinfected with HIV and HBV and/or HCV	Currently available data do not support the need for risk minimization.	None

5 Part VI: Summary of activities in the risk management plan by product

5.1 Part VI.1 Elements for summary tables in the EPAR

Table 5-1 Part VI.1.1 Summary table of safety concerns

Summary of safety concerns	
Important identified risks	Severe skin reactions
	Hepatotoxicity
	Hyperglycemia
	Lipid abnormalities
	Pancreatitis
	Immune Reconstitution Inflammatory Syndrome
	Development of Drug resistance
	Overdose due to Medication Error
	Drug-Drug Interactions
Important potential risks	Coronary Artery Events
	Cardiac Conduction Abnormalities
	Convulsions
	Growth Abnormalities in the Paediatric Population
Important potential risks Darunavir (DRV)/cobicistat (COBI)	Off –Label Use of DRV/COBI in the Paediatric Population and in ARV treatment-experienced patients with HIV-I RNA > 100,000 copies/mL
	Renal toxicity of DRV/COBI
Missing information	Older People (65 years and above)
	Pregnant and breast-feeding women
	Subjects with severe hepatic impairment (ChildPugh C)
	Subjects with renal impairment
Missing information Darunavir (DRV)/ritonavir (rtv)	Long-term safety data in children from 3 to 17 years of age
Missing information Darunavir (DRV)/cobicistat (COBI)	Long-term safety in adults
	Children < 18 years of age
	Subjects coinfected with HIV and HBV and/or HCV

Table 5-2 Part VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

None

Table 5-3 Part VI.1.3 Summary of Post authorization efficacy development plan

None

Table 5-4 Part VI.1.4 Summary table of risk minimization measures

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Severe skin reactions	Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None
Hepatotoxicity	Guidance is provided in section 4.2 Posology and method of administration, section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction, section 4.8 Undesirable effects and section 5.3 Preclinical safety data of the SmPC.	None
Hyperglycemia	Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None
Lipid abnormalities	Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None
Pancreatitis	Guidance is provided in section 4.8 Undesirable effects of the SmPC.	None
Immune reconstitution inflammatory syndrome	Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None
Development of drug resistance	Guidance is provided in section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction, and section 5.1 Pharmacodynamic properties of the SmPC.	None
Overdose due to medication error	Guidance is provided in section 4.9 Overdose of the SmPC.	None
Drug-drug interactions	Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.5 Interaction with other medicinal products and other forms of interaction of the SmPC.	None
Coronary Artery Events	Guidance is provided in section 4.8 Undesirable effects of the SmPC.	None
Cardiac conduction abnormalities	Guidance is provided in section 4.5 Interaction with other medicinal products and other forms of interaction and section 4.8 Undesirable effects of the SmPC.	None
Convulsions	Guidance is provided in section 4.8 Undesirable effects of the SmPC.	None
Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Growth Abnormalities in the paediatric population	Currently available data do not support the need for risk minimization.	None

Off-Label use of DRV/COBI in the paediatric population and in ARV treatmentexperienced patients with HIV-I RNA > 100,000 copies/mL	Guidance is provided in section 4.1 Indications of the SmPC.	None
Renal toxicity of DRV/COBI	Guidance is provided in section 4.4 Special warnings and precautions for use of the SmPC.	None
Older people (65 years and above)	Guidance is provided in section 4.2 Posology and method of administration, section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties of the SmPC.	None
Pregnant and breast feeding women	Guidance is provided in section 4.6 Fertility, pregnancy and lactation of the SmPC.	None
Subjects with severe hepatic impairment (ChildPugh C)	Guidance is provided in section 4.2 Posology and method of administration, section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction, section 4.8 Undesirable effects and section 5.2 Pharmacokinetic properties of the SmPC.	None
Subjects with renal impairment	Guidance is provided in section 4.2 Posology and method of administration, section 4.4 Special warnings and precautions for use and 4.5 Interaction with other medicinal products of the SmPC.	None
Darunavir/ritonavir: Long-term safety data in children from 3 to 17 years of age	Guidance is provided in section 4.2 Posology and method of administration of the SmPC.	None
Darunavir/cobicistat: Long-term safety in adults	Currently available data do not support the need for risk minimization.	None
Darunavir/cobicistat: Children < 18 years of age	Guidance is provided in section 4.2 Posology and method of administration of the SmPC.	None
Darunavir/cobicistat: Subjects coinfected with HIV and HBV and/or HCV	Currently available data do not support the need for risk minimization.	None

5.2 Part VI.2 Elements for a Public Summary

5.2.1 Part VI.2.1 Overview of Disease Epidemiology

HIV infections in Adults:

HIV, the virus that causes AIDS, “acquired immunodeficiency syndrome,” has become one of the world’s most serious health and development challenges. There are approximately 36.9 million people currently living with HIV. The global occurrence rate (ages 15-49) is 0.8%. While new cases have been reported in all regions of the world, approximately 70% are in

sub-Saharan Africa [Henry J. Kaiser Family Foundation (HJKF Foundation), 2015]. Over 90% of people living with HIV/AIDS do not know they are infected and even if they did, anti-retroviral therapies (medicines for AIDS) are not at present an option for them [Morison L, 2001]. Women represent approximately half (51%) of all adults living with HIV worldwide. HIV is the leading cause of death among women of reproductive age. Most infections are transmitted heterosexually, although risk factors vary. In some countries, men who have sex with men, injecting drug users, and sex workers are disproportionally affected by HIV [HJKF Foundation, 2015].

HIV infections in Pediatric patients

Globally, there were 2.6 million children living with HIV [HJKF Foundation, 2015]. An estimated 5.1 million children world-wide have been infected with HIV [Morison L, 2001]. An approximate of 88% of children with HIV infections live in Sub-Saharan Africa [HJKF Foundation, 2015]. Mother-to-child transmission (MTCT) is believed to be responsible for more than 90% of these infections. Around two-thirds of MTCT occurs in utero and at delivery and one-third occurs during breast feeding [Morison L, 2001]. It is estimated that half of all new episodes of HIV transmission to children occur during the breastfeeding period when the majority of breastfeeding women are not receiving the prophylaxis necessary to prevent HIV transmission [UNAID, 2013]. Globally, 40% of people living with HIV are receiving treatment, which includes 41% of adults and 32% of children living with HIV [HJKF Foundation, 2015].

5.2.2 Part VI.2.2 Summary of treatment benefits

Darunavir belongs to the group of medicines called protease inhibitors. It is used together with ritonavir as part of a combined therapy against Human Immunodeficiency Virus (HIV) infection in patients who were or were not treated with HIV medication in the past. In patients having been treated before with HIV medication, the efficacy of darunavir boosted with ritonavir was not inferior to that of lopinavir boosted with ritonavir after 48 weeks or was significantly better than boosted lopinavir after 48 and 96 weeks in 2 clinical trials, respectively. This was determined by a significant reduction in the number of viruses in the darunavir treated group [McKeage K, 2009]. Darunavir became the first medicine of the group of protease inhibitors to be approved by the health agencies at two different daily dosages. The main advantages of darunavir combined with ritonavir once daily are a lower pill burden, better tolerability, lower metabolic impact (half ritonavir dose), improvement in maintaining the treatment, and lower pharmaceutical costs due to lower darunavir and ritonavir doses. Darunavir is one of the 12 antiretroviral drugs that have been approved for use in children [Kogawa, 2015]. In clinical trials, ritonavir-boosted darunavir also had sustained efficacy in children and/or adolescents with HIV infection who were treated with HIV medication in the past [Keating GM, 2015]. Darunavir, when studied in pregnant HIVinfected women in the third trimester and after birth, was not associated with abnormalities present before birth, and no child was infected with HIV. [Colbers A, 2015].

5.2.1 Part VI.2.3 Unknowns relating to treatment benefits

There are no adequate and well controlled studies with darunavir in pregnant women. Limited information is available on the use of darunavir in patients aged 65 and over.

The safety and efficacy of darunavir have not been established in patients with severe underlying liver disorders.

Cobicistat has not been studied in patients receiving dialysis; therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients.

5.2.2 Part VI.2.4 Summary of safety concerns

Table 5-5 Important identified risks

Risk	What is known	Preventability
Severe skin reactions	Patients taking darunavir may develop a skin rash. Infrequently a rash may become severe or potentially lifethreatening. The rash is usually mild to moderate. A skin rash might also be a symptom of a rare severe situation. One of the rare possible side effects of darunavir is skin lesions. Skin reactions by darunavir include: Nettle rash, severe swelling of the skin and other tissues (most often the lips or the eyes), skin lesions, 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)]	Patient should contact doctor whenever a rash develops. The doctor will advise how to deal with symptoms or whether darunavir must be stopped.
Injury to the liver caused by the drug (Hepatotoxicity)	Liver problems that may occasionally be severe have been reported. Signs and symptoms of liver problems include yellowing of skin or whites of eyes, dark (tea colored) urine, pale colored stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on right side below ribs.	Patients should not take darunavir if they have severe liver problems. The patient should ask the doctor if he/she is unsure about the severity of a liver disorder. Some additional tests might be necessary. The doctor should be informed if a patient has had any sign or symptoms of a liver disorder before, including hepatitis B or C. The doctor may evaluate how severe the liver disease is before deciding if the patient can take darunavir. The doctor should do blood tests prior to initiating darunavir. If the patient has chronic hepatitis B or C infection, the doctor should check blood tests more often because there can be increased chance of developing liver problems.

Raised blood sugar	Diabetes was observed commonly during use of darunavir.	Patients should tell their doctor if having diabetes. Darunavir

Risk	What is known	Preventability
(Hyperglycemia)	Some side effects are typical for antiHIV medicines in the same family as darunavir. These include raised blood sugar and worsening of diabetes.	might increase sugar levels in the blood. The dosage of other medicines might need to be changed since either their own or darunavir's therapeutic effect or side effects may be influenced when combined. The doctor should be informed if a patient takes metformin to treat Type 2 diabetes.
Abnormalities of blood fat levels (Lipid abnormalities)	Increased blood fat levels were observed commonly with use of darunavir.	Blood fat levels can be seen in the results of blood tests.
Inflammation of the pancreas (Pancreatitis)	Inflammation of the pancreas was uncommonly observed during treatment with darunavir.	Patients should inform their doctor about pain in the abdominal region.

Inflammatory reaction to symptom-free or residual microorganisms which usually dont cause illness, but cause disease when a person's immune response to infections is impaired (Immune reconstitution inflammatory syndrome)	In HIV infected patients with severe immune deficiency at the time of start of combination antiretroviral therapy (CART), an inflammatory reaction to symptom-free or residual microorganisms which usually dont cause illness, but cause disease when a person's immune response to infections is impaired can occur. This reaction 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 are Cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumonia (inflammatory condition of the lung affecting primarily the microscopic air sacs known as alveoli) caused by Pneumocystis jirovecii. 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 studies with darunavir coadministered with low dose ritonavir. Autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) have also been reported to occur at the time when immune system begins to recover; however, the reported time of	The patient should inform his/her doctor if there are any symptoms of inflammation. These need to be evaluated and treatment initiated.

Risk	What is known	Preventability
	start is more variable and these events can occur many months after start of treatment.	
Ability of the virus to multiply even in the presence of a specific drug treatment and diminishing effect of darunavir against the virus as a result of exposure to similarly acting drugs (Development of drug resistance)	Certain medicines like rifapentine, rifampicin, St John's wort and lopinavir have been shown to cause prominent decreases in concentrations of darunavir in blood, which can result in loss of effect of darunavir and development of resistance. However, viruses resistant to most protease (enzyme) inhibitors remain susceptible to darunavir.	Regular assessment of effect of darunavir is advised. In case of lack or loss of effect, resistance testing should be performed. Certain medicines like rifampicin, St John's wort and lopinavir should not be taken in parallel with darunavir.
Overdose due to medication error	Experience regarding overdose of darunavir in combination with cobicistat or ritonavir is limted.	The patient should tell his/her doctor in case an overdosage happened.

Drug-drug interactions	Patients should not combine darunavir with any of the following medicines: Avanafil (to treat erectile dysfunction), Astemizole or terfenadine (to treat allergy symptoms), Triazolam and oral (taken by mouth) midazolam (to help to sleep and/or relieve anxiety), Cisapride (to treat some stomach conditions), in case of kidney and/or liver problems Colchicine (to treat gout), Pimozide, Quetiapine or Sertindole (to treat psychiatric conditions), Ergot alkaloids like Ergotamine, Dihydroergotamine, Ergometrine and Methylergonovine (to treat migraine and headaches), Amiodarone, Bepridil, Dronedarone, Quinidine, Ranolazine and systemic Lidocaine (to treat certain heart disorders, e.g. abnormal heart beat), Lovastatin and Simvastatin (to lower cholesterol levels), Rifampicin (to treat some infections such as tuberculosis), the combination product Lopinavir/Ritonavir (this anti-HIV medicine belongs to the same class as darunavir), Alfuzosin (to treat enlarged prostate), Sildenafil (to treat high blood pressure in the pulmonary circulation), Ticagrelor (to help stop the clumping of platelets in the treatment of patients with a history of a heart attack), and products that contain St John's wort (Hypericum perforatum).	The doctor should be informed about all medicines that the patient is taking.
Risk	What is known	Preventability
	The effects of other medicines might be influenced if patients take darunavir. The doctor should be informed if a patient takes Amlodipine, Diltiazem, Disopyramide, Carvedilol, Felodipine, Flecainide, Metoprolol, Mexiletine, Nifedipine, Nicardipine, Propafenone, Timolol, Verapamil (for different heart diseases) as the therapeutic effect or side effects of these medicines may be increased. This is not a complete list of medicines.	

Table 5-6 Important potential risks

Risk	What is known
Effects on the blood vessels nourishing the heart (Coronary Artery Events)	Reports of patients treated with darunavir/ritonavir experiencing myocardial infarction have been received. The frequency is uncommon or rare.

Conduction disorders of the heart causing an irregular heart beat (Cardiac Conduction Abnormalities)	Heart attack, slow heart beating, palpitations (noticeably rapid, strong, or irregular heartbeat) are few rare side effects of darunavir. Chest pain, changes in electrocardiogram, rapid heart beating are few uncommon side effects of darunavir.
Convulsions	Convulsions have been observed in patients treated with darunavir/ritonavir.
Growth abnormalities in the paediatric population	There is no sufficient data available for the assessment of an association of darunavir with growth abnormalities in children.
Off-label use of DRV/COBI in the paediatric population and in ARV treatmentexperienced patients with HIV-I RNA > 100,000 copies/mL	There is no sufficient data available for the assessment of a possible off-label use in this patient group. Indications are clearly labeled.
Renal toxicity of DRV/COBI	It is known that cobicistat reduces the clearance of creatinine in the kidneys.

Table 5-7 Missing information

Risk	What is known
Older people (65 years and above)	Darunavir has only been used in limited numbers of patients 65 years or older. If patients belong to this age group, it should be discussed with the doctor if the patient can use darunavir.
Pregnant and breast feeding women	The patient should tell her doctor immediately if she is pregnant or breast-feeding. Pregnant or breast-feeding women must not take darunavir unless specifically directed by the doctor. It is recommended that HIV infected women must not breast-feed their infants because of both the possibility of their baby becoming infected with HIV through breast milk and because of the unknown effects of the medicine on the baby.
Risk	What is known

Subjects with severe hepatic impairment (liver dysfunction)	Liver problems that may occasionally be severe have been reported. The doctor should do blood tests prior to initiating darunavir. If patient has chronic hepatitis B or C infection, doctor should check blood tests more often because there can be increased chance of developing liver problems. Patients should not take darunavir if having severe liver problems. The doctor should be asked if a patient is unsure about the severity of his/her liver disease. Some additional tests might be necessary. The doctor should be informed if a patient has had problems with the liver before, including hepatitis B or C. The doctor may evaluate how severe the liver disease is before deciding if the patient can take darunavir. The doctor should be informed about the signs and symptoms of liver problems. These may include yellowing of skin or whites of eyes, dark (tea colored) urine, pale colored stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on right side below ribs.
Subjects with renal impairment	No special precautions or dose adjustments are required in patients with kidney insufficiency.
Darunavir/ritonavir: Long-term safety data in children from 3 to 17 years of age	There is no sufficient data available for the assessment of long-term safety in children from 3 to 17 years of age.
Darunavir/cobicistat: Long-term safety in adults	There is no sufficient data available for the assessment of long-term safety in adults.
Combined treatment with cobicistat and darunavir in children (Darunavir/cobicistat: children < 18 years of age))	Cobicistat with darunavir should not be used in children as the dose of cobicistat to be used with darunavir in children less than 18 years of age has not been established.
Darunavir/cobicistat: Treatment in patient that also have hepatitis (Darunavir/cobicistat: Subjects coinfected with HIV and HBV and/or HCV)	There is no sufficient data available for the assessment of safety and efficacy in patients with co-infections.

5.2.3 Part VI.2.5 Summary of risk minimization measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other HCPs with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

5.2.1 Part VI.2.6 Planned post authorization development plan

None

5.2.2 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable (first submission)

6 Part VII: Annexes

6.1 Annex 1 – Eudravigilance Interface

Available in electronic format only

6.2 Annex 2 – SmPC & Package Leaflet

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

{[Nationally completed name] 75 mg film-coated tablets}

{[Nationally completed name] 150 mg film-coated tablets}

{[Nationally completed name] 300 mg film-coated tablets}

{[Nationally completed name] 600 mg film-coated tablets}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

{[Nationally completed name] 75 mg film-coated tablets} Each film-coated tablet contains 75 mg darunavir.

{[Nationally completed name] 150 mg film-coated tablets} Each film-coated tablet contains 150 mg darunavir.

{[Nationally completed name] 300 mg film-coated tablets} Each film-coated tablet contains 300 mg darunavir.
Excipient(s) with known effect: Each tablet contains 1.296 mg sunset yellow FCF (E110)

{[Nationally completed name] 600 mg film-coated tablets} Each film-coated tablet contains 600 mg darunavir.
Excipient(s) with known effect: Each tablet contains 2.592 mg sunset yellow FCF (E110)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

{[Nationally completed name] 75 mg film-coated tablets}
White caplet shaped film-coated tablet, debossed with ‘75’ on one side and plain on the other side.
Approx. size

{[Nationally completed name] 150 mg film-coated tablets}
White, oval shaped film-coated tablet, debossed with ‘150’ on one side and plain on the other side.
Approx. size

{[Nationally completed name] 300 mg film-coated tablets}
Orange oval shaped film-coated tablet, debossed with ‘300’ on one side and plain on the other side.
Approx. size

{[Nationally completed name] 600 mg film-coated tablets}
Orange oval shaped film-coated tablet, debossed with ‘600’ on one side and plain on the other side.
Approx. size

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[NATIONALLY COMPLETED NAME], co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection.

[NATIONALLY COMPLETED NAME] 75 mg [150 mg] [300 mg] [600 mg] tablets may be used to provide suitable dose regimens (see section 4.2):

- For the treatment of HIV-1 infection in antiretroviral treatment (ART)-experienced adult patients, including those that have been highly pre-treated.
- For the treatment of HIV-1 infection in paediatric patients from the age of 3 years and at least 15 kg body weight.

In deciding to initiate treatment with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of [NATIONALLY COMPLETED NAME].

4.2 Posology and method of administration

Therapy should be initiated by a health care provider experienced in the management of HIV infection. After therapy with [NATIONALLY COMPLETED NAME] has been initiated, patients should be advised not to alter the dosage, dose form or discontinue therapy without discussing with their health care provider.

Posology
[NATIONALLY COMPLETED NAME] must always be given orally with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of ritonavir must, therefore, be consulted prior to initiation of therapy with [NATIONALLY COMPLETED NAME].

Darunavir is also available as an oral suspension for use in patients who are unable to swallow [NATIONALLY COMPLETED NAME] tablets.

ART-experienced adult patients
The recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food. [NATIONALLY COMPLETED NAME] 75 mg [150 mg] [300 mg] [600 mg] tablets can be used to construct the twice daily 600 mg regimen.

The use of 75 mg tablets to achieve the recommended dose is appropriate when there is a possibility of hypersensitivity to specific colouring agents, or difficulty in swallowing the 300 mg or 600 mg tablets.

[**[150 mg]:**
The use of 150 mg tablets to achieve the recommended dose is appropriate when there is a possibility of hypersensitivity to specific colouring agents, or difficulty in swallowing the 300 mg or 600 mg tablets.]

[**[300 mg]:** The use of 75 and 150 mg tablets to achieve the recommended dose is appropriate when there is a possibility of hypersensitivity to specific colouring agents, or difficulty in swallowing the 300 mg tablets.]

[600 mg]: The use of 75 and 150 mg tablets to achieve the recommended dose is appropriate when there is a possibility of hypersensitivity to specific colouring agents, or difficulty in swallowing the 600 mg tablets.]
A dose regimen of 800 mg once daily with cobicistat 150 mg once daily or ritonavir 100 mg 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 the Summary of Product Characteristics for [NATIONALLY COMPLETED NAME] 400 mg and 800 mg tablets).
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

ART-naïve adult patients
For dosage recommendations in ART-naïve patients see the Summary of Product Characteristics for [NATIONALLY COMPLETED NAME] 400 mg and 800 mg tablets.

ART-naïve paediatric patients (3 to 17 years of age and weighing at least 15 kg)
The weight-based dose of [NATIONALLY COMPLETED NAME] and ritonavir in paediatric patients is provided in the table below.

Recommended dose for treatment-naïve paediatric patients (3 to 17 years) with [NATIONALLY COMPLETED NAME]	
Body weight (kg) a	**Dose (once daily with food)**
15 kg to < 30 kg	600 mg [NATIONALLY COMPLETED NAME]/100 mg ritonavir once daily
30 kg to < 40 kg	675 mg [NATIONALLY COMPLETED NAME]/100 mg ritonavir once daily
40 kg	800 mg [NATIONALLY COMPLETED NAME]/100 mg ritonavir once daily

a ritonavir oral solution: 80 mg/ml

ART-experienced paediatric patients (3 to 17 years of age and weighing at least 15 kg)
[NATIONALLY COMPLETED NAME] twice daily taken with ritonavir taken with food is usually recommended.

A once daily dose regimen of [NATIONALLY COMPLETED NAME] taken with ritonavir 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.
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The weight-based dose of [NATIONALLY COMPLETED NAME] and ritonavir in paediatric patients is provided in the table below. The recommended dose of [NATIONALLY COMPLETED NAME] with low dose ritonavir should not exceed the recommended adult dose (600/100 mg twice daily or 800/100 mg once daily).

[**[300 mg]:** The recommended dose of [NATIONALLY COMPLETED NAME] with low dose ritonavir for paediatric patients is based on body weight. The adult dose of [NATIONALLY COMPLETED NAME]/ritonavir (600/100 mg twice daily or 800/100 mg once daily) may be used in paediatric patients of 40 kg or more.]

[**[600 mg]:** The recommended dose of [NATIONALLY COMPLETED NAME] with low dose ritonavir for paediatric patients is based on body weight and should not exceed the recommended adult dose (600/100 mg twice daily or 800/100 mg once daily).]

Recommended dose for treatment-experienced paediatric patients (3 to 17 years of age) for [NATIONALLY COMPLETED NAME] tablets and ritonavir[a]		
Body weight (kg)	**Dose (once daily with food)**	**Dose (twice daily with food)**
≥ 15 kg–< 30 kg	600 mg [NATIONALLY COMPLETED NAME]/100 mg ritonavir once daily	375 mg [NATIONALLY COMPLETED NAME]/50 mg ritonavir twice daily
≥ 30 kg–< 40 kg	675 mg [NATIONALLY COMPLETED NAME]/100 mg ritonavir once daily	450 mg [NATIONALLY COMPLETED NAME]/60 mg ritonavir twice daily
≥ 40 kg	800 mg [NATIONALLY COMPLETED NAME]/100 mg ritonavir once daily	600 mg [NATIONALLY COMPLETED NAME]/100 mg ritonavir twice daily

[a] with ritonavir oral solution: 80 mg/ml

For ART-experienced paediatric patients HIV genotypic testing is recommended. However, when HIV genotypic testing is not feasible, the [NATIONALLY COMPLETED NAME]/ritonavir once daily dosing regimen is recommended in HIV protease inhibitor-naïve paediatric patients and the twice daily dosing regimen is recommended in HIV protease inhibitor-experienced patients.

The use of only 75 mg and 150 mg tablets or the 100 mg/ml oral suspension to achieve the recommended dose of [NATIONALLY COMPLETED NAME] could be appropriate when there is a possibility of hypersensitivity to specific colouring agents.

Advice on missed doses
In case a dose of [NATIONALLY COMPLETED NAME] and/or ritonavir was missed within 6 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of [NATIONALLY COMPLETED NAME] and ritonavir with food as soon as possible. If this was noticed later than 6 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

This guidance is based on the 15 hour half-life of darunavir in the presence of ritonavir and the recommended dosing interval of approximately 12 hours.

Special populations

Elderly
Limited information is available in this population, and therefore, [NATIONALLY COMPLETED NAME] should be used with caution in this age group (see sections 4.4 and 5.2).

Hepatic impairment

Darunavir is metabolised by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, [NATIONALLY COMPLETED NAME] should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir exposure and a worsening of its safety profile. Therefore, [NATIONALLY COMPLETED NAME] must not be used in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.3, 4.4 and 5.2).

Renal impairment
No dose adjustment is required in patients with renal impairment (see sections 4.4 and 5.2).

Paediatric population
[NATIONALLY COMPLETED NAME]/ritonavir should not be used in children with a body weight of less than 15 kg as the dose for this population has not been established in a sufficient number of patients (see section 5.1).
[NATIONALLY COMPLETED NAME]/ritonavir should not be used in children below 3 years of age because of safety concerns (see sections 4.4 and 5.3).

Darunavir exposures in treatment-naïve adolescents 12 to 17 years weighing at least 40 kg receiving [NATIONALLY COMPLETED NAME] 800 mg once daily have been determined and were found to be within the therapeutic range as has been established in adults receiving [NATIONALLY COMPLETED NAME] 800 mg once daily. As a consequence, since [NATIONALLY COMPLETED NAME] once daily has also been registered for use in treatment-experienced adults 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, the same indication of [NATIONALLY COMPLETED NAME] once daily applies to treatment-experienced children 3 to 17 years weighing at least 15 kg.
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

Method of administration
Patients should be instructed to take [NATIONALLY COMPLETED NAME] with low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir (see sections 4.4, 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Patients with severe (Child-Pugh Class C) hepatic impairment.

Combination of rifampicin with [NATIONALLY COMPLETED NAME] with concomitant low dose ritonavir (see section 4.5).

Co-administration with the combination product lopinavir/ritonavir (see section 4.5).

Co-administration with herbal preparations containing St John's wort (Hypericum perforatum) (see section 4.5).

Co-administration of [NATIONALLY COMPLETED NAME] with low dose ritonavir, with active substances that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These active substances include e.g.:

- alfuzosin (alpha 1-adrenoreceptor antagonist)

- amiodarone, bepridil, dronedarone, quinidine, ranolazine, systemic lidocaine (antiarrhythmics/antianginals)
- astemizole, terfenadine (antihistamines)
- colchicine when used in patients with renal and/or hepatic impairment (antigout) (see section 4.5)
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- cisapride (gastrointestinal motility agent)
- pimozide, quetiapine, sertindole (antipsychotics/neuroleptics) (see section 4.5)
- triazolam, midazolam administered orally (sedatives/hypnotics) (for caution on parenterally administered midazolam, see section 4.5)
- sildenafil - when used for the treatment of pulmonary arterial hypertension, avanafil (PDE-5 inhibitors)
- simvastatin and lovastatin (HMG-CoA reductase inhibitors) (see section 4.5)
- ticagrelor (antiplatelets) (see section 4.5).

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy 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.

Regular assessment of virological response is advised. In the setting of lack or loss of virological response, resistance testing should be performed.

[NATIONALLY COMPLETED NAME] should only be used in combination with low dose ritonavir as a pharmacokinetic enhancer (see section 5.2).

Increasing the dose of ritonavir from that recommended in section 4.2 did not significantly affect darunavir concentrations and is not recommended.

Darunavir binds predominantly to 1-acid glycoprotein. This protein binding is concentrationdependent indicative for saturation of binding. Therefore, protein displacement of medicinal products highly bound to 1-acid glycoprotein cannot be ruled out (see section 4.5).

ART-experienced patients – once daily dosing
[NATIONALLY COMPLETED NAME] used in combination with cobicistat or low dose ritonavir once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA ≥ 100,000 copies/ml or CD4+ cell count

< 100 cells x 10^6/l (see section 4.2). Combinations with optimised background regimen (OBRs) other than ≥ 2 NRTIs have not been studied in this population. Limited data are available in patients with HIV-1 clades other than B (see section 5.1).

Paediatric population
[NATIONALLY COMPLETED NAME] is not recommended for use in paediatric patients below 3 years of age or less than 15 kg body weight (see sections 4.2 and 5.3).

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

Severe skin reactions
During the 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. [NATIONALLY COMPLETED NAME]/ritonavir 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 by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Rash occurred more commonly in treatment-experienced patients receiving regimens containing [NATIONALLY COMPLETED NAME] + raltegravir compared to patients receiving [NATIONALLY COMPLETED NAME] without raltegravir or raltegravir without [NATIONALLY COMPLETED NAME] (see section 4.8).

Darunavir contains a sulphonamide moiety. [NATIONALLY COMPLETED NAME] should be used with caution in patients with a known sulphonamide allergy.

Hepatotoxicity
Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with [NATIONALLY COMPLETED NAME]. During the clinical development program (N=3,063), hepatitis was reported in 0.5% of patients receiving combination antiretroviral therapy with [NATIONALLY COMPLETED NAME]/ritonavir. Patients with pre-existing liver dysfunction, including chronic active 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 [NATIONALLY COMPLETED NAME]/ritonavir 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 [NATIONALLY COMPLETED NAME]/ritonavir 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 [NATIONALLY COMPLETED NAME]/ritonavir, interruption or discontinuation of treatment should be considered promptly.

Patients with coexisting conditions

Hepatic impairment
The safety and efficacy of [NATIONALLY COMPLETED NAME] have not been established in patients with severe underlying liver disorders and [NATIONALLY COMPLETED NAME] is therefore contraindicated in patients with severe hepatic impairment.
Due to an increase in the unbound darunavir plasma concentrations, [NATIONALLY COMPLETED NAME] should be used with caution in patients with mild or moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal impairment
No special precautions or dose adjustments are required in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be

significantly removed by haemodialysis or peritoneal dialysis. Therefore, no special precautions or dose adjustments are required in these patients (see sections 4.2 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 PIs. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with 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.

Diabetes mellitus/hyperglycaemia
New onset diabetes mellitus, hyperglycaemia, or exacerbation of existing diabetes mellitus has been reported in patients receiving antiretroviral therapy, including PIs. In some of these patients the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia.

Fat redistribution and metabolic disorders
Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

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

Immune reconstitution inflammatory syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (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 are 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 studies with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir.

Autoimmune disorders (such as Graves' disease) 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).

Interactions with medicinal products
Several of the interaction studies have been performed with darunavir at lower than recommended doses. The effects on co-administered medicinal products may thus be

underestimated and clinical monitoring of safety may be indicated. For full information on interactions with other medicinal products see section 4.5.

Efavirenz in combination with [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily may result in sub-optimal darunavir Cmin. If efavirenz is to be used in combination with [NATIONALLY COMPLETED NAME]/ritonavir, the [NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily regimen should be used. See the Summary of Product Characteristics for [NATIONALLY COMPLETED NAME] 150 mg, 300 mg or 600 mg tablets (see section 4.5).

[**[300 mg]:** [NATIONALLY COMPLETED NAME] tablets contain sunset yellow FCF (E110) which may cause an allergic reaction.]

[**[600 mg]:** [NATIONALLY COMPLETED NAME] tablets contain sunset yellow FCF (E110) which may cause an allergic reaction.]

Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A and P-glycoprotein (P-gp; see sections 4.3 and 4.5)

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Darunavir and ritonavir are inhibitors of CYP3A, CYP2D6 and P-gp. Co-administration of darunavir and ritonavir and medicinal products primarily metabolised by CYP3A and/or CYP2D6 or transported by P-gp may result in increased systemic exposure to such medicinal products, which could increase or prolong their therapeutic effect and adverse reactions.

[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir 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).

The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily. Therefore, [NATIONALLY COMPLETED NAME] must only be used in combination with low dose ritonavir as a pharmacokinetic enhancer (see sections 4.4 and 5.2).

A clinical study utilising a cocktail of medicinal products that are metabolised by cytochromes CYP2C9, CYP2C19 and CYP2D6 demonstrated an increase in CYP2C9 and CYP2C19 activity and inhibition of CYP2D6 activity in the presence of [NATIONALLY COMPLETED NAME]/ritonavir, which may be attributed to the presence of low dose ritonavir. Co-administration of darunavir and ritonavir and medicinal products which are primarily metabolised by CYP2D6 (such as flecainide, propafenone, metoprolol) may result in increased plasma concentrations of these medicinal products, which could increase or prolong their therapeutic effect and adverse reactions. Co-administration of darunavir and ritonavir and medicinal products primarily metabolised by CYP2C9 (such as warfarin) and CYP2C19 (such as methadone) may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Although the effect on CYP2C8 has only been studied *in vitro*, co-administration of darunavir and ritonavir and medicinal products primarily metabolised by CYP2C8 (such as paclitaxel, rosiglitazone, repaglinide) may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Medicinal products that affect darunavir/ritonavir exposure
Darunavir and ritonavir are metabolised by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir (e.g. rifampicin, St John's wort, lopinavir).
Co-administration of darunavir and ritonavir and other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir (e.g. indinavir, systemic azoles like ketoconazole and clotrimazole). These interactions are described in the interaction table below.

Interaction table
Interactions between [NATIONALLY COMPLETED NAME]/ritonavir and antiretroviral and nonantiretroviral medicinal products are listed in the table below (not determined as "ND"). The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (↔), below (↓) or above (↑) the 80-125% range.

Several of the interaction studies (indicated by # in the table below) have been performed at lower than recommended doses of darunavir or with a different dosing regimen (see section 4.2 Posology). The effects on co-administered medicinal products may thus be underestimated and clinical monitoring of safety may be indicated.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
HIV ANTIRETROVIRALS		
Integrase strand transfer inhibitors		
Dolutegravir	dolutegravir AUC ↓ 32% dolutegravir C24h 38% dolutegravir Cmax ↓ 11% darunavir ↔* * Using cross-study comparisons to historical pharmacokinetic data	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and dolutegravir can be used without dose adjustment.

Elvitegravir	elvitegravir AUC ↔ elvitegravir Cmin ↔ elvitegravir Cmax ↔ darunavir AUC ↔ darunavir Cmin 17% darunavir Cmax ↔	When [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir (600/100 mg twice daily) is used in combination with elvitegravir, the dose of elvitegravir should be 150 mg once daily. The pharmacokinetics and dosing recommendations for other doses of darunavir or with elvitegravir/cobicistat have not been established. Therefore, coadministration of [NATIONALLY COMPLETED NAME] with low dose ritonavir in doses other than 600/100 mg twice daily and elvitegravir is not recommended. Co-administration of [NATIONALLY COMPLETED NAME] with low dose ritonavir and elvitegravir in the presence of cobicistat is not recommended.
Raltegravir	Some clinical studies suggest raltegravir may cause a modest decrease in darunavir plasma concentrations.	At present the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically relevant. [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and raltegravir can be used without dose adjustments.
Nucleo(s/t)ide reverse transcriptase inhibitors (NRTIs)		
Didanosine 400 mg once daily	didanosine AUC ↓ 9% didanosine Cmin ND didanosine Cmax ↓ 16% darunavir AUC ↔ darunavir Cmin ↔ darunavir Cmax ↔	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and didanosine can be used without dose adjustments. Didanosine is to be administered on an empty stomach, thus it should be administered 1 hour before or 2 hours after [NATIONALLY COMPLETED NAME]/ritonavir given with food.

Tenofovir disoproxil fumarate 300 mg once daily	tenofovir AUC ↑ 22% tenofovir Cmin ↑ 37% tenofovir Cmax ↑ 24% #darunavir AUC ↑ 21% # darunavir Cmin ↑ 24% # darunavir Cmax ↑ 16% (↑ tenofovir from effect on MDR-1 transport in the renal tubules)	Monitoring of renal function may be indicated when [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir is given in combination with tenofovir, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.

Abacavir Emtricitabine Lamivudine Stavudine Zidovudine	Not studied. Based on the different elimination pathways of the other NRTIs zidovudine, emtricitabine, stavudine, lamivudine, that are primarily renally excreted, and abacavir for which metabolism is not mediated by CYP450, no interactions are expected for these medicinal compounds and [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir.	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir can be used with these NRTIs without dose adjustment.
Non-nucleo(s/t)ide reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg once daily	efavirenz AUC ↑ 21% efavirenz Cmin ↑ 17% efavirenz Cmax ↑ 15% #darunavir AUC ↓ 13% #darunavir Cmin ↓ 31% #darunavir Cmax ↓ 15% (↑ efavirenz from CYP3A inhibition) (↓ darunavir from CYP3A induction)	Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated when [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir is given in combination with efavirenz. Efavirenz in combination with [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily may result in sub-optimal darunavir Cmin. If efavirenz is to be used in combination with [NATIONALLY COMPLETED NAME]/ritonavir, the [NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily regimen should be used (see section 4.4).
Etravirine 100 mg twice daily	etravirine AUC ↓ 37% etravirine Cmin ↓ 49% etravirine Cmax ↓ 32% darunavir AUC ↑ 15% darunavir Cmin ↔ darunavir Cmax ↔	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and etravirine **200 mg twice daily** can be used without dose adjustments.
Nevirapine 200 mg twice daily	nevirapine AUC ↑ 27% nevirapine Cmin ↑ 47% nevirapine Cmax ↑ 18% #darunavir: concentrations were consistent with historical data (↑ nevirapine from CYP3A inhibition)	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and nevirapine can be used without dose adjustments.
Rilpivirine 150 mg once daily	rilpivirine AUC ↑ 130% rilpivirine Cmin ↑ 178% rilpivirine Cmax ↑ 79% darunavir AUC ↔ darunavir Cmin ↓ 11% darunavir Cmax ↔	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and rilpivirine can be used without dose adjustments.

HIV Protease inhibitors (PIs) - without additional co-administration of low dose ritonavir †		
Atazanavir 300 mg once daily	atazanavir AUC ↔ atazanavir Cmin ↑ 52% atazanavir Cmax ↓ 11% #darunavir AUC ↔ #darunavir Cmin ↔ #darunavir Cmax ↔ Atazanavir: comparison of atazanavir/ritonavir 300/100 mg once daily vs. atazanavir 300 mg once daily in combination with darunavir/ritonavir 400/100 mg twice daily. Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg twice daily in combination with atazanavir 300	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and atazanavir can be used without dose adjustments.
Indinavir 800 mg twice daily	mindinavirg once AUCdaily. ↑ 23% indinavir Cmin ↑ 125% indinavir Cmax ↔ #darunavir AUC ↑ 24% #darunavir Cmin ↑ 44% #darunavir Cmax ↑ 11% Indinavir: comparison of indinavir/ritonavir 800/100 mg twice daily vs. indinavir/darunavir/ritonavir 800/400/100 mg twice daily. Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with indinavir 800 mg twice daily.	When used in combination with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir, dose adjustment of indinavir from 800 mg twice daily to 600 mg twice daily may be warranted in case of intolerance.

Saquinavir 1,000 mg twice daily	#darunavir AUC ↓ 26% #darunavir Cmin ↓ 42% #darunavir Cmax ↓ 17% saquinavir AUC ↓ 6% saquinavir Cmin ↓ 18% saquinavir Cmax ↓ 6% Saquinavir: comparison of saquinavir/ritonavir 1,000/100 mg twice daily vs. saquinavir/darunavir/ritonavir 1,000/400/100 mg twice daily Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with saquinavir 1,000 mg twice daily.	It is not recommended to combine [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir with saquinavir.
***HIV Protease inhibitors (PIs) - with co-administration of low dose ritonavir*†**		
Lopinavir/ritonavir 400/100 mg twice daily Lopinavir/ritonavir 533/133.3 mg twice daily	lopinavir AUC ↑ 9% lopinavir Cmin ↑ 23% lopinavir Cmax ↓ 2% darunavir AUC ↓ 38%‡ darunavir Cmin ↓ 51%‡ darunavir Cmax ↓ 21%‡ lopinavir AUC ↔ lopinavir Cmin ↑ 13% lopinavir Cmax ↑ 11% darunavir AUC ↓ 41% darunavir Cmin ↓ 55% darunavir Cmax ↓ 21% ‡ based upon non dose normalised	Due to a decrease in the exposure (AUC) of darunavir by 40%, appropriate doses of the combination have not been established. Hence, concomitant use of [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and the combination product lopinavir/ritonavir is contraindicated (see section 4.3).
CCR5 ANTAGONIST	values	
Maraviroc 150 mg twice daily	maraviroc AUC ↑ 305% maraviroc Cmin ND maraviroc Cmax ↑ 129% darunavir, ritonavir concentrations were consistent with historical data	The maraviroc dose should be 150 mg twice daily when co-administered with [NATIONALLY COMPLETED NAME] with low dose ritonavir.
ANAESTHETIC		

Alfentanil	Not studied. The metabolism of alfentanil is mediated via CYP3A, and may as such be inhibited by [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir.	The concomitant use with [NATIONALLY COMPLETED NAME] and low dose ritonavir may require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression.
ANTIANGINA/ANTIARRHYTHMIC		
Disopyramide Flecainide Mexiletine Propafenone Amiodarone Bepridil Dronedarone Lidocaine (systemic) Quinidine Ranolazine	Not studied. [NATIONALLY COMPLETED NAME] 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 [NATIONALLY COMPLETED NAME] with low dose ritonavir. [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and amiodarone, bepridil, dronedarone, systemic lidocaine, quinidine, or ranolazine is contraindicated (see section 4.3).
Digoxin 0.4 mg single dose	digoxin AUC ↑ 61% digoxin Cmin ND digoxin Cmax ↑ 29% (↑ digoxin from probable inhibition of Pgp)	Given that digoxin has a narrow therapeutic index, it is recommended that the lowest possible dose of digoxin should initially be prescribed in case digoxin is given to patients on darunavir/ritonavir therapy. The digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state of the subject.
ANTIBIOTIC		
Clarithromycin 500 mg twice daily	clarithromycin AUC ↑ 57% clarithromycin Cmin ↑ 174% clarithromycin Cmax ↑ 26% #darunavir AUC ↓ 13% #darunavir Cmin ↑ 1% #darunavir Cmax ↓ 17% 14-OH-clarithromycin concentrations were not detectable when combined with [NATIONALLY COMPLETED NAME]/ritonavir. (↑ clarithromycin from CYP3A inhibition and possible P-gp inhibition)	Caution should be exercised when clarithromycin is combined with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir.
ANTICOAGULANTS		

Apixaban Dabigatran etexilate Rivaroxaban	Not studied. Co-administration of [NATIONALLY COMPLETED NAME] with these anticoagulants may increase concentrations of the anticoagulant. (CYP3A and/or P-gp inhibition).	The use of [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and these anticoagulants is not recommended.
Warfarin	Not studied. Warfarin concentrations may be affected when co-administered with darunavir with low dose ritonavir.	It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir.
ANTICONVULSANTS		

Phenobarbital Phenytoin	Not studied. Phenobarbital and phenytoin are expected to decrease plasma concentrations of darunavir. (induction of CYP450 enzymes)	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir should not be used in combination with these medicines.
Carbamazepine 200 mg twice daily	carbamazepine AUC ↑ 45% carbamazepine Cmin ↑ 54% carbamazepine Cmax ↑ 43% darunavir AUC ↔ darunavir Cmin ↓ 15% darunavir Cmax ↔	No dose adjustment for [NATIONALLY COMPLETED NAME]/ritonavir is recommended. If there is a need to combine [NATIONALLY COMPLETED NAME]/ritonavir and carbamazepine, patients should be monitored for potential carbamazepine-related adverse events. Carbamazepine concentrations should be monitored and its dose should be titrated for adequate response. Based upon the findings, the carbamazepine dose may need to be reduced by 25% to 50% in the presence of
ANTIDEPRESSANTS		[NATIONALLY COMPLETED

Paroxetine 20 mg once daily Sertraline 50 mg once daily Amitriptyline Desipramine Imipramine Nortriptyline Trazodone	paroxetine AUC ↓ 39% paroxetine Cmin ↓ 37% paroxetine Cmax ↓ 36% #darunavir AUC ↔ #darunavir Cmin ↔ #darunavir Cmax ↔ sertraline AUC ↓ 49% sertraline Cmin ↓ 49% sertraline Cmax ↓ 44% #darunavir AUC ↔ #darunavir Cmin ↓ 6% #darunavir Cmax ↔ Concomitant use of [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and these antidepressants may increase concentrations of the antidepressant. (CYP2D6 and/or CYP3A inhibition).	If antidepressants are coadministered with [NATIONALLY COMPLETED NAME] with low dose ritonavir, the recommended approach is a dose titration of the antidepressant based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of these antidepressants who start treatment with [NATIONALLY COMPLETED NAME] with low dose ritonavir should be monitored for antidepressant response. Clinical monitoring is recommended when co-administering [NATIONALLY COMPLETED NAME] with low dose ritonavir with these antidepressants and a dose adjustment of the antidepressant may be needed.
ANTIFUNGALS		
Voriconazole	Not studied. Ritonavir may decrease plasma concentrations of voriconazole. (induction of CYP450 enzymes by ritonavir)	Voriconazole should not be combined with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.

Ketoconazole 200 mg twice daily	ketoconazole AUC ↑ 212% ketoconazole Cmin ↑ 868% ketoconazole Cmax ↑ 111% #darunavir AUC ↑ 42% #darunavir Cmin ↑ 73% #darunavir Cmax ↑ 21% (CYP3A inhibition)	Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of ketoconazole should not exceed 200 mg.
Posaconazole	Not studied. [NATIONALLY COMPLETED NAME] may increase antifungal plasma concentrations (P-gp inhibition) and posaconazole may increase darunavir concentrations. (CYP3A inhibition)	Caution is warranted and clinical monitoring is recommended.

Itraconazole	Not studied. Concomitant systemic use of itraconazole and darunavir coadministered with low dose ritonavir may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of itraconazole may be increased by darunavir co-administered with low dose ritonavir. (CYP3A inhibition)	Caution is warranted and clinical monitoring is recommended. When co-administration is required the daily dose of itraconazole should not exceed 200 mg.
Clotrimazole	Not studied. Concomitant systemic use of clotrimazole and darunavir coadministered with low dose ritonavir may increase plasma concentrations of darunavir. darunavir AUC24h ↑ 33% (based on population pharmacokinetic model)	Caution is warranted and clinical monitoring is recommended, when coadministration of clotrimazole is required.
ANTIGOUT MEDICINES		
Colchicine	Not studied. Concomitant use of colchicine and darunavir coadministered with low dose ritonavir may increase the exposure to colchicine.	A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir is required. Patients with renal or hepatic impairment should not be given colchicine with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir (see section 4.4).
ANTIMALARIALS		
Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours	artemether AUC ↓ 16% artemether Cmin ↔ artemether Cmax ↓ 18% dihydroartemisinin AUC ↓ 18% dihydroartemisinin Cmin ↔ dihydroartemisinin Cmax ↓ 18% lumefantrine AUC ↑ 175% lumefantrine Cmin ↑ 126% lumefantrine Cmax ↑ 65% darunavir AUC ↔ darunavir Cmin ↓ 13% darunavir Cmax ↔	The combination of [NATIONALLY COMPLETED NAME] 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 Rifapentine	Not studied. Rifapentine and rifampicin are strong CYP3A inducers and have been shown to cause profound decreases in concentrations of other protease inhibitors, which can result in virological failure and resistance development (CYP450 enzyme induction). During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with low dose ritonavir, a high frequency of liver reactions was seen with	The combination of rifapentine and [NATIONALLY COMPLETED NAME] with concomitant low dose ritonavir is not recommended. The combination of rifampicin and [NATIONALLY COMPLETED NAME] with concomitant low dose ritonavir is contraindicated (see section 4.3).

Rifabutin 150 mg once every other day	rifabutin AUC** ↑ 55% rifabutin Cmin** ↑ ND rifabutin Cmax ** ↔ darunavir AUC ↑ 53% darunavir Cmin ↑ 68% darunavir Cmax ↑ 39% ** sum of active moieties of rifabutin (parent drug + 25-*O*-desacetyl metabolite) The interaction trial showed a comparable daily systemic exposure for rifabutin between treatment at 300 mg once daily alone and 150 mg once every other day in combination with [NATIONALLY COMPLETED NAME]/ritonavir (600/100 mg twice daily) with an about 10-fold increase in the daily exposure to the active metabolite 25-*O*-desacetylrifabutin. Furthermore, AUC of the sum of active moieties of rifabutin (parent drug + 25*O*-desacetyl metabolite) was increased 1.6-fold, while Cmax remained comparable. Data on comparison with a 150 mg once daily reference dose is lacking. (Rifabutin is an inducer and substrate of CYP3A.) An increase of systemic exposure to darunavir was observed	A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e. rifabutin 150 mg once every other day) and increased monitoring for rifabutin related adverse events is warranted in patients receiving the combination. In case of safety issues, a further increase of the dosing interval for rifabutin and/or monitoring of rifabutin levels should be considered. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients. Based upon the safety profile of [NATIONALLY COMPLETED NAME]/ritonavir, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for [NATIONALLY COMPLETED NAME]/ritonavir. Based on pharmacokinetic modeling, this dosage reduction of 75% is also applicable if patients receive rifabutin at doses other than 300 mg/day.
ANTINEOPLASTICS	when [NATIONALLY COMPLETED	
Dasatinib Nilotinib Vinblastine Vincristine Everolimus	Not studied. [NATIONALLY COMPLETED NAME] is expected to increase these antineoplastic plasma concentrations. (CYP3A inhibition)	Concentrations of these medicinal products may be increased when coadministered with [NATIONALLY COMPLETED NAME] with low dose ritonavir resulting in the potential for increased adverse events usually associated with these agents. Caution should be exercised when combining one of these antineoplastic agents with [NATIONALLY COMPLETED NAME] with low dose ritonavir. Concominant use of everolimus and [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir is not recommended.
ANTIPLATELETS		

Ticagrelor	Not studied. Co-administration with darunavir boosted with low dose ritonavir may lead to a substantial increase in exposure to ticagrelor	Concomitant administration of [NATIONALLY COMPLETED NAME] with low dose ritonavir with ticagrelor is contraindicated. Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended.
ANTIPSYCHOTICS/NEUROLEPTICS		
Quetiapine	Due to CYP3A inhibition by darunavir, concentrations of the antipsychotics / neuroleptics are expected to increase.	Concomitant administration of [NATIONALLY COMPLETED NAME] with low dose ritonavir and quetiapine is contraindicated as it may increase quetiapine-related toxicity. Increased concentrations of quetiapine may lead to coma.
Risperidone Thioridazine Pimozide Sertindole	Not studied. [NATIONALLY COMPLETED NAME] is expected to increase these antipsychotic plasma concentrations. (CYP2D6 inhibition and/or P-gp)	A dose decrease may be needed for these drugs when co-administered with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir. Concominant administration of [NATIONALLY COMPLETED NAME] with low dose ritonavir and pimozide or sertindole is contraindicated.
β-BLOCKERS		
Carvedilol Metoprolol Timolol	Not Studied. [NATIONALLY COMPLETED NAME] is expected to increase these β-blocker plasma concentrations. (CYP2D6 inhibition)	Clinical monitoring is recommended when co-administering [NATIONALLY COMPLETED NAME] with β-blockers. A lower dose of the βblocker should be considered.
CALCIUM CHANNEL BLOCKERS		
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Not studied. [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir can be expected to increase the plasma concentrations of calcium channel blockers. (CYP3A and/or CYP2D6 inhibition)	Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with [NATIONALLY COMPLETED NAME] with low dose ritonavir.
CORTICOSTEROIDS		

Fluticasone Budesonide	In a clinical study where ritonavir 100 mg capsules twice daily were coadministered with 50 g intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, fluticasone propionate plasma concentrations increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% CI 82-89%). Greater effects may be expected when fluticasone is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone; this could also occur with other corticosteroids metabolised via the P4503A pathway, e.g., budesonide. The effects of high fluticasone systemic	Concomitant administration of [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid which is not a substrate for CYP3A (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids, progressive dose reduction may have to be performed over a longer period.
Dexamethasone (systemic)	exposureNot studied. on Dexamethasoneritonavir plasma levels may are decrease plasma concentrations of darunavir. (CYP3A induction)	Systemic dexamethasone should be used with caution when combined with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir.
Prednisone	Not studied. Darunavir may increase plasma concentrations of prednisone. (CYP3A inhibition)	Concomitant use of [NATIONALLY COMPLETED NAME] with low dose ritonavir and prednisone may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Clinical monitoring is recommended when coadministering [NATIONALLY COMPLETED NAME] with low dose ritonavir with corticosteroids.
ENDOTHELIN RECEPTOR ANTAGONISTS		
Bosentan	Not studied. Concomitant use of bosentan and darunavir coadministered with low dose ritonavir may increase plasma concentrations of bosentan.	When administered concomitantly with [NATIONALLY COMPLETED NAME] and low dose ritonavir, the patient's tolerability of bosentan should be monitored.
HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS		
NS3-4A protease inhibitors		

Telaprevir 750 mg every 8 hours	telaprevir AUC ↓ 35% telaprevir Cmin ↓ 32% telaprevir Cmax ↓ 36% darunavir AUC12 ↓ 40% darunavir Cmin ↓ 42% darunavir Cmax ↓ 40%	It is not recommended to coadminister [NATIONALLY COMPLETED NAME] with low dose ritonavir and telaprevir

Boceprevir 800 mg three times daily	boceprevir AUC ↓ 32% boceprevir Cmin ↓ 35% boceprevir Cmax ↓ 25% darunavir AUC ↓ 44% darunavir Cmin ↓ 59% darunavir Cmax ↓ 36%	It is not recommended to coadminister [NATIONALLY COMPLETED NAME] with low dose ritonavir and boceprevir.
Simeprevir	simeprevir AUC ↑ 159% simeprevir Cmin ↑ 358% simeprevir Cmax ↑ 79% darunavir AUC ↑ 18% darunavir Cmin ↑ 31% darunavir Cmax □ The dose of simeprevir in this interaction study was 50 mg when coadministered in combination with darunavir/ritonavir, compared to 150 mg in the simeprevir alone treatment group.	It is not recommended to coadminister [NATIONALLY COMPLETED NAME] with low dose ritonavir and simeprevir.
HERBAL PRODUCTS		
St John's wort *(Hypericum perforatum)*	Not studied. St John's wort is expected to decrease the plasma concentrations of darunavir and ritonavir. (CYP450 induction)	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir must not be used concomitantly with products containing St John's wort (*Hypericum perforatum*) (see section 4.3). If a patient is already taking St John's wort, stop St John's wort and if possible check viral levels. Darunavir exposure (and also ritonavir exposure) may increase on stopping St John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort.
HMG CO-A REDUCTASE INHIBITORS		

Lovastatin Simvastatin	Not studied. Lovastatin and simvastatin are expected to have markedly increased plasma concentrations when co-administered with darunavir coadministered with low dose ritonavir. (CYP3A inhibition)	Increased plasma concentrations of lovastatin or simvastatin may cause myopathy, including rhabdomyolysis. Concomitant use of [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir with lovastatin and simvastatin is therefore contraindicated (see section 4.3).

Atorvastatin 10 mg once daily	atorvastatin AUC ↑ 3-4 fold atorvastatin Cmin ↑ ≈5.5-10 fold atorvastatin Cmax ↑ ≈2 fold #darunavir	When administration of atorvastatin and [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir is desired, it is recommended to start with an atorvastatin dose of 10 mg once daily. A gradual dose increase of atorvastatin may be tailored to the clinical response.
Pravastatin 40 mg single dose	pravastatin AUC ↑ 81%¶ pravastatin Cmin ND pravastatin Cmax ↑ 63% ¶ an up to five-fold increase was seen in a limited subset of subjects	When administration of pravastatin and [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effect while monitoring for safety.
Rosuvastatin 10 mg once daily	rosuvastatin AUC ↑ 48%‖ rosuvastatin Cmax ↑ 144%‖ ‖ based on published data	When administration of rosuvastatin and [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir is required, it is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety.
H2-RECEPTOR ANTAGONISTS		
Ranitidine 150 mg twice daily	#darunavir AUC ↔ #darunavir Cmax ↔ #darunavir Cmax ↔	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir can be co-administered with H2-receptor antagonists without dose adjustments.
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus Everolimus	Not studied. Exposure to these immunosuppressants will be increased when co-administered with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir. (CYP3A inhibition)	Therapeutic drug monitoring of the immunosuppressive agent must be done when co-administration occurs. Concomitant use of everolimus and [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir is not recommended.
INHALED BETA AGONISTS		

Salmeterol	Not studied. Concomitant use of salmeterol and darunavir coadministered with low dose ritonavir may increase plasma concentrations of salmeterol.	Concomitant use of salmeterol and [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse event with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESICS / TREATMENT OF OPIOID DEPENDENCE		
Methadone individual dose ranging from 55 mg to 150 mg once daily	R(-) methadone AUC ↓ 16% R(-) methadone Cmin ↓ 15% R(-) methadone Cmax ↓ 24%	No adjustment of methadone dosage is required when initiating coadministration with [NATIONALLY COMPLETED NAME]/ritonavir. However, increased methadone dose may be necessary when concomitantly administered for a longer period of time due to induction of metabolism by ritonavir. Therefore, clinical monitoring is recommended, as maintenance therapy may need to be adjusted in some patients.
Buprenorphine/naloxone 8/2 mg–16/4 mg once daily	buprenorphine AUC ↓ 11% buprenorphine Cmin ↔ buprenorphine Cmax ↓ 8% norbuprenorphine AUC ↑ 46% norbuprenorphine Cmin ↑ 71% norbuprenorphine Cmax ↑ 36% naloxone AUC ↔ naloxone Cmin ND naloxone Cmax ↔	The clinical relevance of the increase in norbuprenorphine pharmacokinetic parameters has not been established. Dose adjustment for buprenorphine may not be necessary when coadministered with [NATIONALLY COMPLETED NAME]/ritonavir but a careful clinical monitoring for signs of opiate toxicity is recommended.
OESTROGEN-BASED CONTRACEPTIVES		
Ethinylestradiol Norethindrone 35 g/1 mg once daily	ethinylestradiol AUC ↓ 44% ethinylestradiol Cmin ↓ 62% ethinylestradiol Cmax ↓ 32% norethindrone AUC ↓ 14% norethindrone Cmin ↓ 30% norethindrone Cmax ↔	Alternative or additional contraceptive measures are recommended when oestrogen-based contraceptives are co-administered with [NATIONALLY COMPLETED NAME] and low dose ritonavir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.
PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS		

For the treatment of erectile dysfunction Avanafil Sildenafil Tadalafil Vardenafil	In an interaction study #, a comparable systemic exposure to sildenafil was observed for a single intake of 100 mg sildenafil alone and a single intake of 25 mg sildenafil co-administered with [NATIONALLY COMPLETED NAME] and low dose ritonavir.	The combination of avanafil and [NATIONALLY COMPLETED NAME] with low dose ritonavir is contraindicated (see section 4.3). Concomitant use of other PDE-5 inhibitors for the treatment of erectile dysfunction with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir should be done with caution. If concomitant use of [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir 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
For the treatment of pulmonary arterial hypertension Sildenafil Tadalafil	Not studied. Concomitant use of sildenafil or tadalafil for the treatment of pulmonary arterial hypertension and darunavir co-administered with low dose ritonavir may increase plasma concentrations of sildenafil or tadalafil.	A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension co-administered with [NATIONALLY COMPLETED NAME] and low dose ritonavir has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension, prolonged erection and syncope). Therefore, coadministration of [NATIONALLY COMPLETED NAME] with low dose ritonavir 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 [NATIONALLY COMPLETED NAME] and low dose ritonavir is not recommended.
PROTON PUMP INHIBITORS		
Omeprazole 20 mg once daily	#darunavir AUC ↔ # darunavir Cmin ↔ # darunavir Cmax ↔	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir can be co-administered with proton pump inhibitors without dose adjustments.
SEDATIVES/HYPNOTICS		

Buspirone Clorazepate Diazepam Estazolam Flurazepam Triazolam Zoldipem	Not studied. Sedative/hypnotics are extensively metabolised by CYP3A. Coadministration with [NATIONALLY COMPLETED NAME]/ritonavir may cause a large increase in the concentration of these medicines.	Clinical monitoring is recommended when co-administering [NATIONALLY COMPLETED NAME] with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir is contraindicated with triazolam.
Midazolam	Based on data for other CYP3A inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir. If parenteral midazolam is coadministered with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir it may cause a large increase in the concentration of this benzodiazepine. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels.	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir is contraindicated with orally administered midazolam (see section 4.3); whereas, caution should be used with co-administration of [NATIONALLY COMPLETED NAME] with low dose ritonavir and parenteral midazolam. If parenteral midazolam is coadministered with [NATIONALLY COMPLETED NAME] with a low dose ritonavir, it should be done in an intensive care unit (ICU) 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.

† The efficacy and safety of the use of [NATIONALLY COMPLETED NAME] with 100 mg ritonavir and any other HIV PI (e.g. (fos)amprenavir, nelfinavir and tipranavir) has not been established in HIV patients. According to current treatment guidelines, dual therapy with protease inhibitors is generally not recommended

4.6 Fertility, pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account.

There are no adequate and well controlled studies with darunavir 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).

[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk.

Breast-feeding
It is not known whether darunavir is excreted in human milk. Studies in rats have demonstrated that darunavir is excreted in milk and at high levels (1,000 mg/kg/day) resulted in toxicity. 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 under any circumstances if they are receiving [NATIONALLY COMPLETED NAME].

Fertility
No human data on the effect of darunavir on fertility are available. There was no effect on mating or fertility with darunavir treatment in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

[NATIONALLY COMPLETED NAME] in combination with ritonavir has no or negligible influence on the ability to drive and use machines. However, dizziness has been reported in some patients during treatment with regimens containing [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and should be borne in mind when considering a patient's ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
During the clinical development program (N=2,613 treatment-experienced subjects who initiated therapy with [NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily), 51.3% of subjects experienced at least one adverse reaction. The total mean treatment duration for subjects was 95.3 weeks. The most frequent adverse reactions reported in clinical trials and as spontaneous reports are diarrhoea, nausea, rash, headache and vomiting. The most frequent serious reactions are acute renal failure, myocardial infarction, immune reconstitution inflammatory syndrome, thrombocytopenia, osteonecrosis, diarrhoea, hepatitis and pyrexia.

In the 96 week analysis, the safety profile of [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily in treatment-naïve subjects was similar to that seen with [NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily in treatment-experienced subjects except for nausea which was observed more frequently in treatment-naïve subjects. This was driven by mild intensity nausea. No new safety findings were identified in the 192 week analysis of the treatment-naïve subjects in which the mean treatment duration of [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily was 162.5 weeks.

Tabulated list of adverse reactions
Adverse reactions are listed by system organ class (SOC) and frequency category. Within each frequency category, adverse reactions are presented in order of decreasing seriousness. 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).

Adverse reactions in clinical trials and post-marketing

MedDRA system organ class **Frequency category**	**Adverse reaction**
Infections and infestations	
uncommon	herpes simplex

Blood and lymphatic system disorders	
uncommon	thrombocytopenia, neutropenia, anaemia, leukopenia
rare	increased eosinophil count
Immune system disorders	
uncommon	immune reconstitution inflammatory syndrome, (drug) hypersensitivity
Endocrine disorders	
uncommon	hypothyroidism, increased blood thyroid stimulating hormone
Metabolism and nutrition disorders	
common	lipodystrophy (including lipohypertrophy, lipodystrophy, lipoatrophy), diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia
uncommon	gout, anorexia, decreased appetite, decreased weight, increased weight, hyperglycaemia, insulin resistance, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase
Psychiatric disorders	
common	insomnia
uncommon	depression, disorientation, anxiety, sleep disorder, abnormal dreams, nightmare, decreased libido
	confusional state, altered mood, restlessness
rare	
Nervous system disorders	
common	headache, peripheral neuropathy, dizziness
uncommon	lethargy, paraesthesia, hypoaesthesia, dysgeusia, disturbance in attention, memory impairment, somnolence
rare	syncope, convulsion, ageusia, sleep phase rhythm disturbance
Eye disorders	
uncommon conjunctival hyperaemia, dry eye rare visual disturbance	
Ear and labyrinth disorders	
uncommon	vertigo

Cardiac disorders	
uncommon	myocardial infarction, angina pectoris, prolonged electrocardiogram QT, tachycardia
rare	acute myocardial infarction, sinus bradycardia, palpitations
Vascular disorders	
uncommon	hypertension, flushing
Respiratory, thoracic and mediastinal disorders	
uncommon	dyspnoea, cough, epistaxis, throat irritation
rare	rhinorrhoea
Gastrointestinal disorders	
very common	diarrhoea
common	vomiting, nausea, abdominal pain, increased blood amylase, dyspepsia, abdominal distension, flatulence
uncommon	pancreatitis, gastritis, gastrooesophageal reflux disease, aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia
rare	stomatitis, haematemesis, cheilitis, dry lip, coated tongue
Hepatobiliary disorders	
common	increased alanine aminotransferase
uncommon	hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased gamma-glutamyltransferase
Skin and subcutaneous tissue disorders	

common	rash (including macular, maculopapular, papular, erythematous and pruritic rash), pruritus
uncommon	angioedema, generalised rash, allergic dermatitis, urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, dry skin, nail pigmentation
rare	DRESS, Stevens-Johnson syndrome, erythema multiforme, dermatitis, seborrhoeic dermatitis, skin lesion, xeroderma
not known	toxic epidermal necrolysis, acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders	
uncommon	myalgia, osteonecrosis, muscle spasms, muscular weakness, arthralgia, pain in extremity, osteoporosis, increased blood creatine phosphokinase
rare	musculoskeletal stiffness, arthritis, joint stiffness
Renal and urinary disorders	
uncommon	acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria
rare	decreased creatinine renal clearance
Reproductive system and breast disorders	
uncommon	erectile dysfunction, gynaecomastia
General disorders and administration site conditions	
common	asthenia, fatigue
uncommon	pyrexia, chest pain, peripheral oedema, malaise, feeling hot, irritability, pain
rare	chills, abnormal feeling, xerosis

Description of selected adverse reactions

Rash
In clinical trials, rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. In cases of severe skin reaction see the warning in section 4.4.

During the clinical development program of raltegravir in treatment-experienced patients, rash, irrespective of causality, was more commonly observed with regimens containing [NATIONALLY COMPLETED NAME] + raltegravir compared to those containing [NATIONALLY COMPLETED

NAME] without raltegravir or raltegravir without [NATIONALLY COMPLETED NAME]. Rash considered by the investigator to be drug-related occurred at similar rates. The exposure-adjusted rates of rash (all causality) were 10.9, 4.2, and 3.8 per 100 patient-years (PYR), respectively; and for drug-related rash were 2.4, 1.1, and 2.3 per 100 PYR, respectively. The rashes observed in clinical studies were mild to moderate in severity and did not result in discontinuation of therapy (see section 4.4).

Lipodystrophy
Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see section 4.4).

Metabolic abnormalities
Combination antiretroviral therapy has also been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

Musculoskeletal abnormalities
Increased CPK, myalgia, myositis and rarely, rhabdomyolysis have been reported with the use of protease inhibitors, particularly in combination with NRTIs.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (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 initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) 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).

Paediatric population
The safety assessment in paediatric patients is based on the 48-week analysis of safety data from three Phase II trials. The following patient populations were evaluated (see section 5.1):

- 80 ART-experienced HIV-1 infected paediatric patients aged from 6 to 17 years and weighing at least 20 kg who received darunavir tablets with low dose ritonavir twice daily in combination with other antiretroviral agents.
- 21 ART-experienced HIV-1 infected paediatric patients aged from 3 to < 6 years and weighing 10 kg to < 20 kg (16 participants from 15 kg to < 20 kg) who received darunavir oral suspension with low dose ritonavir twice daily in combination with other antiretroviral agents.
- 12 ART-naïve HIV-1 infected paediatric patients aged from 12 to 17 years and weighing at least 40 kg who received darunavir tablets with low dose ritonavir once daily in combination with other antiretroviral agents (see section 5.1).

Overall, the safety profile in these paediatric patients was similar to that observed in the adult population.

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

Among 1,968 treatment-experienced patients receiving [NATIONALLY COMPLETED NAME] coadministered 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 (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 [NATIONALLY COMPLETED NAME] coadministered with low dose ritonavir is limited. Single doses up to 3,200 mg of darunavir as oral solution alone and up to 1,600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

There is no specific antidote for overdose with [NATIONALLY COMPLETED NAME]. Treatment of overdose with [NATIONALLY COMPLETED NAME] consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis.
Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitors, ATC code: J05AE10.

Mechanism of ac tion
Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (KD of

4.5×10^{-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.

Antiviral activity *in vitro*
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 peripheral blood mononuclear cells and human monocytes/macrophages with median EC50 values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/ml). Darunavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC50 values ranging from < 0.1 to 4.3 nM.

These EC50 values are well below the 50% cellular toxicity concentration range of 87 µM to > 100 µM.

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: 23-50fold) 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.

The clinical trial data from ART-experienced patients (*TITAN* trial and the pooled analysis of the *POWER* 1, 2 and 3 and *DUET* 1 and 2 trials) showed that virologic response to [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir was decreased when 3 or more darunavir RAMs (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V and L89V) were present at baseline or when these mutations developed during treatment.

Increasing baseline darunavir fold change in EC50 (FC) was associated with decreasing virologic response. A lower and upper clinical cut-off of 10 and 40 were identified. Isolates with baseline FC ≤ 10 are susceptible; isolates with FC > 10 to 40 have decreased susceptibility; isolates with FC > 40 are resistant (see Clinical results).

Viruses isolated from patients on [NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily experiencing virologic failure by rebound that were susceptible to tipranavir at baseline remained susceptible to tipranavir after treatment in the vast majority of cases.

The lowest rates of developing resistant HIV virus are observed in ART-naïve patients who are treated for the first time with darunavir in combination with other ART.

The table below shows the development of mutations and loss of susceptibility to PIs in virologic failures at endpoint in the *ARTEMIS*, *ODIN* and *TITAN* trials.

	ARTEMIS	ODIN		TITAN
	[NATIONALLY COMPLETED NAME]/ ritonavir 800/100 mg once daily N=343	[NATIONALLY COMPLETED NAME]/ ritonavir 800/100 mg once daily N=294	[NATIONALLY COMPLETED NAME]/ ritonavir 600/100 mg twice daily N=296	[NATIONALLY COMPLETED NAME]/ ritonavir 600/100 mg twice daily N=298
Total number of virologic failures[a], n (%) Rebounders Never suppressed	55 (16.0%) 39 (11.4%) 16 (4.7%)	65 (22.1%) 11 (3.7%) 54 (18.4%)	54 (18.2%) 11 (3.7%) 43 (14.5%)	31 (10.4%) 16 (5.4%) 15 (5.0%)
subjects Number of subjects with virologic failure and paired baseline/endpoint genotypes, developing mutations[b] at endpoint, n/N				
Primary (major) PI mutations PI RAMs	0/43 4/43	1/60 7/60	0/42 4/42	6/28 10/28
Number of subjects with virologic failure and paired baseline/endpoint phenotypes, showing loss of susceptibility to PIs at endpoint compared to baseline, n/N				

PI darunavir				
amprenavir	0/39	1/58	0/41	3/26
atazanavir	0/39	1/58	0/40	0/22
indinavir	0/39	2/56	0/40	0/22
lopinavir	0/39	2/57	0/40	1/24
saquinavir	0/39	1/58	0/40	0/23
tipranavir	0/39	0/56	0/40	0/22
	0/39	0/58	0/41	1/25

a TLOVR non-VF censored algorithm based on HIV-1 RNA < 50 copies/ml, except for *TITAN* (HIV-1 RNA < 400 copies/ml)

b IAS-USA lists

Cross-resistance

Darunavir FC was less than 10 for 90% of 3,309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to most PIs remain susceptible to darunavir.

In the virologic failures of the *ARTEMIS* trial no cross-resistance with other PIs was observed.

Clinical results

Adult patients

For clinical trial results in ART-naïve adult patients, refer to the Summary of Product Characteristics for [NATIONALLY COMPLETED NAME] 400 mg and 800 mg tablets or 100 mg/ml oral suspension.

Efficacy of NATIONALLY COMPLETED NAME] 600 mg twice daily co-administered with 100 mg ritonavir twice daily in ART-experienced patients

The evidence of efficacy of [NATIONALLY COMPLETED NAME] co-administered with ritonavir (600/100 mg twice daily) in ART-experienced patients is based on the 96 weeks analysis of the Phase III trial *TITAN* in ART-experienced lopinavir naïve patients, on the 48 week analysis of the Phase III trial *ODIN* in ART-experienced patients with no DRV-RAMs, and on the analyses of 96 weeks data from the Phase IIb trials *POWER* 1 and 2 in ART-experienced patients with high level of PI resistance.

TITAN is a randomised, controlled, open-label Phase III trial comparing [NATIONALLY COMPLETED NAME] co-administered with ritonavir (600/100 mg twice daily) versus lopinavir/ritonavir (400/100 mg twice daily) in ART-experienced, lopinavir naïve HIV-1 infected adult patients. Both arms used an Optimised Background Regimen (OBR) consisting of at least 2 antiretrovirals (NRTIs with or without NNRTIs).

The table below shows the efficacy data of the 48 week analysis from the *TITAN* trial.

TITAN			
Outcomes	[NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily + OBR N=298	Lopinavir/ritonavir 400/100 mg twice daily + OBR N=297	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/ml[a]	70.8% (211)	60.3% (179)	10.5% (2.9; 18.1)[b]
median CD4+ cell count change from baseline (x 10 6 c /l)	88	81	

[a] Imputations according to the TLOVR algorithm [b] Based on a normal approximation of the difference in % response [c] NC=F

At 48 weeks non-inferiority in virologic response to the [NATIONALLY COMPLETED NAME]/ritonavir treatment, defined as the percentage of patients with plasma HIV-1 RNA level < 400 and < 50 copies/ml, was demonstrated (at the pre-defined 12% non-inferiority margin) for both ITT and OP populations. These results were confirmed in the analysis of data at 96 weeks of treatment in the *TITAN* trial, with 60.4% of patients in the [NATIONALLY COMPLETED NAME]/ritonavir arm having HIV-1 RNA < 50 copies/ml at week 96 compared to 55.2% in the lopinavir/ritonavir arm [difference: 5.2%, 95% CI (-2.8; 13.1)].

ODIN is a Phase III, randomised, open-label trial comparing [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily versus [NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily in ART-experienced HIV-1 infected patients with screening genotype resistance testing showing no darunavir RAMs (i.e. V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) and a screening HIV-1 RNA > 1,000 copies/ml. Efficacy analysis is based on 48 weeks of treatment (see table below). Both arms used an optimised background regimen (OBR) of ≥ 2 NRTIs.

ODIN			
Outcomes	[NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily + OBR N=294	[NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily + OBR N=296	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/ml[a]	72.1% (212)	70.9% (210)	1.2% (-6.1; 8.5)[b]
With Baseline HIV-1 RNA (copies/ml)			
< 100,000	77.6% (198/255)	73.2% (194/265)	4.4% (-3.0; 11.9)
≥ 100,000	35.9% (14/39)	51.6% (16/31)	-15.7% (-39.2; 7.7)
With Baseline CD4+ cell count (x 10^6/l)			
≥ 100	75.1% (184/245)	72.5% (187/258)	2.6% (-5.1; 10.3)
< 100	57.1% (28/49)	60.5% (23/38)	-3.4% (-24.5; 17.8)
With HIV-1 clade			
Type B	70.4% (126/179)	64.3% (128/199)	6.1% (-3.4; 15.6)
Type AE	90.5% (38/42)	91.2% (31/34)	-0.7% (-14.0; 12.6)
Type C	72.7% (32/44)	78.8% (26/33)	-6.1% (-2.6; 13.7)
Other[c]	55.2% (16/29)	83.3% (25/30)	-28.2% (-51.0; -5.3)

mean CD4+ cell count change from baseline (x 10^6/l)[e]	108	112	-5[d] (-25; 16)

[a] Imputations according to the TLOVR algorithm [b] Based on a normal approximation of the difference in % response [c] Clades A1, D, F1, G, K, CRF02_AG, CRF12_BF, and CRF06_CPX [d] Difference in means [e] Last Observation Carried Forward imputation

At 48 weeks, virologic response, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/ml, with [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily treatment was demonstrated to be non-inferior (at the pre-defined 12% non-inferiority margin) compared to [NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily for both ITT and OP populations.

[NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA≥ 100,000 copies/ml or CD4+ cell count < 100 cells x

Outcomes	[NATIONALLY COMPLETED NAME]/ ritonavir 600/100 mg twice daily n=131	Control n=124	Treatment difference	[NATIONALLY COMPLETED NAME]/ ritonavir 600/100 mg twice daily n=131	Control n=124	Treatment difference
HIV RNA < 50 copies/ml[a]	45.0% (59)	11.3% (14)	33.7% (23.4%;	38.9% (51)	8.9% (11)	30.1% (20.1; 40.0)[c]
CD4+ cell count mean change from baseline (x 6 b	103	17	86 (57; 114)[c]	133	15	118 (83.9; 153.4)[c]

10^6/l (see section 4.2 and 4.4). Limited data is available in patients with HIV-1 clades other than B.

POWER 1 *and* ***POWER 2*** are randomised, controlled trials comparing [NATIONALLY COMPLETED NAME] co-administered with ritonavir (600/100 mg twice daily) with a control group receiving an investigator-selected PI(s) regimen in HIV-1 infected patients who had previously failed more than 1 PI containing regimen. An OBR consisting of at least 2 NRTIs with or without enfuvirtide (ENF) was used in both trials.

The table below shows the efficacy data of the 48-week and 96-week analyses from the pooled *POWER* 1 and *POWER* 2 trials.

	POWER 1 and POWER 2 pooled data	
	Week 48	Week 96

10 /l) [a] Imputations according to the TLOVR algorithm [b] Last Observation Carried Forward imputation [c] 95% confidence intervals.

Analyses of data through 96 weeks of treatment in the *POWER* trials demonstrated sustained antiretroviral efficacy and immunologic benefit.

Out of the 59 patients who responded with complete viral suppression (< 50 copies/ml) at week 48, 47 patients (80% of the responders at week 48) remained responders at week 96.

Baseline genotype or phenotype and virologic outcome
Baseline genotype and darunavir FC (shift in susceptibility relative to reference) were shown to be a predictive factor of virologic outcome.

Proportion (%) of patients with response (HIV-1 RNA < 50 copies/ml at week 24) to [NATIONALLY COMPLETED NAME] co-administered with ritonavir (600/100 mg twice daily) by baseline genotype[a], and baseline darunavir FC and by use of enfuvirtide (ENF): As treated analysis of the POWER and DUET trials.

	Number of baseline mutations[a]				**Baseline DRV FC[b]**			
Response (HIV-1 RNA < 50 copies/ml at week 24)	**All ranges**	**0-2**	**3**	**≥4**	**All ranges**	**≥10**	**10-40**	**> 40**
All patients	45% 455/1,014	54% 359/660	39% 67/172	12% 20/171	45% 455/1,014	55% 364/659	29% 59/203	8% 9/118
Patients with no/non-naïve use of ENF[c]	39% 290/741	50% 238/477	29% 35/120	7% 10/135	39% 290/741	51% 244/477	17% 25/147	5% 5/94
Patients with naïve use of ENF[d]	60% 165/273	66% 121/183	62% 32/52	28% 10/36	60% 165/273	66% 120/182	61% 34/56	17% 4/24

[a] Number of mutations from the list of mutations associated with a diminished response to [NATIONALLY COMPLETED NAME]/ritonavir (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V) [b] fold change in EC_{50}

[c] "Patients with no/non-naïve use of ENF" are patients who did not use ENF or who used ENF but not for the first time

[d] "Patients with naïve use of ENF" are patients who used ENF for the first time

Paediatric patients
For clinical trial results in ART-naïve paediatric patients aged 12 to 17 years, refer to the Summary of Product Characteristics for [NATIONALLY COMPLETED NAME] 400 mg and 800 mg tablets or darunavir 100 mg/ml oral suspension.

ART-experienced paediatric patients from the age of 6 to < 18 years, and weighing at least 20 kg
DELPHI is an open-label, Phase II trial evaluating the pharmacokinetics, safety, tolerability, and

efficacy of [NATIONALLY COMPLETED NAME] with low dose ritonavir in 80 ART-experienced HIV-1 infected paediatric patients aged 6 to 17 years and weighing at least 20 kg. These patients received [NATIONALLY COMPLETED NAME]/ritonavir twice daily in combination with other antiretroviral agents (see section 4.2 for dosage recommendations per body weight). Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 log10 versus baseline.

In the study, patients who were at risk of discontinuing therapy due to intolerance of ritonavir oral solution (e.g. taste aversion) were allowed to switch to the capsule formulation. Of the 44 patients taking ritonavir oral solution, 27 switched to the 100 mg capsule formulation and exceeded the weight-based ritonavir dose without changes in observed safety.

Outcomes at week 48 DE	.PHI[NATIONALLY COMPLETED NAME]/ritonavir N=80
HIV-1 RNA < 50 copies/ml[a]	47.5% (38)
b	147

CD4+ cell count mean change from baseline [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.

According to the TLOVR non-virologic failure censored algorithm 24 (30.0%) patients experienced virological failure, of which 17 (21.3%) patients were rebounders and 7 (8.8%) patients were non-responders.

ART-experienced paediatric patients from the age of 3 to <6 years
The pharmacokinetics, safety, tolerability and efficacy of [NATIONALLY COMPLETED NAME]/ritonavir b.i.d. in combination with other antiretroviral agents in 21 ART-experienced HIV-1 infected paediatric patients aged 3 to< 6 years and weighing 10 kg to < 20 kg was evaluated in an open-label, Phase II trial, ***ARIEL***.
Patients received a weight-based twice daily treatment regimen, patients weighing 10 kg to < 15 kg received darunavir/ritonavir 25/3 mg/kg b.i.d, and patients weighing 15 kg to < 20 kg received darunavir/ritonavir 375/50 mg b.i.d. At week 48, the virologic response, defined as the percentage of patients with confirmed plasma viral load < 50 HIV-1 RNA copies/ml, was evaluated in 16 paediatric patients 15 kg to < 20 kg and 5 paediatric patients 10 kg to < 15 kg receiving [NATIONALLY COMPLETED NAME]/ritonavir in combination with other antiretroviral agents (see section 4.2 for dosage recommendations per body weight).

ARIEL		
Outcomes at week 48	[NATIONALLY COMPLETED NAME]/rit	Darunavir
	10 kg to < 15 kg N=5	15 kg to < 20 kg N=16
HIV-1 RNA < 50 copies/ml[a]	80.0% (4)	81.3% (13)
CD4+ percent change from baseline[b]	4	4
CD4+ cell count mean b change from baseline	16	241

a Imputations according to the TLOVR algorithm.

b NC=F

Limited efficacy data are available in paediatric patients below 15 kg and no recommendation on a posology can be made.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of darunavir, co-administered with ritonavir, have been evaluated in healthy adult volunteers and in HIV-1 infected patients. Exposure to darunavir was higher in HIV-1 infected patients than in healthy subjects. The increased exposure to darunavir in HIV-1 infected patients compared to healthy subjects may be explained by the higher concentrations of α1-acid glycoprotein (AAG) in HIV-1 infected patients, resulting in higher darunavir binding to plasma AAG and, therefore, higher plasma concentrations.

Darunavir is primarily metabolised by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

Absorption

Darunavir was rapidly absorbed following oral administration. Maximum plasma concentration of darunavir in the presence of low dose ritonavir is generally achieved within 2.5-4.0 hours.

The absolute oral 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 overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily (see section 4.4).

When administered without food, the relative bioavailability of darunavir in the presence of low dose ritonavir is 30% lower as compared to intake with food. Therefore, [NATIONALLY COMPLETED NAME] tablets should be taken with ritonavir and with food. The type of food does not affect exposure to darunavir.

Distribution

Darunavir is approximately 95% bound to plasma protein. Darunavir binds primarily to plasma α1acid 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.

Biotransformation

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.

Elimination

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 terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir.
The intravenous clearance of darunavir alone (150 mg) and in the presence of low dose ritonavir was 32.8 l/h and 5.9 l/h, respectively.

Special populations

Paediatric population
The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 74 treatmentexperienced paediatric patients, aged 6 to 17 years and weighing at least 20 kg, showed that the administered weight-based doses of [NATIONALLY COMPLETED NAME]/ritonavir resulted in darunavir exposure comparable to that in adults receiving [NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 14 treatmentexperienced paediatric patients, aged 3 to < 6 years and weighing at least 15 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving [NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily (see section
4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 12 ART-naïve paediatric patients, aged 12 to < 18 years and weighing at least 40 kg, showed that [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily results in darunavir exposure that was comparable to that achieved in adults receiving [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily. Therefore the same once daily dosage may be used in treatmentexperienced adolescents aged 12 to < 18 years and weighing at least 40 kg 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 4.2).
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 10 treatmentexperienced paediatric patients, aged 3 to < 6 years and weighing at least 14 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily (see section 4.2). In addition, pharmacokinetic modeling and simulation of darunavir exposures in paediatric patients across the ages of 3 to < 18 years confirmed the darunavir exposures as observed in the clinical studies and allowed the identification of weight-based [NATIONALLY COMPLETED NAME]/ritonavir once daily dosing regimens for paediatric patients weighing at least 15 kg that are either ART-naïve or treatment-experienced paediatric patients without 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 4.2). * DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

Elderly
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) (see section 4.4). However, only limited data were available in patients above the age of 65 year.

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

Renal impairment

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 (CrCl between 30-60 ml/min, n=20) (see sections 4.2 and 4.4).

Hepatic impairment
Darunavir is primarily metabolised and eliminated by the liver. In a multiple dose study with [NATIONALLY COMPLETED NAME] co-administered with 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) and100% (Child-Pugh Class B) higher, respectively. The clinical relevance of this increase is unknown therefore, [NATIONALLY COMPLETED NAME] should be used with caution. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see sections
4.2, 4.3 and 4.4).

5.3 Preclinical safety data
Animal toxicology studies have been conducted at exposures up to clinical exposure levels with darunavir alone, in mice, rats and dogs and in combination with ritonavir in rats and dogs.

In repeated-dose toxicology studies in mice, rats and dogs, there were only limited effects of treatment with darunavir. In rodents the target organs identified were the haematopoietic system, the blood coagulation system, liver and thyroid. A variable but limited decrease in red blood cell-related parameters was observed, together with increases in activated partial thromboplastin time.

Changes were observed in liver (hepatocyte hypertrophy, vacuolation, increased liver enzymes) and thyroid (follicular hypertrophy). In the rat, the combination of darunavir with ritonavir lead to a small increase in effect on RBC parameters, liver and thyroid and increased incidence of islet fibrosis in the pancreas (in male rats only) compared to treatment with darunavir alone. In the dog, no major toxicity findings or target organs were identified up to exposures equivalent to clinical exposure at the recommended dose.

In a study conducted in rats, the number of corpora lutea and implantations were decreased in the presence of maternal toxicity. Otherwise, there were no effects on mating or fertility with darunavir treatment up to 1,000 mg/kg/day and exposure levels below (AUC-0.5 fold) of that in human at the clinically recommended dose. Up to same dose levels, there was no teratogenicity with darunavir in rats and rabbits when treated alone nor in mice when treated in combination with ritonavir. The exposure levels were lower than those with the recommended clinical dose in humans. In a pre- and postnatal development assessment in rats, darunavir with and without ritonavir, caused a transient reduction in body weight gain of the offspring pre-weaning and there was a slight delay in the opening of eyes and ears. Darunavir in combination with ritonavir caused a reduction in the number

of pups that exhibited the startle response on day 15 of lactation and a reduced pup survival during lactation. These effects may be secondary to pup exposure to the active substance via the milk and/or maternal toxicity. No post weaning functions were affected with darunavir alone or in combination with ritonavir. In juvenile rats receiving darunavir up to days 23-26, increased mortality was observed with convulsions in some animals. Exposure in plasma, liver and brain was considerably higher than in adult rats after comparable doses in mg/kg between days 5 and 11 of age. After day 23 of life, the exposure was comparable to that in adult rats. The increased exposure was likely at least partly due to immaturity of the drug-metabolising enzymes in juvenile animals. No treatment related mortalities were noted in juvenile rats dosed at 1,000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats.

Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, [NATIONALLY COMPLETED NAME] with low dose ritonavir should not be used in paediatric patients below 3 years of age.

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1,000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular and thyroid tumours in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses.

After 2 years administration of darunavir at exposures at or below the human exposure, kidney changes were observed in mice (nephrosis) and rats (chronic progressive nephropathy).

Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Microcrystalline cellulose (E460)
Crospovidone (E1202)
Magnesium stearate (E470b)

Coating:
{[Nationally completed name] 75 mg film-coated tablets}
Poly (vinyl alcohol) (E1203)
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)

{[Nationally completed name] 150 mg film-coated tablets}
Poly (vinyl alcohol) (E1203)
Titanium dioxide (E171)

Macrogol (E1521)
Talc (E553b)

{[Nationally completed name] 300 mg film-coated tablets}
Poly (vinyl alcohol) (E1203)
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)
Sunset yellow FCF (E110)

{[Nationally completed name] 600 mg film-coated tablets}
Poly (vinyl alcohol) (E1203)
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)
Sunset yellow FCF (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

1 year

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

High Density Polyethylene (HDPE) bottles stoppered with polypropylene (PP) child resistant closure.
Packsizes:

Aluminium-PVC/PE/PVDC blisters.

Packsizes:

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

{[Nationally completed name] 400 mg film-coated tablets}

{[Nationally completed name] 800 mg film-coated tablets}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

{[Nationally completed name] 400 mg film-coated tablets} Each film-coated tablet contains 400 mg darunavir.

Excipient(s) with known effect: Each tablet contains 0.258 mg sunset yellow FCF (E110).

{[Nationally completed name] 800 mg film-coated tablets} Each film-coated tablet contains 800 mg darunavir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

{[Nationally completed name] 400 mg film-coated tablets}
Light orange oval shaped film-coated tablet, debossed with ‘400’ on one side and plain on the other side.
Approx. size

{[Nationally completed name] 800 mg film-coated tablets}
Dark red oval shaped film-coated tablet, debossed with ‘800’ on one side and plain on the other side.
Approx. size

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[NATIONALLY COMPLETED NAME], co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection.

[NATIONALLY COMPLETED NAME], co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV1) infection in adult patients (see section 4.2).

[NATIONALLY COMPLETED NAME] 400 mg [800 mg] tablets may be used to provide suitable dose regimens for the treatment of HIV-1 infection in adult and paediatric patients from the age of 12 years and at least 40 kg body weight who are:

- antiretroviral therapy (ART)-naïve (see section 4.2).
- ART-experienced with no 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. In deciding to initiate treatment with [NATIONALLY COMPLETED NAME] in such ARTexperienced patients, genotypic testing should guide the use of [NATIONALLY COMPLETED NAME] (see sections 4.2, 4.3, 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a health care provider experienced in the management of HIV infection. After therapy with [NATIONALLY COMPLETED NAME] has been initiated, patients should be advised not to alter the dosage, dose form or discontinue therapy without discussing with their health care provider.

The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as pharmacokinetic enhancer. Darunavir may therefore have different contraindications and recommendations for concomitant medications depending on whether the compound is boosted with ritonavir or cobicistat (see sections 4.3, 4.4 and 4.5).

Posology

[NATIONALLY COMPLETED NAME] must always be given orally with cobicistat or low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of cobicistat or ritonavir as appropriate, must therefore be consulted prior to initiation of therapy with [NATIONALLY COMPLETED NAME].
Cobicistat is not indicated for use in twice daily regimens or for use in the pediatric population.

Darunavir is also available as an oral suspension for use in patients who are unable to swallow [NATIONALLY COMPLETED NAME] tablets.

ART-naïve adult patients

The recommended dose regimen is 800 mg once daily with cobicistat 150 mg once daily or ritonavir 100 mg once daily taken with food. [NATIONALLY COMPLETED NAME] 400 mg [800 mg] tablets can be used to construct the once daily 800 mg regimen.

ART-experienced adult patients

The recommended dose regimens are as follows:

- In ART-experienced patients with no 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 4.1) a regimen of 800 mg once daily with cobicistat 150 mg once daily or ritonavir 100 mg once daily taken with food may be used. [NATIONALLY COMPLETED NAME] 400 mg [800 mg] tablets can be used to construct the once daily 800 mg regimen.
- In all other ART-experienced patients or if HIV-1 genotype testing is not available, the recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food. See the Summary of Product Characteristics for darunavir 100 mg/ml oral suspension, 75 mg, 150 mg, 300 mg or 600 mg tablets.

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

ART-naïve paediatric patients (3 to 17 years of age and weighing at least 40 kg)
The recommended dose regimen is 800 mg once daily with ritonavir 100 mg once daily taken with food. The dose of cobicistat to be used with [NATIONALLY COMPLETED NAME] in children less than 18 years of age has not been established.

ART-experienced paediatric patients (3 to 17 years of age and weighing at least 40 kg) The dose of cobicistat to be used with [NATIONALLY COMPLETED NAME] in children less than 18 years of age has not been established.

The recommended dose regimens are as follows:
- In ART-experienced patients without 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 4.1) a regimen of 800 mg once daily with ritonavir 100 mg once daily taken with food may be used. [NATIONALLY COMPLETED NAME] 400 mg [800 mg] tablets can be used to construct the once daily 800 mg regimen.
- In all other ART-experienced patients or if HIV-1 genotype testing is not available, the recommended dose regimen described in the Summary of Product Characteristics for darunavir 100 mg/ml oral suspension,75 mg, 150 mg, 300 mg or 600 mg tablets.

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

Advice on missed doses
If a once daily dose of [NATIONALLY COMPLETED NAME] and/or cobicistat or ritonavir is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of [NATIONALLY COMPLETED NAME] and cobicistat or ritonavir with food as soon as possible. If this is noticed later than 12 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

This guidance is based on the half-life of darunavir in the presence of cobicistat or ritonavir and the recommended dosing interval of approximately 24 hours.

Special populations

Elderly
Limited information is available in this population, and therefore, [NATIONALLY COMPLETED NAME] should be used with caution in this age group (see sections 4.4 and 5.2).

Hepatic impairment
Darunavir is metabolised by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, [NATIONALLY COMPLETED NAME] should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir exposure and a worsening of its safety profile. Therefore, [NATIONALLY COMPLETED NAME] must not be used in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.3, 4.4 and 5.2).

Renal impairment
No dose adjustment is required for darunavir/ritonavir in patients with renal impairment (see sections 4.4 and 5.2). Cobicistat has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients.

Cobicistat inhibits the tubular secretion of creatinine and may cause modest increases in serum creatinine and modest declines in creatinine clearance. Hence, the use of creatinine clearance as an estimate of renal elimination capacity may be misleading. Cobicistat as a pharmacokinetic enhancer of darunavir should, therefore, not be initiated in patients with creatine clearance less than 70 ml/min if any co-administered agent requires dose adjustment based on creatinine clearance: e.g.

emtricitabine, lamivudine, tenofovir disoproxil fumarate or adefovir dipovoxil.
For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Paediatric population
[NATIONALLY COMPLETED NAME] should not be used in paediatric patients below 3 years of age or less than 15 kg body weight (see sections 4.4 and 5.3).

ART-naïve paediatric patients (less than 3 years of age or less than 15 kg body weight) No recommendations on posology can be made in this population.

ART-experienced paediatric patients (3 to 17 years of age and weighing at least 40 kg) Darunavir exposures in treatment-naïve adolescents 12 to 17 years weighing at least 40 kg receiving [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily have been determined and were found to be within the therapeutic range as has been established in adults receiving [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily. As a consequence, since [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily has also been registered for use in treatment-experienced adults 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, the same indication of [NATIONALLY COMPLETED NAME] 800 mg once daily applies to treatment-experienced children 3 to 17 years weighing at least 40 kg. The dose of darunavir with cobicistat has not been established in this patient population.
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

For dosage recommendations in children see the Summary of Product Characteristics for [NATIONALLY COMPLETED NAME]
75 mg, 150 mg, 300 mg, 600 mg tablets and 100 mg/ml oral suspension.

[NATIONALLY COMPLETED NAME] should not be used in children less than 15 kg body weight as the dose for this population has not been established in a sufficient number of patients.
[NATIONALLY COMPLETED NAME] should not be used in children below 3 years of age because of safety concerns.

Method of administration
Patients should be instructed to take [NATIONALLY COMPLETED NAME] with cobicistat or low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir (see sections 4.4, 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Use in patients with severe (Child-Pugh Class C) hepatic impairment.

Concomitant treatment with any of the following medicinal products is contraindicated given the expected decrease in plasma concentrations of darunavir, ritonavir and cobicistat and the potential for loss of therapeutic effect (see sections 4.4 and 4.5).

Applicable to darunavir boosted with either ritonavir or cobicistat:
- The combination product lopinavir/ritonavir (see section 4.5).
- The strong CYP3A inducers rifampicin and herbal preparations containing St John's wort (*Hypericum perforatum*). Co-administration is expected to reduce plasma concentrations of darunavir, ritonavir and cobicistat, which could lead to loss of therapeutic effect and possible development of resistance (see sections 4.4 and 4.5).

Applicable to darunavir boosted with cobicistat, not when boosted with ritonavir:

- Darunavir boosted with cobicistat is more sensitive for CYP3A induction than darunavir boosted with ritonavir. Concomitant use with strong CYP3A inducers is contraindicated, since these may reduce the exposure to cobicistat and darunavir leading to loss of therapeutic effect. Strong CYP3A inducers include e.g. carbamazepine, phenobarbital and phenytoin (see sections 4.4 and 4.5).

Darunavir boosted with either ritonavir or cobicistat inhibits the elimination of active substances that are highly dependent on CYP3A for clearance, which results in increased exposure to the coadministered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (applies to darunavir boosted with either ritonavir or cobicistat). These active substances include e.g.:
- alfuzosin (alpha 1-adrenoreceptor antagonist)
- amiodarone, bepridil, dronedarone, quinidine, ranolazine, systemic lidocaine (antiarrhythmics/antianginals)
- astemizole, terfenadine (antihistamines)
- colchicine when used in patients with renal and/or hepatic impairment (antigout) (see section - 4.5)
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- cisapride (gastrointestinal motility agents)
- pimozide, quetiapine, sertindole (antipsychotics/neuroleptics) (see section 4.5)
- triazolam, midazolam administered orally (sedatives/hypnotics) (for caution on parenterally administered midazolam, see section 4.5)
- sildenafil - when used for the treatment of pulmonary arterial hypertension, avanafil (PDE-5 inhibitors)
- simvastatin and lovastatin (HMG-CoA reductase inhibitors) (see section 4.5) - ticagrelor (antiplatelets) (see section 4.5).

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy 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.

Regular assessment of virological response is advised. In the setting of lack or loss of virological response, resistance testing should be performed.

[NATIONALLY COMPLETED NAME] must always be given orally with cobicistat or low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products (see section 5.2). The Summary of Product Characteristics of cobicistat or ritonavir as appropriate, must therefore be consulted prior to initiation of therapy with [NATIONALLY COMPLETED NAME].

Increasing the dose of ritonavir from that recommended in section 4.2 did not significantly affect darunavir concentrations. It is not recommended to alter the dose of cobicistat or ritonavir.

Darunavir binds predominantly to 1-acid glycoprotein. This protein binding is concentrationdependent indicative for saturation of binding. Therefore, protein displacement of medicinal products highly bound to 1-acid glycoprotein cannot be ruled out (see section 4.5).

ART-experienced patients – once daily dosing
[NATIONALLY COMPLETED NAME] used in combination with cobicistat or low dose ritonavir once daily in ART-experienced patients should not be used in patients with one or more darunavir

resistance associated mutations (DRV-RAMs) or HIV-1 RNA ≥ 100,000 copies/ml or CD4+ cell count < 100 cells x 10^6/l (see section 4.2). Combinations with optimised background regimen (OBRs) other than ≥ 2 NRTIs have not been studied in this population. Limited data are available in patients with HIV-1 clades other than B (see section 5.1).

Paediatric population
[NATIONALLY COMPLETED NAME] is not recommended for use in paediatric patients below 3 years of age or less than 15 kg body weight (see sections 4.2 and 5.3).

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

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. [NATIONALLY COMPLETED NAME] 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 by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Rash occurred more commonly in treatment-experienced patients receiving regimens containing [NATIONALLY COMPLETED NAME]/ritonavir + raltegravir compared to patients receiving [NATIONALLY COMPLETED NAME]/ritonavir without raltegravir or raltegravir without [NATIONALLY COMPLETED NAME] (see section 4.8).

Darunavir contains a sulphonamide moiety. [NATIONALLY COMPLETED NAME] should be used with caution in patients with a known sulphonamide allergy.

Hepatotoxicity
Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with [NATIONALLY COMPLETED NAME]. During the darunavir/ritonavir clinical development program (N=3,063), hepatitis was reported in 0.5% of patients receiving combination antiretroviral therapy with [NATIONALLY COMPLETED NAME]/ritonavir. Patients with pre-existing liver dysfunction, including chronic active 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 [NATIONALLY COMPLETED NAME] used in combination with cobicistat or low dose ritonavir 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 [NATIONALLY COMPLETED NAME] used in combination with cobicistat or low dose ritonavir 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 [NATIONALLY COMPLETED NAME] used in

combination with cobicistat or low dose ritonavir, interruption or discontinuation of treatment should be considered promptly.

Patients with coexisting conditions

Hepatic impairment
The safety and efficacy of [NATIONALLY COMPLETED NAME] have not been established in patients with severe underlying liver disorders and [NATIONALLY COMPLETED NAME] is therefore contraindicated in patients with severe hepatic impairment.
Due to an increase in the unbound darunavir plasma concentrations, [NATIONALLY COMPLETED NAME] should be used with caution in patients with mild or moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal impairment
No special precautions or dose adjustments for darunavir/ritonavir are required in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis. Therefore, no special precautions or dose adjustments are required in these patients (see sections 4.2 and 5.2).
Cobicistat has not been studied in patients receiving dialysis, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients (see section 4.2).

Cobicistat decreases the estimated creatinine clearance due to inhibition of tubular secretion of creatinine. This should be taken into consideration if darunavir with cobicistat is administered to patients in whom the estimated creatinine clearance is used to adjust doses of co-administered medicinal products (see section 4.2 and cobicistat SmPC).

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

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 PIs. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with 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.

Diabetes mellitus/hyperglycaemia
New onset diabetes mellitus, hyperglycaemia, or exacerbation of existing diabetes mellitus has been reported in patients receiving antiretroviral therapy, including PIs. In some of these patients the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia.

Fat redistribution and metabolic disorders
Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

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

Immune reconstitution inflammatory syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (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 are 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 studies with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir.

Autoimmune disorders (such as Graves' disease) 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).

Interactions with medicinalproducts
Pharmacokinetic enhancer and concomitant medications
Darunavir has different interaction profiles depending on whether the compound is boosted with ritonavir or cobicistat:
- Darunavir boosted with cobicistat is more sensitive for CYP3A induction: concomitant use of darunavir/cobicistat and strong CYP3A inducers is therefore contraindicated (see section 4.3), and concomitant use with weak to moderate CYP3A inducers is not recommended (see section 4.5). Concomitant use of darunavir/ritonavir and darunavir/cobicistat with lopinavir/ritonavir, rifampicin and herbal products containing St John's wort, *Hypericum perforatum*, is contraindicated (see section 4.5).
- Unlike ritonavir, cobicistat does not have inducing effects on enzymes or transport proteins (see section 4.5). If switching the pharmacoenhancer from ritonavir to cobicistat, caution is required during the first two weeks of treatment with darunavir/cobicistat, particularly if doses of any concomitantly administered medicinal products have been titrated or adjusted during use of ritonavir as a pharmacoenhancer. A dose reduction of the co-administered drug may be needed in these cases.

Efavirenz in combination with [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily may result in sub-optimal darunavir Cmin. If efavirenz is to be used in combination with [NATIONALLY COMPLETED NAME]/ritonavir, the [NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily regimen should be used. See the Summary of Product Characteristics for [NATIONALLY COMPLETED NAME] 75 mg, 150 mg, 300 mg or 600 mg tablets (see section 4.5).

Only applicable for 400 mg tablets:
[NATIONALLY COMPLETED NAME] tablets contain sunset yellow FCF (E110) which may cause an allergic reaction.

Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A and P-glycoprotein (P-gp; see sections 4.3 and 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

The interaction profile of darunavir may differ depending on whether ritonavir or cobicistat is used as pharmacoenhancer. The recommendations given for concomitant use of darunavir and other medicinal products may therefore differ depending on whether darunavir is boosted with ritonavir or cobicistat (see sections 4.3 and 4.4), and caution is also required during the first time of treatment if switching the pharmacoenhancer from ritonavir to cobicistat (see section 4.4).

Medicinal products that affect darunavir exposure (ritonavir as pharmacoenhancer) Darunavir and ritonavir are metabolised by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of these compounds and consequently that of darunavir, leading to loss of therapeutic effect and possible development of resistance (see sections 4.3 and 4.4). CYP3A inducers that are contraindicated include rifampicin, St John's wort and lopinavir.

Co-administration of darunavir and ritonavir with other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir, which may result in increased plasma concentrations of darunavir and ritonavir. Co-administration with strong CYP3A4 inhibitors is not recommended and caution is warranted, these interactions are described in the interaction table below (e.g. indinavir, systemic azoles like ketoconazole and clotrimazole).

Medicinal products that affect darunavir exposure (cobicistat as pharmacoenhancer)
Darunavir and cobicistat are metabolised by CYP3A, and co-administration with CYP3A inducers may therefore result in subtherapeutic plasma exposure to darunavir. Darunavir boosted with cobicistat is more sensitive to CYP3A induction than ritonavir-boosted darunavir: coadministration of darunavir/cobicistat with medicinal products that are strong inducers of CYP3A (e.g. St John's wort, rifampicin, carbamazepine, phenobarbital, and phenytoin) is contraindicated (see section 4.3).
Co-administration of darunavir/cobicistat with weak to moderate CYP3A inducers (e.g. efavirenz, etravirine, nevirapine, boceprevir, telaprevir, fluticasone, and bosentan) is not recommended (see interaction table below).

For co-administration with strong CYP3A4 inhibitors, the same recommendations apply independent of whether darunavir is boosted with ritonavir or with cobicistat (see section above).

Medicinal products that may be affected by darunavir boosted with ritonavir Darunavir and ritonavir are inhibitors of CYP3A, CYP2D6 and P-gp. Co-administration of darunavir/ritonavir with medicinal products primarily metabolised by CYP3A and/or CYP2D6 or transported by P-gp may result in increased systemic exposure to such medicinal products, which could increase or prolong their therapeutic effect and adverse reactions.

Darunavir co-administered with low dose ritonavir 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).

The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily. Cobicistat 150 mg given with darunavir 800 mg once daily enhances darunavir pharmacokinetic parameters in a comparable way to ritonavir (see section 5.2).Therefore, darunavir must only be used in combination with a pharmacokinetic enhancer (see section 5.2).

A clinical study utilising a cocktail of medicinal products that are metabolised by cytochromes CYP2C9, CYP2C19 and CYP2D6 demonstrated an increase in CYP2C9 and CYP2C19 activity and inhibition of CYP2D6 activity in the presence of darunavir/ritonavir, which may be attributed to the presence of low dose ritonavir. Co-administration of darunavir and ritonavir with medicinal products

which are primarily metabolised by CYP2D6 (such as flecainide, propafenone, metoprolol) may result in increased plasma concentrations of these medicinal products, which could increase or prolong their therapeutic effect and adverse reactions. Co-administration of darunavir and ritonavir and medicinal products primarily metabolised by CYP2C9 (such as warfarin) and CYP2C19 (such as methadone) may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Although the effect on CYP2C8 has only been studied *in vitro*, co-administration of darunavir and ritonavir and medicinal products primarily metabolised by CYP2C8 (such as paclitaxel, rosiglitazone, repaglinide) may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Ritonavir inhibits the transporters P-glycoprotein, OATP1B1 and OATP1B3, and co-administration with substrates of these transporters can result in increased plasma concentrations of these compounds (e.g. dabigatran etexilate, digoxin, statins and bosentan; see the Interaction table below).

Medicinal products that may be affected by darunavir boosted with cobicistat The recommendations for darunavir boosted with ritonavir are adequate also for darunavir boosted with cobicistat with regard to substrates of CYP3A4, CYP2D6, P-glycoprotein, OATP1B1 and OATP1B3 (see contraindications and recommendations presented in the section above). Cobicistat 150 mg given with darunavir 800 mg once daily enhances darunavir pharmacokinetic parameters in a comparable way to ritonavir (see section 5.2).

Unlike ritonavir, cobicistat does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGT1A1. For further information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Interaction table
Interaction studies have only been performed in adults.

Several of the interaction studies (indicated by # in the table below) have been performed at lower than recommended doses of darunavir or with a different dosing regimen (see section 4.2 Posology). The effects on co-administered medicinal products may thus be underestimated and clinical monitoring of safety may be indicated.

The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as pharmacokinetic enhancer. Darunavir may therefore have different recommendations for concomitant medications depending on whether the compound is boosted with ritonavir or cobicistat. No interaction studies presented in the table have been performed with darunavir boosted with cobicistat. The same recommendations apply, unless specifically indicated. For further information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Interactions between darunavir/ritonavir and antiretroviral and non-antiretroviral medicinal products are listed in the table below (not determined as “ND”). The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (↔), below (↓) or above (↑) the 80-125% range.
In the table below the specific pharmacokinetic enhancer is specified when recommendeations differ. When the recommendation is the same for [NATIONALLY COMPLETED NAME] when coadministered with a low dose ritonavir or cobicistat, the term “boosted [NATIONALLY COMPLETED NAME]” is used.

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS

Medicinal products by therapeutic areas	Interaction Geometric mean change (%)	Recommendations concerning co-administration
HIV ANTIRETROVIRALS		
Integrase strand transfer inhibitors		
Dolutegravir	dolutegravir AUC ↓ 32% dolutegravir C24h 38% dolutegravir Cmax ↓ 11% darunavir ↔* * Using cross-study comparisons to historical pharmacokinetic data	Boosted [NATIONALLY COMPLETED NAME] and dolutegravir can be used without dose adjustment.
Elvitegravir	elvitegravir AUC ↔ elvitegravir Cmin ↔ elvitegravir Cmax ↔ darunavir AUC ↔ darunavir Cmin 17% darunavir Cmax ↔	When [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir (600/100 mg twice daily) is used in combination with elvitegravir, the dose of elvitegravir should be 150 mg once daily. [NATIONALLY COMPLETED NAME] co-administered with cobicistat should not be used in combination with another antiretroviral that requires pharmacoenhancement since dosing recommendations for such combination have not been established. The pharmacokinetics and dosing recommendations for other doses of darunavir or with elvitegravir/cobicistat have not been established. Therefore, coadministration of [NATIONALLY COMPLETED NAME] with low dose ritonavir in doses other than 600/100 mg twice daily and elvitegravir is not recommended. Co-administration of [NATIONALLY COMPLETED NAME] with low dose ritonavir and elvitegravir in the presence of cobicistat is not recommended.
Raltegravir	Some clinical studies suggest raltegravir may cause a modest decrease in darunavir plasma concentrations.	At present the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically relevant. Boosted [NATIONALLY COMPLETED NAME] and raltegravir can be used without dose adjustments.

Nucleo(s/t)ide reverse transcriptase inhibitors (NRTIs)		
Didanosine 400 mg once daily	didanosine AUC ↓ 9% didanosine Cmin ND didanosine Cmax ↓ 16% darunavir AUC ↔ darunavir Cmin ↔ darunavir Cmax ↔	Boosted [NATIONALLY COMPLETED NAME] and didanosine can be used without dose adjustments. Didanosine is to be administered on an empty stomach, thus it should be administered 1 hour before or 2 hours after boosted [NATIONALLY COMPLETED NAME] given with food.
Tenofovir disoproxil fumarate 300 mg once daily	tenofovir AUC ↑ 22% tenofovir Cmin ↑ 37% tenofovir Cmax ↑ 24% #darunavir AUC ↑ 21% # darunavir Cmin ↑ 24% # darunavir Cmax ↑ 16% (↑ tenofovir from effect on MDR-1 transport in the renal tubules)	Monitoring of renal function may be indicated when boosted [NATIONALLY COMPLETED NAME] is given in combination with tenofovir, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents. [NATIONALLY COMPLETED NAME] co-administered with cobicistat lowers the creatinine clearance. Refer to section 4.4 if creatinine clearance is used for dose adjustment of tenofovir.
Abacavir Emtricitabine Lamivudine Stavudine Zidovudine	Not studied. Based on the different elimination pathways of the other NRTIs zidovudine, emtricitabine, stavudine, lamivudine, that are primarily renally excreted, and abacavir for which metabolism is not mediated by CYP450, no interactions are expected for these medicinal compounds and boosted [NATIONALLY COMPLETED NAME].	Boosted [NATIONALLY COMPLETED NAME] can be used with these NRTIs without dose adjustment. [NATIONALLY COMPLETED NAME] co-administered with cobicistat lowers the creatinine clearance. Refer to section 4.4 if creatinine clearance is used for dose adjustment of emtricitabine or lamivudine.
Non-nucleo(s/t)ide reverse transcriptase inhibitors (NNRTIs)		

Efavirenz 600 mg once daily	efavirenz AUC ↑ 21% efavirenz Cmin ↑ 17% efavirenz Cmax ↑ 15% #darunavir AUC ↓ 13% # darunavir Cmin ↓ 31% # darunavir Cmax ↓ 15% (↑ efavirenz from CYP3A inhibition) (↓ darunavir from CYP3A induction)	Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated when [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir is given in combination with efavirenz. Efavirenz in combination with [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily may result in sub-optimal darunavir Cmin. If efavirenz is to be used in combination with [NATIONALLY COMPLETED NAME]/ritonavir, the [NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily regimen should be used (see section 4.4). Co-administration with [NATIONALLY COMPLETED NAME] co-administered with cobicistat is not recommended (see section 4.4).
Etravirine 100 mg twice daily	etravirine AUC ↓ 37% etravirine Cmin ↓ 49% etravirine Cmax ↓ 32% darunavir AUC ↑ 15% darunavir Cmin ↔ darunavir Cmax ↔	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and etravirine **200 mg twice daily** can be used without dose adjustments. Co-administration with [NATIONALLY COMPLETED NAME] co-administered with cobicistat is not recommended (see section 4.4).
Nevirapine 200 mg twice daily	nevirapine AUC ↑ 27% nevirapine Cmin ↑ 47% nevirapine Cmax ↑ 18% #darunavir: concentrations were consistent with historical data (↑ nevirapine from CYP3A inhibition)	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and nevirapine can be used without dose adjustments. Co-administration with [NATIONALLY COMPLETED NAME] co-administered with cobicistat is not recommended (see section 4.4).

Rilpivirine 150 mg once daily	rilpivirine AUC ↑ 130% rilpivirine Cmin ↑ 178% rilpivirine Cmax ↑ 79% darunavir AUC ↔ darunavir Cmin ↓ 11% darunavir Cmax ↔	Boosted [NATIONALLY COMPLETED NAME] and rilpivirine can be used without dose adjustments.
HIV Protease inhibitors (PIs) - without additional co-administration of low dose ritonavir †		
Atazanavir 300 mg once daily	atazanavir AUC ↔ atazanavir Cmin ↑ 52% atazanavir Cmax ↓ 11% #darunavir AUC ↔ # darunavir Cmin ↔ # darunavir Cmax ↔ Atazanavir: comparison of atazanavir/ritonavir 300/100 mg once daily vs. atazanavir 300 mg once daily in combination with darunavir/ritonavir 400/100 mg twice daily. Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg twice daily in combination with atazanavir 300 mg once daily.	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir and atazanavir can be used without dose adjustments. [NATIONALLY COMPLETED NAME] co-administered with cobicistat should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 (see section 4.5).
Indinavir 800 mg twice daily	indinavir AUC ↑ 23% indinavir Cmin ↑ 125% indinavir Cmax ↔ #darunavir AUC ↑ 24% #darunavir Cmin ↑ 44% #darunavir Cmax ↑ 11% Indinavir: comparison of indinavir/ritonavir 800/100 mg twice daily vs. indinavir/darunavir/ritonavir 800/400/100 mg twice daily. Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with indinavir 800 mg twice daily.	When used in combination with [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir, dose adjustment of indinavir from 800 mg twice daily to 600 mg twice daily may be warranted in case of intolerance. [NATIONALLY COMPLETED NAME] co-administered with cobicistat should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 (see section 4.5).

Saquinavir 1,000 mg twice daily	#darunavir AUC ↓ 26% #darunavir Cmin ↓ 42% #darunavir Cmax ↓ 17% saquinavir AUC ↓ 6% saquinavir Cmin ↓ 18% saquinavir Cmax ↓ 6% Saquinavir: comparison of saquinavir/ritonavir 1,000/100 mg twice daily vs. saquinavir/darunavir/ritonavir 1,000/400/100 mg twice daily Darunavir: comparison of darunavir/ritonavir 400/100 mg twice daily vs. darunavir/ritonavir 400/100 mg in combination with saquinavir 1,000 mg	It is not recommended to combine [NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir with saquinavir. [NATIONALLY COMPLETED NAME] co-administered with cobicistat should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 (see section 4.5).
HIV Protease inhibitors (PIs) - with co-administration of low dose ritonavir†		
Lopinavir/ritonavir 400/100 mg twice daily Lopinavir/ritonavir 533/133.3 mg twice daily	lopinavir AUC ↑ 9% lopinavir Cmin ↑ 23% lopinavir Cmax ↓ 2% darunavir AUC ↓ 38%‡ darunavir Cmin ↓ 51%‡ darunavir Cmax ↓ 21%‡ lopinavir AUC ↔ lopinavir Cmin ↑ 13% lopinavir Cmax ↑ 11% darunavir AUC ↓ 41% darunavir Cmin ↓ 55% darunavir Cmax ↓ 21% ‡	Due to a decrease in the exposure (AUC) of darunavir by 40%, appropriate doses of the combination have not been established. Hence, concomitant use of boosted [NATIONALLY COMPLETED NAME] and the combination product lopinavir/ritonavir is contraindicated (see section 4.3).
CCR5 ANTAGONIST	based upon non dose normalised	
Maraviroc 150 mg twice daily	maraviroc AUC ↑ 305% maraviroc Cmin ND maraviroc Cmax ↑ 129% darunavir, ritonavir concentrations were consistent with historical data	The maraviroc dose should be 150 mg twice daily when coadministered with boosted [NATIONALLY COMPLETED NAME].
ANAESTHETIC		
Alfentanil Not studied.	The metabolism of The concomitant mediated via CYP3A, and boosted such be inhibited by boosted may [NATIONALLY COMPLETED NAME].	use with alfentanil is [NATIONALLY may as COMPLETED NAME] require to lower the dose of alfentanil and requires monitoring for risks of prolonged or delayed respiratory depression.
ANTIANGINA/ANTIARRHYTHMIC		

Disopyramide Flecainide Mexiletine Propafenone Amiodarone Bepridil Dronedarone Lidocaine (systemic) Quinidine Ranolazine	Not studied. Boosted [NATIONALLY COMPLETED NAME] 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 coadministered with boosted [NATIONALLY COMPLETED NAME]. Boosted [NATIONALLY COMPLETED NAME] and amiodarone, bepridil, dronedarone, systemic lidocaine, quinidine, or ranolazine is contraindicated (see section 4.3).
Digoxin 0.4 mg single dose	digoxin AUC ↑ 61% digoxin Cmin ND digoxin Cmax ↑ 29% (↑ digoxin from probable inhibition of Pgp)	Given that digoxin has a narrow therapeutic index, it is recommended that the lowest possible dose of digoxin should initially be prescribed in case digoxin is given to patients on boosted [NATIONALLY COMPLETED NAME] therapy. The digoxin dose should be carefully titrated to obtain the desired clinical effect while assessing the overall clinical state
ANTIBIOTIC		of the subject.
Clarithromycin 500 mg twice daily	clarithromycin AUC ↑ 57% clarithromycin Cmin ↑ 174% clarithromycin Cmax ↑ 26% #darunavir AUC ↓ 13% # darunavir Cmin ↑ 1% # darunavir Cmax ↓ 17% max 14-OH-clarithromycin concentrations were not detectable when combined with [NATIONALLY COMPLETED NAME]/ritonavir. (↑ clarithromycin from CYP3A inhibition and possible P-gp inhibition)	Caution should be exercised when clarithromycin is combined with boosted [NATIONALLY COMPLETED NAME]. For patients with renal impairment the Summary of Product Characteristics for clarithromycin should be consulted for the recommended dose.
ANTICOAGULANTS		
Apixaban Dabigatran etexilate Rivaroxaban	Not studied. Co-administration of boosted [NATIONALLY COMPLETED NAME] with these anticoagulants may increase concentrations of the anticoagulant. (CYP3A and/or P-gp inhibition)	The use of boosted [NATIONALLY COMPLETED NAME] and these anticoagulants is not recommended.

Warfarin	Not studied. Warfarin concentrations may be affected when co-administered with boosted [NATIONALLY COMPLETED NAME].	It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with boosted [NATIONALLY COMPLETED NAME].

ANTICONVULSANTS		
Phenobarbital Phenytoin	Not studied. Phenobarbital and phenytoin are expected to decrease plasma concentrations of darunavir and its pharmacoenhancer. (induction of CYP450 enzymes)	[NATIONALLY COMPLETED NAME] co-administered with low dose ritonavir should not be used in combination with these medicines. The use of these medicines with [NATIONALLY COMPLETED NAME]/cobicistat is contraindicated (see section 4.3).
Carbamazepine 200 mg twice daily	carbamazepine AUC ↑ 45% carbamazepine Cmin ↑ 54% carbamazepine Cmax ↑ 43% darunavir AUC ↔ darunavir Cmin ↓ 15% darunavir Cmax ↔	No dose adjustment for [NATIONALLY COMPLETED NAME]/ritonavir is recommended. If there is a need to combine [NATIONALLY COMPLETED NAME]/ritonavir and carbamazepine, patients should be monitored for potential carbamazepine-related adverse events. Carbamazepine concentrations should be monitored and its dose should be titrated for adequate response. Based upon the findings, the carbamazepine dose may need to be reduced by 25% to 50% in the presence of [NATIONALLY COMPLETED NAME]/ritonavir. The use of carbamazepine with [NATIONALLY COMPLETED NAME] co-administered with cobicistat is contraindicated (see section 4.3).
ANTIDEPRESSANTS		

Paroxetine 20 mg once daily Sertraline 50 mg once daily Amitriptyline Desipramine Imipramine Nortriptyline Trazodone	paroxetine AUC ↓ 39% paroxetine Cmin ↓ 37% paroxetine Cmax ↓ 36% #darunavir AUC ↔ #darunavir C ↔ min #darunavir C ↔ max sertraline AUC ↓ 49% sertraline Cmin ↓ 49% sertraline Cmax ↓ 44% #darunavir AUC ↔ # darunavir Cmin ↓ 6% # darunavir Cmax ↔ In contrast to these data with [NATIONALLY COMPLETED NAME]/ritonavir, [NATIONALLY COMPLETED NAME]/cobicistat may increase these antidepressant plasma concentrations (CYP2D6 and/or CYP3A inhibition). Concomitant use of boosted [NATIONALLY COMPLETED NAME] and these antidepressants may increase concentrations of the antidepressant. (CYP2D6 and/or	If antidepressants are coadministered with boosted [NATIONALLY COMPLETED NAME], the recommended approach is a dose titration of the antidepressant based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of these antidepressants who start treatment with boosted [NATIONALLY COMPLETED NAME] should be monitored for antidepressant response. Clinical monitoring is recommended when coadministering boosted [NATIONALLY COMPLETED NAME] with these antidepressants and a dose adjustment of the antidepressant
ANTI-DIABETICS	CYP3A inhibition)	may be needed.
Metformin	Not studied. Based on theoretical considerations [NATIONALLY COMPLETED NAME] co-administered with cobicistat is expected to increase metformin plasma concentrations. (MATE1 inhibition)	Careful patient monitoring and dose adjustment of metformin is recommended in patients who are taking [NATIONALLY COMPLETED NAME] co-administered with cobicistat. (not applicable for [NATIONALLY COMPLETED NAME] co-administered with ritonavir)
ANTIFUNGALS		
Voriconazole	Not studied. Ritonavir may decrease plasma concentrations of voriconazole. (induction of CYP450 enzymes) Concentrations of voriconazole may increase or decrease when coadministered with [NATIONALLY COMPLETED NAME] co-administered with cobicistat. (inhibition of CYP450 enzymes)	Voriconazole should not be combined with boosted [NATIONALLY COMPLETED NAME] unless an assessment of the benefit/risk ratio justifies the use of voriconazole.

Ketoconazole 200 mg twice daily	ketoconazole AUC ↑ 212% ketoconazole Cmin ↑ 868% ketoconazole Cmax ↑ 111% #darunavir AUC ↑ 42% # darunavir Cmin ↑ 73% # darunavir Cmax ↑ 21% (CYP3A inhibition)	Caution is warranted and clinical monitoring is recommended when combined with boosted [NATIONALLY COMPLETED NAME]. When co-administration is required the daily dose of ketoconazole should not exceed 200 mg.
Fluconazole Posaconazole	Not studied. Boosted [NATIONALLY COMPLETED NAME] may increase antifungal plasma concentrations (P-gp inhibition) and posaconazole or fluconazole may increase darunavir concentrations.	Caution is warranted and clinical monitoring is recommended.
Itraconazole	(NotCYP3A studied. inhibition) Conco mitant systemic use of itraconazole and boosted [NATIONALLY COMPLETED NAME] may increase plasma concentrations of darunavir and itraconazole. (CYP3A inhibition)	Caution is warranted and clinical monitoring is recommended when combined with boosted [NATIONALLY COMPLETED NAME]. When co-administration is required the daily dose of itraconazole should not exceed 200 mg.
Clotrimazole	Not studied. Concomitant systemic use of clotrimazole andboosted [NATIONALLY COMPLETED NAME]may increase plasma concentrations of darunavir and/or clotrimazole. darunavir AUC24h ↑ 33% (based on population pharmacokinetic model)	Caution is warranted and clinical monitoring is recommended, when co-administration of clotrimazole is required.
ANTIGOUT MEDICINES		
Colchicine	Not studied. Concomitant use of colchicine and boosted [NATIONALLY COMPLETED NAME] may increase the exposure to colchicine. (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 boosted [NATIONALLY COMPLETED NAME] is required. For patients with renal or hepatic impairment colchicine with boosted [NATIONALLY COMPLETED NAME] is contraindicated (see section 4.3).
ANTIMALARIALS		

Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours	artemether AUC ↓ 16% artemether Cmin ↔ artemether Cmax ↓ 18% dihydroartemisinin AUC ↓ 18% dihydroartemisinin Cmin ↔ dihydroartemisinin Cmax ↓ 18% lumefantrine AUC ↑ 175% lumefantrine Cmin ↑ 126% lumefantrine Cmax ↑ 65% darunavir AUC ↔ darunavir Cmin ↓ 13% darunavir Cmax ↔	The combination of boosted [NATIONALLY COMPLETED NAME] 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 Rifapentine	Not studied. Rifapentine and rifampicin are strong CYP3A inducers and have been shown to cause profound decreases in concentrations of other protease inhibitors, which can result in virological failure and resistance development (CYP450 enzyme induction). During attempts to overcome the decreased exposure by increasing the dose of other protease inhibitors with low dose ritonavir, a high frequency of liver reactions was seen with rifampicin.	The combination of rifapentine and boosted [NATIONALLY COMPLETED NAME] is not recommended. The combination of rifampicin and boosted [NATIONALLY COMPLETED NAME] is contraindicated (see section 4.3).

Rifabutin 150 mg once every other day	rifabutin AUC** ↑ 55% rifabutin Cmin** ↑ ND ** rifabutin Cmax** ↔ darunavir AUC ↑ 53% darunavir Cmin ↑ 68% darunavir Cmax ↑ 39% ** sum of active moieties of rifabutin (parent drug + 25-*O*-desacetyl metabolite) The interaction trial showed a comparable daily systemic exposure for rifabutin between treatment at 300 mg once daily alone and 150 mg once every other day in combination with [NATIONALLY COMPLETED NAME]/ritonavir (600/100 mg twice daily) with an about 10-fold increase in the daily exposure to the active metabolite 25-*O*-desacetylrifabutin. Furthermore, AUC of the sum of active moieties of rifabutin (parent drug + 25*O*-desacetyl metabolite) was increased 1.6-fold, while Cmax remained comparable. Data on comparison with a 150 mg once daily reference dose is lacking. (Rifabutin is an inducer and substrate of CYP3A.) An increase of systemic exposure to darunavir was observed when [NATIONALLY COMPLETED NAME] co-administered with 100 mg	A dosage reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e. rifabutin 150 mg once every other day) and increased monitoring for rifabutin related adverse events is warranted in patients receiving the combination with [NATIONALLY COMPLETED NAME] co-administered with ritonavir. In case of safety issues, a further increase of the dosing interval for rifabutin and/or monitoring of rifabutin levels should be considered. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients. Based upon the safety profile of [NATIONALLY COMPLETED NAME]/ritonavir, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for [NATIONALLY COMPLETED NAME]/ritonavir. Based on pharmacokinetic modeling, this dosage reduction of 75% is also applicable if patients receive rifabutin at doses other than 300 mg/day. Co-administration of [NATIONALLY COMPLETED NAME] co-administered with
ANTINEOPLASTICS		

Dasatinib Nilotinib Vinblastine Vincristine Everolimus	Not studied. Boosted [NATIONALLY COMPLETED NAME] is expected to increase these antineoplastic plasma concentrations. (CYP3A inhibition)	Concentrations of these medicinal products may be increased when co-administered with boosted [NATIONALLY COMPLETED NAME] resulting in the potential for increased adverse events usually associated with these agents. Caution should be exercised when combining one of these antineoplastic agents with boosted [NATIONALLY COMPLETED NAME]. Concominant use of everolimus and boosted [NATIONALLY COMPLETED NAME] is not recommended.
ANTIPLATELETS		
Ticagrelor	Not studied. Co-administration with boosted [NATIONALLY COMPLETED NAME] may lead to a substantial increase in exposure to ticagrelor.	Concomitant administration of boosted [NATIONALLY COMPLETED NAME] with ticagrelor is contraindicated. Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended.
ANTIPSYCHOTICS/NEUROLEPTICS		
Quetiapine	Not studied. Boosted [NATIONALLY COMPLETED NAME] is expected to increase these antipsychotic plasma concentrations. (CYP3A inhibition)	Concomitant administration of boosted [NATIONALLY COMPLETED NAME] and quetiapine is contraindicated as it may increase quetiapine-related toxicity. Increased concentrations of quetiapine may lead to coma.
Perphenazine Risperidone Thioridazine Pimozide Sertindole	Not studied. Boosted [NATIONALLY COMPLETED NAME] is expected to increase these antipsychotic plasma concentrations. (CYP2D6 inhibition and/or P-gp)	A dose decrease may be needed for these drugs when coadministered with boosted [NATIONALLY COMPLETED NAME]. Concominant administration of boosted [NATIONALLY COMPLETED NAME] and pimozide or sertindole is
β-BLOCKERS		contraindicated.

Carvedilol Metoprolol Timolol	Not Studied. Boosted [NATIONALLY COMPLETED NAME] is expected to increase these β-blocker plasma concentrations. (CYP2D6 inhibition)	Clinical monitoring is recommended when coadministering boosted [NATIONALLY COMPLETED NAME] with β-blockers. A lower dose of the β-blocker should be considered.
CALCIUM CHANNEL BLOCKERS		
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Not studied. Boosted [NATIONALLY COMPLETED NAME] can be expected to increase the plasma concentrations of calcium channel blockers. (CYP3A and/or CYP2D6 inhibition)	Clinical monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with boosted [NATIONALLY COMPLETED NAME].
CORTICOSTEROIDS		

Fluticasone Budesonide	In a clinical study where ritonavir 100 mg capsules twice daily were coadministered with 50 g intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, fluticasone propionate plasma concentrations increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% CI 82-89%). Greater effects may be expected when fluticasone is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone; this could also occur with other corticosteroids metabolised via the P4503A pathway, e.g., budesonide. The effects of high fluticasone systemic	Concomitant administration of boosted [NATIONALLY COMPLETED NAME] and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid which is not a substrate for CYP3A (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids, progressive dose reduction may have to be performed over a longer period.
Dexamethasone (systemic)	exposureNot studied. on Dexamethasoneritonavir plasma levels may are decrease plasma concentrations of darunavir. (CYP3A induction)	Systemic dexamethasone should be used with caution when combined with boosted
Prednisone	Not studied. Boosted [NATIONALLY COMPLETED NAME] may increase plasma concentrations of prednisone. (CYP3A inhibition)	[ConcomitantNATIONALLY COMPLETED use of boosted [NATIONALLY COMPLETED NAME] with low dose ritonavir and prednisone may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Clinical monitoring is recommended when coadministering boosted [NATIONALLY COMPLETED NAME] with corticosteroids.
ENDOTHELIN RECEPTOR ANTAGONISTS		

Bosentan	Not studied. Concomitant use of bosentan and boosted darunavir may increase plasma concentrations of bosentan. Bosentan is expected to decrease plasma concentrations of darunavir and/or its pharmacoenhancer. (CYP3A induction)	When administered concomitantly with [NATIONALLY COMPLETED NAME] and low dose ritonavir, the patient's tolerability of bosentan should be monitored. Co administration of [NATIONALLY COMPLETED NAME] co-administered with cobicistat and bosentan is not recommended.
HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS		
NS3-4A protease inhibitors		

Telaprevir 750 mg every 8 hours	telaprevir AUC ↓ 35% telaprevir Cmin ↓ 32% telaprevir Cmax ↓ 36% darunavir AUC12 ↓ 40% darunavir Cmin ↓ 42% darunavir Cmax ↓ 40%	It is not recommended to coadminister boosted [NATIONALLY COMPLETED NAME] and telaprevir.
Boceprevir 800 mg three times daily	boceprevir AUC ↓ 32% boceprevir Cmin ↓ 35% boceprevir Cmax ↓ 25% darunavir AUC ↓ 44% darunavir Cmin ↓ 59% darunavir Cmax ↓ 36%	It is not recommended to coadminister boosted [NATIONALLY COMPLETED NAME] and boceprevir.
Simeprevir	simeprevir AUC ↑ 159% simeprevir Cmin ↑ 358% simeprevir Cmax ↑ 79% darunavir AUC ↑ 18% darunavir Cmin ↑ 31% darunavir Cmax □ The dose of simeprevir in this interaction study was 50 mg when coadministered in combination with darunavir/ritonavir, compared to 150 mg in the simeprevir alone treatment group.	It is not recommended to coadminister boosted [NATIONALLY COMPLETED NAME] and simeprevir.
HERBAL PRODUCTS		
St John's wort *(Hypericum perforatum)*	Not studied. St John's wort is expected to decrease the plasma concentrations of darunavir or its pharmacoenhancers. (CYP450 induction)	Boosted [NATIONALLY COMPLETED NAME] must not be used concomitantly with products containing St John's wort (*Hypericum perforatum*) (see section 4.3). If a patient is already taking St John's wort, stop St John's wort and if possible check viral levels. Darunavir exposure (and also ritonavir exposure) may increase on stopping St John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort.
HMG CO-A REDUCTASE INHIBITORS		
Lovastatin Simvastatin	Not studied. Lovastatin and simvastatin are expected to have markedly increased plasma concentrations when co-administered with boosted [NATIONALLY COMPLETED NAME]. (CYP3A inhibition)	Increased plasma concentrations of lovastatin or simvastatin may cause myopathy, including rhabdomyolysis. Concomitant use of boosted [NATIONALLY COMPLETED NAME] with lovastatin and simvastatin is therefore contraindicated (see section 4.3).

Atorvastatin 10 mg once daily	atorvastatin AUC ↑ 3-4 fold atorvastatin Cmin ↑ ≈5.5-10 fold atorvastatin Cmax ↑ ≈2 fold #darunavir	When administration of atorvastatin and boosted [NATIONALLY COMPLETED NAME] is desired, it is recommended to start with an atorvastatin dose of 10 mg once daily. A gradual dose increase of atorvastatin may be tailored to the clinical response.
Pravastatin 40 mg single dose	pravastatin AUC ↑ 81%¶ pravastatin Cmin ND pravastatin Cmax ↑ 63% ¶ an up to five-fold increase was seen in a limited subset of subjects	When administration of pravastatin and boosted [NATIONALLY COMPLETED NAME] is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effect while
Rosuvastatin 10 mg once daily	rosuvastatin AUC ↑ 48%‖ rosuvastatin Cmax ↑ 144%‖ ‖ based on published data	When administration of rosuvastatin and boosted [NATIONALLY COMPLETED NAME] is required, it is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the
H2-RECEPTOR ANTAGONISTS		desired clinical effect while
Ranitidine 150 mg twice daily	#darunavir AUC ↔ # darunavir Cmin ↔ # darunavir Cmax ↔	Boosted [NATIONALLY COMPLETED NAME] can be coadministered with H2-receptor antagonists without dose adjustments.
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus Everolimus	Not studied. Exposure to these immunosuppressants will be increased when co-administered with boosted [NATIONALLY COMPLETED NAME]. (CYP3A inhibition)	Therapeutic drug monitoring of the immunosuppressive agent must be done when coadministration occurs. Concomitant use of everolimus and boosted [NATIONALLY COMPLETED NAME] is not recommended.
INHALED BETA AGONISTS		
Salmeterol	Not studied. Concomitant use of salmeterol and boosted darunavir may increase plasma concentrations of salmeterol.	Concomitant use of salmeterol and boosted [NATIONALLY COMPLETED NAME] is not recommended. The combination may result in increased risk of cardiovascular adverse event with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESICS / TREATMENT OF OPIOID DEPENDENCE		

Methadone individual dose ranging from 55 mg to 150 mg once daily	R(-) methadone AUC ↓ 16% R(-) methadone Cmin ↓ 15% R(-) methadone Cmax ↓ 24% [NATIONALLY COMPLETED NAME]/cobicistat may, in contrast, increase methadone plasma concentrations (see cobicistat SmPC).	No adjustment of methadone dosage is required when initiating co-administration with boosted [NATIONALLY COMPLETED NAME]. However, adjustment of the methadone dose may be necessary when concomitantly administered for a longer period of time. Therefore, clinical monitoring is recommended, as maintenance therapy may need to be adjusted in some patients.
Buprenorphine/naloxone 8/2 mg–16/4 mg once daily	buprenorphine AUC ↓ 11% buprenorphine Cmin ↔ buprenorphine Cmax ↓ 8% norbuprenorphine AUC ↑ 46% norbuprenorphine Cmin ↑ 71% norbuprenorphine Cmax ↑ 36% naloxone AUC ↔ naloxone Cmin ND naloxone Cmax ↔	The clinical relevance of the increase in norbuprenorphine pharmacokinetic parameters has not been established. Dose adjustment for buprenorphine may not be necessary when coadministered with boosted [NATIONALLY COMPLETED NAME] but a careful clinical monitoring for signs of opiate toxicity is recommended.
OESTROGEN-BASED CONTRACEPTIVES		
Ethinylestradiol Norethindrone 35 g/1 mg once daily	ethinylestradiol AUC ↓ 44% ethinylestradiol Cmin ↓ 62% ethinylestradiol Cmax ↓ 32% norethindrone AUC ↓ 14% norethindrone Cmin ↓ 30% norethindrone Cmax ↔	Alternative or additional contraceptive measures are recommended when oestrogenbased contraceptives are coadministered with boosted [NATIONALLY COMPLETED NAME]. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.
PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS		

For the treatment of erectile dysfunction Avanafil Sildenafil Tadalafil Vardenafil	In an interaction study #, a comparable systemic exposure to sildenafil was observed for a single intake of 100 mg sildenafil alone and a single intake of 25 mg sildenafil co-administered with [NATIONALLY COMPLETED NAME] and low dose ritonavir.	The combination of avanafil and boosted [NATIONALLY COMPLETED NAME] is contraindicated (see section 4.3). Concomitant use of other PDE-5 inhibitors for the treatment of erectile dysfunction with boosted [NATIONALLY COMPLETED NAME] should be done with caution. If concomitant use of boosted [NATIONALLY COMPLETED NAME] 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.
For the treatment of pulmonary arterial hypertension Sildenafil Tadalafil	Not studied. Concomitant use of sildenafil or tadalafil for the treatment of pulmonary arterial hypertension and boosted [NATIONALLY COMPLETED NAME] may increase plasma concentrations of sildenafil or tadalafil. (CYP3A inhibition)	A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension co-administered with boosted [NATIONALLY COMPLETED NAME] 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 boosted [NATIONALLY COMPLETED NAME] 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 boosted [NATIONALLY COMPLETED NAME] is not recommended.
PROTON PUMP INHIBITORS		
Omeprazole 20 mg once daily # can pump be co- #darunavir	AUC ↔ darunavir Cmin ↔ # darunavir Cmax ↔ Boosted [NATIONALLY COMPLETED NAME] inhibitors	administered with proton without dose adjustments.
SEDATIVES/HYPNOTICS		

Buspirone Clorazepate Diazepam Estazolam Flurazepam Midazolam (parenteral) Zoldipem	Not studied. Sedative/hypnotics are extensively metabolised by CYP3A. Coadministration with boosted [NATIONALLY COMPLETED NAME] may cause a large increase in the concentration of these medicines.	Clinical monitoring is recommended when coadministering boosted [NATIONALLY COMPLETED NAME] with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered.
Midazolam (oral) Triazolam	If parenteral midazolam is coadministered with boosted [NATIONALLY COMPLETED NAME] it may cause a large increase in the concentration of this benzodiazepine. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 34 fold increase in midazolam plasma levels.	If parenteral midazolam is coadministered with boosted [NATIONALLY COMPLETED NAME], it should be done in an intensive care unit (ICU) 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. Boosted [NATIONALLY COMPLETED NAME] with triazolam or oral midazolam is contraindicated (see section 4.3)

† The efficacy and safety of the use of [NATIONALLY COMPLETED NAME] with 100 mg ritonavir and any other HIV PI (e.g. (fos)amprenavir, nelfinavir and tipranavir) has not been established in HIV patients. According to current treatment guidelines, dual therapy with protease inhibitors is generally not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account.

There are no adequate and well controlled studies with darunavir 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).

[NATIONALLY COMPLETED NAME] co-administered with cobicistat or low dose ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk.

Breast-feeding

It is not known whether darunavir is excreted in human milk. Studies in rats have demonstrated that darunavir is excreted in milk and at high levels (1,000 mg/kg/day) resulted in toxicity. 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 under any circumstances if they are receiving [NATIONALLY COMPLETED NAME].

Fertility
No human data on the effect of darunavir on fertility are available. There was no effect on mating or fertility with darunavir treatment in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

[NATIONALLY COMPLETED NAME] in combination with cobicistat or ritonavir has no or negligible influence on the ability to drive and use machines. However, dizziness has been reported in some patients during treatment with regimens containing [NATIONALLY COMPLETED NAME] co-administered with cobicistat or low dose ritonavir and should be borne in mind when considering a patient's ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
During the clinical development program (N=2,613 treatment-experienced subjects who initiated therapy with [NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily), 51.3% of subjects experienced at least one adverse reaction. The total mean treatment duration for subjects was 95.3 weeks. The most frequent adverse reactions reported in clinical trials and as spontaneous reports are diarrhoea, nausea, rash, headache and vomiting. The most frequent serious reactions are acute renal failure, myocardial infarction, immune reconstitution inflammatory syndrome, thrombocytopenia, osteonecrosis, diarrhoea, hepatitis and pyrexia.

In the 96 week analysis, the safety profile of [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily in treatment-naïve subjects was similar to that seen with [NATIONALLY COMPLETED NAME]/ritonavir 600/100 mg twice daily in treatment-experienced subjects except for nausea which was observed more frequently in treatment-naïve subjects. This was driven by mild intensity nausea. No new safety findings were identified in the 192 week analysis of the treatment-naïve subjects in which the mean treatment duration of [NATIONALLY COMPLETED NAME]/ritonavir 800/100 mg once daily was 162.5 weeks.

During the Phase III clinical trial GS-US-216-130 with darunavir/cobicistat (N=313 treatment-naïve and treatment-experienced subjects), 66.5% of subjects experienced at least one adverse reaction. The mean treatment duration was 58.4 weeks. The most frequent adverse reactions reported were diarrhoea (28%), nausea (23%), and rash (16%). Serious adverse reactions are diabetes mellitus, (drug) hypersensitivity, immune reconstitution inflammatory syndrome, rash and vomiting. For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Tabulated list of adverse reactions
Adverse reactions are listed by system organ class (SOC) and frequency category. Within each frequency category, adverse reactions are presented in order of decreasing seriousness. 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).

Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing

MedDRA system organ class Frequency category	**Adverse reaction**
Infections and infestations	
uncommon	herpes simplex
Blood and lymphatic system disorders	

uncommon	thrombocytopenia, neutropenia, anaemia, leukopenia
rare	increased eosinophil count
Immune system disorders	

uncommon	immune reconstitution syndrome, (drug) hypersensitivity
Endocrine disorders	
uncommon	hypothyroidism, increased blood thyroid stimulating hormone
Metabolism and nutrition disorders	
common lipodystrophy (including lipohypertrophy,	lipodystrophy, lipoatrophy), diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia
uncommon gout, anorexia, decreased appetite,	decreased weight, increased weight, hyperglycaemia, insulin resistance, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase
Psychiatric disorders	
common insomnia uncommon depression, disorientation, anxiety, decreased libido rare confusional state, altered mood, restlessness	sleep disorder, abnormal dreams, nightmare,
Nervous system disorders	
common	headache, peripheral neuropathy, dizziness
uncommon	lethargy, paraesthesia, hypoaesthesia, dysgeusia, disturbance in attention, memory impairment, somnolence
rare	syncope, convulsion, ageusia, sleep phase rhythm disturbance
Eye disorders	
uncommon	conjunctival hyperaemia, dry eye
rare	visual disturbance
Ear and labyrinth disorders	
uncommon	vertigo
Cardiac disorders	

uncommon rare	myocardial infarction, angina pectoris, prolonged electrocardiogram QT, tachycardia acute myocardial infarction, sinus bradycardia, palpitations
Vascular disorders	

uncommon	hypertension, flushing
Respiratory, thoracic and mediastinal disorders	
uncommon rare	dyspnoea, cough, epistaxis, throat irritation rhinorrhoea
Gastrointestinal disorders	
very common common uncommon rare	diarrhoea vomiting, nausea, abdominal pain, increased blood amylase, dyspepsia, abdominal distension, flatulence pancreatitis, gastritis, gastrooesophageal reflux disease, aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia stomatitis, haematemesis, cheilitis, dry lip, coated tongue
Hepatobiliary disorders	
common uncommon	increased alanine aminotransferase hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased gamma-glutamyltransferase
Skin and subcutaneous tissue disorders	

common	rash (including macular, maculopapular, papular, erythematous and pruritic rash), pruritus
uncommon	angioedema, generalised rash, allergic dermatitis, urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, dry skin, nail pigmentation
rare	DRESS, Stevens-Johnson syndrome, erythema multiforme, dermatitis, seborrhoeic dermatitis, skin lesion, xeroderma
not known	toxic epidermal necrolysis, acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders	
uncommon	myalgia, osteonecrosis, muscle spasms, muscular weakness, arthralgia, pain in extremity, osteoporosis, increased blood creatine phosphokinase
rare	musculoskeletal stiffness, arthritis, joint stiffness
Renal and urinary disorders	
uncommon	acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria
rare	decreased creatinine renal clearance
Reproductive system and breast disorders	
uncommon	erectile dysfunction, gynaecomastia
General disorders and administration site conditions	
common	asthenia, fatigue
uncommon	pyrexia, chest pain, peripheral oedema, malaise, feeling hot, irritability, pain
rare	chills, abnormal feeling, xerosis

Adverse reactions with darunavir/cobicistat in adult patients

MedDRA system organ class Frequency category	**Adverse reaction**
Immune system disorders	
common	(drug) hypersensitivity
uncommon	immune reconstitution inflammatory syndrome

Metabolism and nutrition disorders	
common	lipodystrophy (including lipohypertrophy, lipodystrophy, lipoatrophy)*, anorexia, diabetes mellitus, hypercholesterolaemia, hypertriglyceridaemia, hyperlipidaemia
Psychiatric disorders	
common	abnormal dreams
Nervous system disorders	
very common	headache
Gastrointestinal disorders	
very common common uncommon	diarrhoea, nausea vomiting, abdominal pain, abdominal distension, dyspepsia, flatulence, pancreatic enzymes increased pancreatitis acute
Hepatobiliary disorders	
common uncommon	hepatic enzyme increased hepatitis*, cytolytic hepatitis*
Skin and subcutaneous tissue disorders	
very common common rare not known	rash (including macular, maculopapular, papular, erythematous, pruritic rash, generalised rash, and allergic dermatitis) angioedema, pruritus, urticaria drug reaction with eosinophilia and systemic symptoms*, Stevens-Johnson syndrome* toxic epidermal necrolysis*, acute generalised exanthematous pustulosis*
Musculoskeletal and connective tissue disorders	
common	myalgia, osteonecrosis*
Reproductive system and breast disorders	
uncommon	gynaecomastia*
General disorders and administration site conditions	
common fatigue uncommon asthenia	
Investigations	
common	increased blood creatinine

* these adverse drug reactions have not been reported in clinical trial experience with darunavir/cobicistat but have been noted with darunavir/ritonavir treatment and could be expected with darunavir/cobicistat too.

Description of selected adverse reactions

Rash
In clinical trials, rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. In cases of severe skin reaction see the warning in section 4.4. In a single arm trial investigating darunavir 800 mg once daily in combination with cobicistat 150 mg once daily and other antiretrovirals 2.2% of patients discontinued treatment due to rash.

During the clinical development program of raltegravir in treatment-experienced patients, rash, irrespective of causality, was more commonly observed with regimens containing [NATIONALLY COMPLETED NAME]/ritonavir + raltegravir compared to those containing [NATIONALLY COMPLETED NAME]/ritonavir without raltegravir or raltegravir without [NATIONALLY COMPLETED NAME]/ritonavir. Rash considered by the investigator to be drug-related occurred at similar rates. The exposure-adjusted rates of rash (all causality) were 10.9, 4.2, and 3.8 per 100 patient-years (PYR), respectively; and for drug-related rash were 2.4, 1.1, and 2.3 per 100 PYR, respectively. The rashes observed in clinical studies were mild to moderate in severity and did not result in discontinuation of therapy (see section 4.4).

Lipodystrophy
Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see section 4.4).

Metabolic abnormalities
Combination antiretroviral therapy has also been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

Musculoskeletal abnormalities
Increased CPK, myalgia, myositis and rarely, rhabdomyolysis have been reported with the use of protease inhibitors, particularly in combination with NRTIs.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (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 initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) 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).

Paediatric population
The safety assessment in paediatric patients is based on the 48-week analysis of safety data from three Phase II trials. The following patient populations were evaluated (see section 5.1):

- 80 ART-experienced HIV-1 infected paediatric patients aged from 6 to 17 years and weighing at least 20 kg who received [NATIONALLY COMPLETED NAME] tablets with low dose ritonavir twice daily in combination with other antiretroviral agents.
- 21 ART-experienced HIV-1 infected paediatric patients aged from 3 to < 6 years and weighing 10 kg to < 20 kg (16 participants from 15 kg to < 20 kg) who received [NATIONALLY COMPLETED NAME] oral suspension with low dose ritonavir twice daily in combination with other antiretroviral agents.
- 12 ART-naïve HIV-1 infected paediatric patients aged from 12 to 17 years and weighing at least 40 kg who received [NATIONALLY COMPLETED NAME] tablets with low dose ritonavir once daily in combination with other antiretroviral agents (see section 5.1).

Overall, the safety profile in these paediatric patients was similar to that observed in the adult population.

Other special populations

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

Among 1,968 treatment-experienced patients receiving [NATIONALLY COMPLETED NAME] coadministered 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 (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 [NATIONALLY COMPLETED NAME] co-administered with cobicistat or low dose ritonavir is limited. Single doses up to 3,200 mg of darunavir as oral solution alone and up to 1,600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

There is no specific antidote for overdose with [NATIONALLY COMPLETED NAME]. Treatment of overdose with [NATIONALLY COMPLETED NAME] consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis.

Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitors, ATC code: J05AE10.

Mechanism of action

Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (KD of

4.5×10^{-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.

Antiviral activity *in vitro*
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 peripheral blood mononuclear cells and human monocytes/macrophages with median EC50 values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/ml). Darunavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC50 values ranging from < 0.1 to 4.3 nM.

These EC50 values are well below the 50% cellular toxicity concentration range of 87 µM to > 100 µM.

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: 23-50fold) 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.

The clinical trial data from ART-experienced patients (*TITAN* trial and the pooled analysis of the *POWER* 1, 2 and 3 and *DUET* 1 and 2 trials) showed that virologic response to darunavir coadministered with low dose ritonavir was decreased when 3 or more darunavir RAMs (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V and L89V) were present at baseline or when these mutations developed during treatment.

Increasing baseline darunavir fold change in EC50 (FC) was associated with decreasing virologic response. A lower and upper clinical cut-off of 10 and 40 were identified. Isolates with baseline FC ≤ 10 are susceptible; isolates with FC > 10 to 40 have decreased susceptibility; isolates with FC > 40 are resistant (see Clinical results).

Viruses isolated from patients on Darunavir /ritonavir 600/100 mg twice daily experiencing virologic failure by rebound that were susceptible to tipranavir at baseline remained susceptible to tipranavir after treatment in the vast majority of cases.

The lowest rates of developing resistant HIV virus are observed in ART-naïve patients who are treated for the first time with darunavir in combination with other ART.

The table below shows the development of HIV-1 protease mutations and loss of susceptibility to PIs in virologic failures at endpoint in the *ARTEMIS*, *ODIN* and *TITAN* trials.

	ARTEMIS Week 192	ODIN Week 48		TITAN Week 48
	Darunavir / ritonavir 800/100 mg once daily N=343	Darunavir / ritonavir 800/100 mg once daily N=294	Darunavir / ritonavir 600/100 mg twice daily N=296	Darunavir / ritonavir 600/100 mg twice daily N=298
Total number of virologic failures[a], n (%)	55 (16.0%) 39 (11.4%)	65 (22.1%) 11 (3.7%)	54 (18.2%) 11 (3.7%)	31 (10.4%) 16 (5.4%)
Rebounders	16 (4.7%)	54 (18.4%)	43 (14.5%)	15 (5.0%)
Never suppressed subjects				

Number of subjects with virologic failure and paired baseline/endpoint genotypes, developing mutations[b] at endpoint, n/N				
Primary (major) PI mutations	0/43	1/60	0/42	6/28
PI RAMs	4/43	7/60	4/42	10/28
Number of subjects with virologic failure and paired baseline/endpoint phenotypes, showing loss of susceptibility to PIs at endpoint compared to baseline, n/N				
PI darunavir				
amprenavir	0/39	1/58	0/41	3/26
atazanavir	0/39	1/58	0/40	0/22
indinavir	0/39	2/56	0/40	0/22
lopinavir	0/39	2/57	0/40	1/24
saquinavir	0/39	1/58	0/40	0/23
tipranavir	0/39	0/56	0/40	0/22
	0/39	0/58	0/41	1/25

[a] TLOVR non-VF censored algorithm based on HIV-1 RNA < 50 copies/ml, except for *TITAN* (HIV-1 RNA < 400 copies/ml)
[b] IAS-USA lists

Low rates of developing resistant HIV-1 virus were observed in ART-naïve patients who are treated for the first time with darunavir/cobicistat once daily in combination with other ART, and in ART-experienced patients with no darunavir RAMs receiving darunavir/cobicistat in combination with other ART. The table below shows the development of HIV-1 protease mutations and resistance to PIs in virologic failures at endpoint in the GS-US-216-130 trial.

	GS-US-216-130 Week 48	
	Treatment-naïve darunavir/cobicistat 800/150 mg once daily N=295	Treatment-experienced darunavir/cobicistat 800/150 mg once daily N=18
Number of subjects with virologic failure[a] and genotype data that develop mutations[b] at endpoint, n/N		
Primary (major) PI mutations	0/8	1/7
PI RAMs	2/8	1/7
Number of subjects with virologic failure[a] and phenotype data that show resistance to PIs at endpoint[c],		
HIV PI darunavir		
amprenavir	0/8	0/7
atazanavir	0/8	0/7
indinavir	0/8	0/7
lopinavir	0/8	0/7
saquinavir	0/8	0/7
tipranavir	0/8	0/7
	0/8	0/7

[a] Virogic failures were defined as: never suppressed: confirmed H_{10} IV-1 RNA < 1 log reduction from baseline and ≥ 50 copies/ml at the week-8; rebound: HIV-1 RNA < 50 copies/ml followed by confirmed HIV-1 RNA to ≥ 400 copies/ml or confirmed > 1 log10 HIV-1 RNA increase from

the nadir; discontinuations with HIV-1 RNA ≥ 400 copies/ml at last visit [b] IAS-USA lists [c] In GS-US216-130 baseline phenotype was not available

Cross-resistance
Darunavir FC was less than 10 for 90% of 3,309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to most PIs remain susceptible to darunavir.

In the virologic failures of the *ARTEMIS* trial no cross-resistance with other PIs was observed. In the virologic failures of the GS-US-216-130 trial no cross-resistance with other HIV PIs was observed.

Clinical results
All clinical trials were performed with darunavir c o-administered with low dose ritonavir.
The pharmacokinetic enhancing effect of cobicistat on darunavir was evaluated in a Phase I study in healthy subjects that were administered darunavir 800 mg with either cobicistat at 150 mg or ritonavir at 100 mg once daily. The steady-state pharmacokinetic parameters of darunavir were comparable when boosted with cobicistat versus ritonavir. For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Adult patients

Efficacy of darunavir 800 mg once daily co-administered with 150 mg cobicistat once daily in ARTnaïve and ART-experienced patients
GS-US-216-130 is a single arm, open-label, Phase III trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir with cobicistat in 313 HIV-1 infected adult patients (295 treatment-naïve and 18 treatment-experienced). These patients received darunavir 800 mg once daily in combination with cobicistat 150 mg once daily with an investigator selected background regimen consisting of 2 active NRTIs.

HIV-1 infected patients who were eligible for this trial had a screening genotype showing no darunavir RAMs and plasma HIV-1 RNA ≥ 1000 copies/ml. The table below shows the efficacy data of the 48 week analyses from the GS-US-216-130 trial:

	GS-US-216-130		
Outcomes at Week 48	Treatment-naïve darunavir/cobicistat 800/150 mg once daily + OBR N=295	Treatmentexperienced darunavir/cobicistat 800/150 mg once daily + OBR N=18	All subjects darunavir/cobicistat 800/150 mg once daily + OBR N=313
HIV-1 RNA < 50 copies/ml[a]	245 (83.1%)	8 (44.4%)	253 (80.8%)
mean HIV-1 RNA log change from baseline (log10 copies/ml)	-3.01	-2.39	-2.97
CD4+ cell count mean change from baseline[b]	+174	+102	+170

a Imputations according to the TLOVR algorithm

b Last Observation Carried Forward imputation

Efficacy of darunavir 800 mg once daily co-administered with 100 mg ritonavir once daily in ARTnaïve patients

The evidence of efficacy of Darunavir /ritonavir 800/100 mg once daily is based on the analyses of 192 week data from the randomised, controlled, open-label Phase III trial *ARTEMIS* in antiretroviral treatment-naïve HIV-1 infected patients comparing Darunavir /ritonavir 800/100 mg once daily with lopinavir/ritonavir 800/200 mg per day (given as a twice-daily or as a once-daily regimen). Both arms used a fixed background regimen consisting of tenofovir disoproxil fumarate 300 mg once daily and emtricitabine 200 mg once daily.

The table below shows the efficacy data of the 48 week and 96 week analyses from the *ARTEMIS* trial:

ARTEMIS						
	Week 48[a]			Week 96[b]		
Outcomes	Darunavir/ ritonavir 800/100 mg once daily N=343	Lopinavir/ ritonavir 800/200 mg per day N=346	Treatment difference (95% CI of difference)	Darunavir/ ritonavir 800/100 mg once daily N=343	Lopinavir/ ritonavir 800/200 mg per day N=346	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/ml[c] All patients With baseline HIV-RNA < 100,000 With baseline HIV-RNA ≥ 100,000 With baseline CD4+ cell count < 200 With baseline CD4+ cell count ≥ 200	 83.7% (287) 85.8% (194/226) 79.5% (93/117) 79.4% (112/141) 86.6% (175/202)	 78.3% (271) 84.5% (191/226) 66.7% (80/120) 70.3% (104/148) 84.3% (167/198)	 5.3% (-0.5; 11.2)[d] 1.3% (-5.2; 7.9)[d] 12.8% (1.6; 24.1)[d] 9.2% (-0.8; 19.2)[d] 2.3% (-4.6; 9.2)[d]	 79.0% (271) 80.5% (182/226) 76.1% (89/117) 78.7% (111/141) 79.2% (160/202)	 70.8% (245) 75.2% (170/226) 62.5% (75/120) 64.9% (96/148) 75.3% (149/198)	 8.2% (1.7; 14.7)[d] 5.3% (-2.3; 13.0)[d] 13.6% (1.9; 25.3)[d] 13.9% (3.5; 24.2)[d] 4.0% (-4.3; 12.2)[d]
median CD4+ cell count change from baseline (x 6 e	137	141		171	188	

[a] 10 Data based on analyses at week 48/l) [b] Data based on analyses at week 96 [c] Imputations according to the TLOVR algorithm [d] Based on normal approximation to the difference in % response [e] Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0

Non-inferiority in virologic response to the Darunavir /ritonavir treatment, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/ml, was demonstrated (at the predefined 12% non-inferiority margin) for both Intent-To-Treat (ITT) and On Protocol (OP)

populations in the 48 week analysis. These results were confirmed in the analyses of data at 96 weeks of treatment in the *ARTEMIS* trial. These results were sustained up to 192 weeks of treatment in the ARTEMIS trial.

Efficacy of darunavir 800 mg once daily co-administered with 100 mg ritonavir once daily in ARTexperienced patients

ODIN is a Phase III, randomised, open-label trial comparing darunavir/ritonavir 800/100 mg once daily versus darunavir /ritonavir 600/100 mg twice daily in ART-experienced HIV-1 infected patients with screening genotype resistance testing showing no darunavir RAMs (i.e. V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) and a screening HIV-1 RNA > 1,000 copies/ml. Efficacy analysis is based on 48 weeks of treatment (see table below). Both arms used an optimised background regimen (OBR) of ≥ 2 NRTIs.

ODIN			
Outcomes	Darunavir/ritonavir 800/100 mg once daily + OBR N=294	Darunavir /ritonavir 600/100 mg twice daily + OBR N=296	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/ml[a] With Baseline HIV-1 RNA (copies/ml) < 100,000 ≥ 100,000 With Baseline CD4+ cell count (x 10^6/l) ≥ 100 < 100 With HIV-1 clade Type B Type AE Type C Other[c]	72.1% (212) 77.6% (198/255) 35.9% (14/39) 75.1% (184/245) 57.1% (28/49) 70.4% (126/179) 90.5% (38/42) 72.7% (32/44) 55.2% (16/29)	70.9% (210) 73.2% (194/265) 51.6% (16/31) 72.5% (187/258) 60.5% (23/38) 64.3% (128/199) 91.2% (31/34) 78.8% (26/33) 83.3% (25/30)	1.2% (-6.1; 8.5)[b] 4.4% (-3.0; 11.9) -15.7% (-39.2; 7.7) 2.6% (-5.1; 10.3) -3.4% (-24.5; 17.8) 6.1% (-3.4; 15.6) -0.7% (-14.0; 12.6) -6.1% (-2.6; 13.7) -28.2% (-51.0; -5.3)
mean CD4+ cell count change from baseline (x 10^6/l)[e]	108	112	-5[d] (-25; 16)

[a] Imputations according to the TLOVR algorithm [b] Based on a normal approximation of the difference in % response [c] Clades A1, D, F1, G, K, CRF02_AG, CRF12_BF, and CRF06_CPX [d] Difference in means [e] Last Observation Carried Forward imputation

At 48 weeks, virologic response, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/ml, with darunavir/ritonavir 800/100 mg once daily treatment was demonstrated to be noninferior (at the pre-defined 12% non-inferiority margin) compared to Darunavir /ritonavir 600/100 mg twice daily for both ITT and OP populations.

Darunavir/ritonavir 800/100 mg once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1

RNA ≥ 100,000 copies/ml or CD4+ cell count < 100 cells x 10^6/l (see section 4.2 and 4.4). Limited data is available in patients with HIV-1 clades other than B.

Paediatric patients

ART-naïve paediatric patients from the age of 12 years to < 18 years, and weighing at least 40 kg ***DIONE*** is an open-label, Phase II trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir with low dose ritonavir in 12 ART-naïve HIV-1 infected paediatric patients aged 12 to less than 18 years and weighing at least 40 kg. These patients received darunavir /ritonavir 800/100 mg once daily in combination with other antiretroviral agents. Virologic Response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 log10 versus baseline.

DIONE	
Outcomes at week 48	Darunavir/ritonavir N=12
HIV-1 RNA < 50 copies/ml[a]	83.3% (10)
CD4+ percent change from baseline	14
CD4+ cell count mean change from baseline[b]	221
≥ 1.0 log10 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.

For additional clinical study results in ART-experienced adults and paediatric patients, refer to the Summary of Product Characteristics for darunavir 75 mg, 150 mg, 300 mg or 600 mg tablets and 100 mg/ml oral suspension.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of darunavir, co-administered with cobicistat or ritonavir, have been evaluated in healthy adult volunteers and in HIV-1 infected patients. Exposure to darunavir was higher in HIV-1 infected patients than in healthy subjects. The increased exposure to darunavir in HIV-1 infected patients compared to healthy subjects may be explained by the higher concentrations of α1-acid glycoprotein (AAG) in HIV-1 infected patients, resulting in higher darunavir binding to plasma AAG and, therefore, higher plasma concentrations.

Darunavir is primarily metabolised by CYP3A. Cobicistat and ritonavir inhibit CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

For information on cobicistat pharmacokinetic properties, consult the cobicistat Summary of Product Characteristics.

Absorption
Darunavir was rapidly absorbed following oral administration. Maximum plasma concentration of darunavir in the presence of low dose ritonavir is generally achieved within 2.5-4.0 hours.

The absolute oral 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 overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the

systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily (see section 4.4).

When administered without food, the relative bioavailability of darunavir in the presence of cobicistat or low dose ritonavir is lower as compared to intake with food. Therefore, darunavir tablets should be taken with cobicistat or ritonavir and with food. The type of food does not affect exposure to darunavir.

Distribution

Darunavir is approximately 95% bound to plasma protein. Darunavir binds primarily to plasma α1acid 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.

Biotransformation

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.

Elimination

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 terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir.
The intravenous clearance of darunavir alone (150 mg) and in the presence of low dose ritonavir was 32.8 l/h and 5.9 l/h, respectively.

Special populations

Paediatric population
The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 74 treatmentexperienced paediatric patients, aged 6 to 17 years and weighing at least 20 kg, showed that the administered weight-based doses of darunavir/ritonavir resulted in darunavir exposure comparable to that in adults receiving darunavir /ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 14 treatmentexperienced paediatric patients, aged 3 to < 6 years and weighing at least 15 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving darunavir /ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 12 ART-naïve paediatric patients, aged 12 to < 18 years and weighing at least 40 kg, showed that darunavir /ritonavir 800/100 mg once daily results in darunavir exposure that was comparable to that achieved in adults receiving darunavir /ritonavir 800/100 mg once daily. Therefore the same once daily dosage may be used in treatment-experienced adolescents aged 12 to < 18 years and weighing at least 40 kg 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 4.2).
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 10 treatmentexperienced paediatric patients, aged 3 to < 6 years and weighing at least 14 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving darunavir /ritonavir 800/100 mg once daily (see section 4.2). In addition, pharmacokinetic modeling and simulation of darunavir exposures in paediatric patients across the ages of 3 to < 18 years confirmed the darunavir exposures as observed in the clinical studies and allowed the identification of weight-based darunavir /ritonavir once daily dosing regimens for paediatric patients weighing at least 15 kg that are either ART-naïve or treatment-experienced paediatric patients without 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 4.2).
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

Elderly
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) (see section 4.4). However, only limited data were available in patients above the age of 65 year.

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

Renal impairment

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 (CrCl between 30-60 ml/min, n=20) (see sections 4.2 and 4.4).

Hepatic impairment
Darunavir is primarily metabolised and eliminated by the liver. In a multiple dose study with Darunavir co-administered with 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 (ChildPugh 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% (ChildPugh Class B) higher, respectively. The clinical relevance of this increase is unknown therefore, Darunavir should be used with caution. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see sections 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

Animal toxicology studies have been conducted at exposures up to clinical exposure levels with darunavir alone, in mice, rats and dogs and in combination with ritonavir in rats and dogs.

In repeated-dose toxicology studies in mice, rats and dogs, there were only limited effects of treatment with darunavir. In rodents the target organs identified were the haematopoietic system, the blood

coagulation system, liver and thyroid. A variable but limited decrease in red blood cell-related parameters was observed, together with increases in activated partial thromboplastin time.

Changes were observed in liver (hepatocyte hypertrophy, vacuolation, increased liver enzymes) and thyroid (follicular hypertrophy). In the rat, the combination of darunavir with ritonavir lead to a small increase in effect on RBC parameters, liver and thyroid and increased incidence of islet fibrosis in the pancreas (in male rats only) compared to treatment with darunavir alone. In the dog, no major toxicity findings or target organs were identified up to exposures equivalent to clinical exposure at the recommended dose.

In a study conducted in rats, the number of corpora lutea and implantations were decreased in the presence of maternal toxicity. Otherwise, there were no effects on mating or fertility with darunavir treatment up to 1,000 mg/kg/day and exposure levels below (AUC-0.5 fold) of that in human at the clinically recommended dose. Up to same dose levels, there was no teratogenicity with darunavir in rats and rabbits when treated alone nor in mice when treated in combination with ritonavir. The exposure levels were lower than those with the recommended clinical dose in humans. In a pre- and postnatal development assessment in rats, darunavir with and without ritonavir, caused a transient reduction in body weight gain of the offspring pre-weaning and there was a slight delay in the opening of eyes and ears. Darunavir in combination with ritonavir caused a reduction in the number of pups that exhibited the startle response on day 15 of lactation and a reduced pup survival during lactation. These effects may be secondary to pup exposure to the active substance via the milk and/or maternal toxicity. No post weaning functions were affected with darunavir alone or in combination with ritonavir. In juvenile rats receiving darunavir up to days 23-26, increased mortality was observed with convulsions in some animals. Exposure in plasma, liver and brain was considerably higher than in adult rats after comparable doses in mg/kg between days 5 and 11 of age. After day 23 of life, the exposure was comparable to that in adult rats. The increased exposure was likely at least partly due to immaturity of the drug-metabolising enzymes in juvenile animals. No treatment related mortalities were noted in juvenile rats dosed at 1,000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats.

Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, darunavir with low dose ritonavir should not be used in paediatric patients below 3 years of age.

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1,000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular and thyroid tumours in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses.

After 2 years administration of darunavir at exposures at or below the human exposure, kidney changes were observed in mice (nephrosis) and rats (chronic progressive nephropathy).

Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Microcrystalline cellulose (E460)
Crospovidone (E1202)
Colloidal anhydrous silica (E551)
Magnesium stearate (E470b)

Coating:
{[Nationally completed name] 400 mg film-coated tablets}
Poly (vinyl alcohol) (E1203)
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)
Sunset yellow FCF (E110)

{[Nationally completed name] 800 mg film-coated tablets}
Poly (vinyl alcohol) (E1203)
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

1 year

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

High Density Polyethylene (HDPE) bottles stoppered with polypropylene (PP) child resistant closure.
Packsizes:

Aluminium-PVC/PE/PVDC blisters.
Packsizes:

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[NATIONALLY COMPLETED NAME]
75 mg [150 mg] [300 mg] [600 mg] film-coated tablets
darunavir

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 [NATIONALLY COMPLETED NAME] is and what it is used for

What is [NATIONALLY COMPLETED NAME]
[NATIONALLY COMPLETED NAME] contains the active substance darunavir. [NATIONALLY COMPLETED NAME] is an antiretroviral medicine used in the treatment of Human Immunodeficiency Virus (HIV) infection. It belongs to a group of medicines called protease inhibitors. [NATIONALLY COMPLETED NAME] works by reducing the amount of HIV in your body. This will improve your immune system and reduces the risk of developing illnesses linked to HIV infection.

What is it used for?
[NATIONALLY COMPLETED NAME] is used to treat adults and children of 3 years of age and above, and at least 15 kilogram body weight who are infected by HIV and who have already used other antiretroviral medicines.

[NATIONALLY COMPLETED NAME] must be taken in combination with a low dose of ritonavir and other anti-HIV medicines. Your doctor will discuss with you which combination of medicines is best for you.

2. What you need to know before you take [NATIONALLY COMPLETED NAME]

Do not take [NATIONALLY COMPLETED NAME]
- if you are **allergic** to darunavir or any of the other ingredients of this medicine (listed in section 6) or to ritonavir.
- 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.

Do not combine [NATIONALLY COMPLETED NAME] 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
Avanafil	to treat erectile dysfunction
Astemizole or *terfenadine*	to treat allergy symptoms
Triazolam and *oral (*taken by mouth*) midazolam*	to help you sleep and/or relieve anxiety
Cisapride	to treat some stomach conditions
Colchicine (if you have kidney and/or liver problems)	to treat gout
*Pimozide, quetiapine*or *sertindole*	to treat psychiatric conditions
Ergot alkaloids like *ergotamine*, *dihydroergotamine*, *ergometrine* and *methylergonovine*	to treat migraine and headaches
Amiodarone, bepridil, dronedarone, quinidine, ranolazine and *systemic lidocaine*	to treat certain heart disorders e.g. abnormal heart beat
Lovastatin and *simvastatin*	to lower cholesterol levels
Rifampicin	to treat some infections such as tuberculosis
The combination product *lopinavir/ritonavir*	this anti-HIV medicine belongs to the same class as [NATIONALLY COMPLETED NAME]
Alfuzosin	to treat enlarged prostate
Sildenafil	to treat high blood pressure in the pulmonary circulation
Ticagrelor	to help stop the clumping of platelets in the treatment of patients with a history of a heart attack

Do not combine [NATIONALLY COMPLETED NAME] with products that contain St John's wort *(Hypericum perforatum)*.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking [NATIONALLY COMPLETED NAME].

[NATIONALLY COMPLETED NAME] is not a cure for HIV infection. 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 [NATIONALLY COMPLETED NAME] may still develop infections or other illnesses associated with HIV infection. You must keep in regular contact with your doctor.

People taking [NATIONALLY COMPLETED NAME] may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

In patients taking [NATIONALLY COMPLETED NAME] and raltegravir (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.

[NATIONALLY COMPLETED NAME] 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 [NATIONALLY COMPLETED NAME].

Tell your doctor about your situation BEFORE and DURING your treatment
Make sure that you check the following points and tell your doctor if any of these apply to you.

- Tell your doctor if you have had **problems with your liver** before, including hepatitis B or C. Your doctor may evaluate how severe your liver disease is before deciding if you can take [NATIONALLY COMPLETED NAME].
- Tell your doctor if you have **diabetes**. [NATIONALLY COMPLETED NAME] might increase sugar levels in the blood.
- Tell your doctor immediately if you notice any **symptoms of infection** (for example enlarged lymph nodes and fever). In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. 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.
- 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 symptoms of infection or other 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, please inform your doctor immediately to seek necessary treatment.
- Tell your doctor if you **notice changes in body fat**. Redistribution, accumulation or loss of body fat may occur in patients receiving a combination of antiretroviral medicines.
- Tell your doctor if you have **haemophilia**. [NATIONALLY COMPLETED NAME] might increase the risk of bleeding.
- Tell your doctor if you are **allergic to sulphonamides** (e.g. used to treat certain infections).
- Tell your doctor if you notice any **musculoskeletal problems**. Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. 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 please inform your doctor.

Children
[NATIONALLY COMPLETED NAME] is not for use in children younger than 3 years of age or weighing less than 15 kilograms.

Other medicines and [NATIONALLY COMPLETED NAME]
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

There are some medicines that **you must not combine** with [NATIONALLY COMPLETED NAME]. These are mentioned above under the heading 'Do not combine [NATIONALLY COMPLETED NAME] with any of the following medicines:'

In most cases, [NATIONALLY COMPLETED NAME] can be combined with anti-HIV medicines belonging to another class [e.g. NRTIs (nucleoside reverse transcriptase inhibitors), NNRTIs (nonnucleoside reverse transcriptase inhibitors), CCR5 antagonists and FIs (fusion inhibitors)]. [NATIONALLY COMPLETED NAME] with ritonavir has not been tested with all PIs (protease inhibitors) and must not be used with other HIV PIs. 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.

The effects of [NATIONALLY COMPLETED NAME] might be reduced if you take any of the following products.
Tell your doctor if you take:
- *Phenobarbital, phenytoin* (to prevent seizures)
- *Dexamethasone* (corticosteroid)
- *Efavirenz* (HIV infection)
- *Telaprevir, boceprevir* (hepatitis C virus infection)
- *Rifapentine, rifabutin* (medicines to treat some infections such as tuberculosis) - *Saquinavir* (HIV infection).

The effects of other medicines might be influenced if you take [NATIONALLY COMPLETED NAME].
Tell your doctor if you take:
- *Amlodipine, diltiazem, disopyramide, carvedilol, felodipine, flecainide, metoprolol, mexiletine, nifedipine, nicardipine*, *propafenone*, *timolol, verapamil* (for heart disease) as the therapeutic effect or side effects of these medicines may be increased.
- *Apixaban, dabigatran etexilate, rivaroxaban, warfarin* (to reduce clotting of the blood) as their therapeutic effect or side effects may be altered; your doctor may have to check your blood.
- Oestrogen-based hormonal contraceptives and hormonal replacement therapy. [NATIONALLY COMPLETED NAME] might reduce its effectiveness. When used for birth control, alternative methods of non-hormonal contraception are recommended.
- *Atorvastatin, pravastatin, rosuvastatin* (to lower cholesterol levels). The risk of muscle tissue disorder might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation. - *Clarithromycin* (antibiotic)
- *Ciclosporin, everolimus, tacrolimus, sirolimus* (to treat 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.
- *Fluticasone, budesonide* (to control asthma). Its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.
- *Buprenorphine/naloxone* (medicines to treat opiate dependence)
- *Salmeterol* (medicine to treat asthma)
- *Artemether/lumefantrine* (a combination medicine to treat malaria).
- *Dasatinib, everolimus, nilotinib, vinblastine, vincristine* (to treat cancer)
- *Prednisone* (corticosteroid)
- *Sildenafil, tadalafil, vardenafil* (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension).

The dosage of other medicines might need to be changed since either their own or [NATIONALLY COMPLETED NAME]'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)
- *Digoxin* (to treat certain heart disorders)
- *Clarithromycin* (antibiotic)
- *Ketoconazole, itraconazole, posaconazole, clotrimazole* (to treat fungal infections). Voriconazole should only be taken after medical evaluation.
- *Rifabutin* (against bacterial infections)
- *Sildenafil, vardenafil, tadalafil* (for erectile dysfunction or high blood pressure in the pulmonary circulation)

- *Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone* (to treat depression and anxiety)
- *Maraviroc* (to treat HIV infection)
- *Methadone* (to treat opiate dependance)
- *Carbamazepine* (to prevent seizures or to treat certain types of nerve pain)
- *Colchicine* (to treat gout)
- *Bosentan* (to treat high blood pressure int the pulmonary circulation)
- *Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam that is not taken orally, zoldipem* (sedative agents)
- *Risperidone, thioridazine* (to treat psychiatric conditions).

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

[NATIONALLY COMPLETED NAME] with food and drink
See section 3 'How to take [NATIONALLY COMPLETED NAME].'

Pregnancy and breast-feeding
Tell your doctor immediately if you are pregnant or if you are breast-feeding. Pregnant or breastfeeding mothers must not take [NATIONALLY COMPLETED NAME] unless specifically directed by the doctor. It is recommended that HIV infected women must not breast-feed their infants because of both the possibility of your baby becoming infected with HIV through your breast milk and because of the unknown effects of the medicine on your baby.

Driving and using machines
Do not operate machines or drive if you feel dizzy after taking [NATIONALLY COMPLETED NAME].

[**[300 mg]: [NATIONALLY COMPLETED NAME] tablets contain sunset yellow FCF (E110)** which may cause allergic reactions.]

[**[600 mg]: [NATIONALLY COMPLETED NAME] tablets contain sunset yellow FCF (E110)** which may cause allergic reactions.]

3. How to take [NATIONALLY COMPLETED NAME]

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.
Even if you feel better, do not stop taking [NATIONALLY COMPLETED NAME] and ritonavir without talking to your doctor.

After therapy has been initiated, the dose or dosage form must not be changed or therapy must not be stopped without instruction of the doctor.

Dose for children of 3 years of age and above, weighing at least 15 kilograms who have not taken antiretroviral medicines before (your child's doctor will determine this)
The doctor will work out the right once daily dose based on the weight of the child (see table below). This dose must not exceed the recommended adult dose, which is 800 milligram [NATIONALLY COMPLETED NAME] together with 100 milligram ritonavir once a day.
The doctor will inform you on how much [NATIONALLY COMPLETED NAME] tablets and how much ritonavir (capsules, tablets or solution) the child must take.

Weight	One [NATIONALLY COMPLETED NAME] dose is	One ritonavir[a] dose is
between 15 and 30 kilograms	600 milligram	100 milligram
between 30 and 40 kilograms	675 milligram	100 milligram
more than 40 kilograms	800 milligram	100 milligram

a ritonavir oral solution: 80 milligram per milliliter

Dose for children of 3 years of age and above, weighing at least 15 kilograms who have taken antiretroviral medicines before (your child's doctor will determine this)
The doctor will work out the right dose based on the weight of the child (see table below). The doctor will determine if once daily dosing or twice daily dosing is appropriate for the child. This dose must not exceed the recommended adult dose, which is 600 milligram [NATIONALLY COMPLETED NAME] together with 100 milligram ritonavir two times per day or 800 milligram [NATIONALLY COMPLETED NAME] together with 100 milligram ritonavir once a day.
The doctor will inform you on how many [NATIONALLY COMPLETED NAME] tablets and how much ritonavir (capsules, tablets or solution) the child must take. Tablets of other strengths are available and your doctor may have prescribed a certain combination of tablets to construct the appropriate dosing regimen. Darunavir oral suspension is also available. Your doctor will determine whether darunavir tablets or oral suspension is right for the child.

Twice daily dosing

Weight	One dose is
between 15 and 30 kilograms	375 milligram [NATIONALLY COMPLETED NAME] + 50 milligram ritonavir twice a day
between 30 and 40 kilograms	450 milligram [NATIONALLY COMPLETED NAME] + 60 milligram ritonavir twice a day
more than 40 kilograms*	600 milligram [NATIONALLY COMPLETED NAME] + 100 milligram ritonavir twice a day

* For children aged 12 or more and weighing at least 40 kilograms, your child's doctor will determine if [NATIONALLY COMPLETED NAME] 800 milligram once daily dosing may be used. This cannot be administered with these 75 milligram [150 milligram] [300 milligram] [600 milligram] tablets. Other strengths of [NATIONALLY COMPLETED NAME] are available.

Once daily dosing

Weight	One [NATIONALLY COMPLETED NAME] dose is	One ritonavir[a] dose is
between 15 and 30 kilograms	600 milligram	100 milligram
between 30 and 40 kilograms	675 milligram	100 milligram
more than 40 kilograms	800 milligram	100 milligram

a ritonavir oral solution: 80 milligram per milliliter

Instructions for children
- The child must take [NATIONALLY COMPLETED NAME] always together with ritonavir. [NATIONALLY COMPLETED NAME] cannot work properly without ritonavir.
- The child must take the appropriate doses of [NATIONALLY COMPLETED NAME] and ritonavir two times per day or once a day. If prescribed [NATIONALLY COMPLETED NAME] twice daily the child must take one dose in the morning, and one dose in the evening. Your child's doctor will determine the appropriate dosing regimen for your child.
- The child must take [NATIONALLY COMPLETED NAME] with food. [NATIONALLY COMPLETED NAME] cannot work properly without food. The type of food is not important.

- The child must swallow the tablets with a drink such as water or milk.

Dose for adults who have not taken antiretroviral medicines before (your doctor will determine this)
You will require a different dose of [NATIONALLY COMPLETED NAME] which cannot be administered with these 75 milligram [150 milligram] [300 milligram] [600 milligram] tablets. Other strengths of [NATIONALLY COMPLETED NAME] are available.

Dose for adults who have taken antiretroviral medicines before (your doctor will determine this)
The dose is either:
- 600 milligram [NATIONALLY COMPLETED NAME] (2 tablets containing 300 milligram of [NATIONALLY COMPLETED NAME] or 1 tablet containing 600 milligram of [NATIONALLY COMPLETED NAME]) together with 100 milligram ritonavir twice daily. OR
- 800 milligram [NATIONALLY COMPLETED NAME] (2 tablets containing 400 milligram of [NATIONALLY COMPLETED NAME] or 1 tablet containing 800 milligram of [NATIONALLY COMPLETED NAME]) together with 100 milligram ritonavir once daily. [NATIONALLY COMPLETED NAME] 400 milligram and 800 milligram tablets are only to be used to construct the once daily 800 milligram regimen.

Please discuss with your doctor which dose is right for you.

Instructions for adults
- Take [NATIONALLY COMPLETED NAME] always together with ritonavir. [NATIONALLY COMPLETED NAME] cannot work properly without ritonavir.
- In the morning, take 600 milligram [NATIONALLY COMPLETED NAME] together with 100 milligram ritonavir.

[**[300 mg]:**
- In the morning, take two 300 milligram [NATIONALLY COMPLETED NAME] tablets together with 100 milligram ritonavir.]

[**[600 mg]:**
- In the morning, take one 600 milligram [NATIONALLY COMPLETED NAME] tablet together with 100 milligram ritonavir.]
- In the evening, take 600 milligram [NATIONALLY COMPLETED NAME] together with 100 milligram ritonavir.

[**[300 mg]:**
- In the evening, take two 300 milligram [NATIONALLY COMPLETED NAME] tablets together with 100 milligram ritonavir.] [**[600 mg]:**
- In the evening, take one 600 milligram [NATIONALLY COMPLETED NAME] tablet together with 100 milligram ritonavir.]
- Take [NATIONALLY COMPLETED NAME] with food. [NATIONALLY COMPLETED NAME] cannot work properly without food. The type of food is not important.
- Swallow the tablets with a drink such as water or milk.
- [NATIONALLY COMPLETED NAME] 75 milligram and 150 milligram tablets have been developed for use in children, but can also be used in adults in some cases.

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 [NATIONALLY COMPLETED NAME] than you should Contact your doctor, pharmacist or nurse immediately.

If you forget to take [NATIONALLY COMPLETED NAME]
If you notice **within 6 hours**, you must take the tablets immediately. Always take with ritonavir and food. If you notice **after 6 hours**, then skip the intake and take the next doses as usual. Do not take a double dose to make up for a forgotten dose.

Do not stop taking [NATIONALLY COMPLETED NAME] without talking to your doctor first
HIV therapy may increase your sense of well-being. Even when you feel better, do not stop taking [NATIONALLY COMPLETED NAME]. Talk to your doctor first.

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 prior to initiating [NATIONALLY COMPLETED NAME]. 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 colored) urine, pale colored stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on your right side below your ribs.

Skin rash (more often when used in combination with raltegravir), itching. The rash is usually mild to moderate. A skin rash might also be a symptom of a rare severe situation. It is therefore important to contact your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether [NATIONALLY COMPLETED NAME] must be stopped.

Other clinically relevant severe side effects, reported at a common frequency, were diabetes, body changes associated with fat redistribution and increased blood fat levels. Those reported at an uncommon frequency were inflammation of the pancreas.

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

Common side effects (may affect up to 1 in 10 people)
- vomiting, nausea, abdominal pain or distension, dyspepsia, flatulence
- headache, tiredness, dizziness, drowsiness, numbness, tingling or pain in hands or feet, loss of strength, difficulty falling asleep.

Uncommon side effects (may affect up to 1 in 100 people)

- chest pain, changes in electrocardiogram, rapid heart beating
- decreased or abnormal skin sensibility, pins and needles, attention disturbance, loss of memory, problems with your balance
- difficulty breathing, cough, nosebleed, throat irritation
- inflammation of the stomach or mouth, heartburn, retching, dry mouth, discomfort of the abdomen, constipation, belching
- kidney failure, kidney stones, difficult discharge of urine, frequent or excessive passage of urine, sometimes at night
- urticaria, severe swelling of the skin and other tissues (most often the lips or the eyes), eczema, excessive sweating, night sweats, hair loss, acne, scaly skin, colouration of nails - muscle pain, muscle cramps or weakness, pain in extremity, osteoporosis
- slowing down of the thyroid gland function. This can be seen in a blood test.
- high blood pressure, flushing
- red or dry eyes
- fever, swelling of lower limbs due to fluids, malaise, irritability, pain
- symptoms of infection, herpes simplex
- erectile dysfunction, enlargement of breasts
- sleeping problems, sleepiness, depression, anxiety, abnormal dreams, decrease in sexual drive
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood tests. Your doctor will explain these to you. Examples are: low white or red blood cell count, low blood platelet count, high sugar levels, high levels of insulin.

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]
- heart attack, slow heart beating, palpitations
- visual disturbance
- chills, feeling abnormal
- a feeling of confusion or disorientation, altered mood, restlessness
- fainting, epileptic fits, changes or loss of taste
- mouth sores, vomiting blood, inflamation of the lips, dry lips, coated tongue
- running nose
- skin lesions, dry skin
- stiffness of muscles or joints, joint pain with or without inflammation
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood and/or urine tests. Your doctor will explain these to you. Examples are: increase in some white blood cells.

Some side effects are typical for anti-HIV medicines in the same family as [NATIONALLY COMPLETED NAME]. These are:
- raised blood sugar and worsening of diabetes.
- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.
- changes in body shape due to fat redistribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (buffalo hump). The cause and long-term health effects of these conditions are not known at this time.

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 [NATIONALLY COMPLETED NAME]

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

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

[NATIONALLY COMPLETED NAME] does not require any special storage conditions.

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

6. Contents of the pack and other information

What [NATIONALLY COMPLETED NAME] contains
- The active substance is darunavir. Each tablet contains 75 milligram [150 milligram] [300 milligram] [600 milligram] of darunavir.

- The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate. The film-coating contains poly(vinyl alcohol) - partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc.

[150 mg]:
- The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate. The film-coating contains poly(vinyl alcohol) - partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc.]

[**300 mg]:**
- The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate. The film-coating contains poly(vinyl alcohol) - partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc, sunset yellow FCF (E110).]

[600 mg]:
- The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate. The film-coating contains poly(vinyl alcohol) - partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc, sunset yellow FCF (E110).]

What [NATIONALLY COMPLETED NAME] looks like and contents of the pack
White caplet shaped film-coated tablet, debossed with ‘75’ on one side and plain on the other side. 480 tablets in a plastic bottle.

[NATIONALLY COMPLETED NAME] is also available as 150 milligram, 300 milligram, 400 milligram, 600 milligram and 800 milligram film-coated tablets.

[150 mg]:
White, oval shaped film-coated tablet, debossed with ‘150’ on one side and plain on the other side. 240 tablets in a plastic bottle.

[NATIONALLY COMPLETED NAME] is also available as 75 milligram, 300 milligram, 400 milligram, 600 milligram and 800 milligram film-coated tablets.]

[300 mg]:
Orange oval shaped film-coated tablet, debossed with '300' on one side and plain on the other side. 120 tablets in a plastic bottle.

[NATIONALLY COMPLETED NAME] is also available as 75 milligram, 150 milligram, 400 milligram, 600 milligram and 800 milligram film-coated tablets.]

[600 mg]:
Orange oval shaped film-coated tablet, debossed with '600' on one side and plain on the other side. 60 tablets in a plastic bottle.

[NATIONALLY COMPLETED NAME] is also available as 75 milligram, 150 milligram, 300 milligram, 400 milligram and 800 milligram film-coated tablets.]

Marketing Authorisation Holder
[To be completed nationally]

Manufacturer
[To be completed nationally]

This leaflet was last revised in {MM/YYYY}.
[To be completed nationally]

PACKAGE LEAFLET

[NATIONALLY COMPLETED NAME] 400 mg
[800 mg] film-coated tablets darunavir

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 [NATIONALLY COMPLETED NAME] is and what it is used for

What is [NATIONALLY COMPLETED NAME]?
[NATIONALLY COMPLETED NAME] contains the active substance darunavir. [NATIONALLY COMPLETED NAME] is an antiretroviral medicine used in the treatment of Human Immunodeficiency Virus (HIV) infection. It belongs to a group of medicines called protease inhibitors. [NATIONALLY COMPLETED NAME] works by reducing the amount of HIV in your body. This will improve your immune system and reduces the risk of developing illnesses linked to HIV infection.

What is it used for?
[NATIONALLY COMPLETED NAME] 400 milligram [800 milligram] is used to treat adults and children (12 years of age and above, at least 40 kilograms body weight)
- who are infected by HIV and who have not used antiretroviral medicines before
- in certain patients who have used antiretroviral medicines before (your doctor will determine this)

[NATIONALLY COMPLETED NAME] must be taken in combination with a low dose of cobicistat or ritonavir and other anti-HIV medicines. Your doctor will discuss with you which combination of medicines is best for you.

2. What you need to know before you take [NATIONALLY COMPLETED NAME]
Do not take [NATIONALLY COMPLETED NAME]
- if you are **allergic** to darunavir or any of the other ingredients of this medicine (listed in section 6) or to cobicistat or ritonavir.
- 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.

Do not combine [NATIONALLY COMPLETED NAME] 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
Avanafil	to treat erectile dysfunction
Astemizole or *terfenadine*	to treat allergy symptoms
Triazolam and *oral (*taken by mouth*) midazolam*	to help you sleep and/or relieve anxiety
Cisapride	to treat some stomach conditions
Colchicine (if you have kidney and/or liver problems)	to treat gout
*Pimozide, quetiapine*or *sertindole*	to treat psychiatric conditions
Ergot alkaloids like *ergotamine*, *dihydroergotamine*, *ergometrine* and *methylergonovine*	to treat migraine and headaches
Amiodarone, bepridil, dronedarone, quinidine, ranolazine and *systemic lidocaine*	to treat certain heart disorders e.g. abnormal heart beat
Lovastatin and *simvastatin*	to lower cholesterol levels
Rifampicin	to treat some infections such as tuberculosis
The combination product *lopinavir/ritonavir*	this anti-HIV medicine belongs to the same class as [NATIONALLY COMPLETED NAME]
Alfuzosin	to treat enlarged prostate
Sildenafil	to treat high blood pressure in the pulmonary circulation
Ticagrelor	to help stop the clumping of platelets in the treatment of patients with a history of a heart attack

Do not combine [NATIONALLY COMPLETED NAME] with products that contain St John's wort *(Hypericum perforatum)*

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking [NATIONALLY COMPLETED NAME].

[NATIONALLY COMPLETED NAME] is not a cure for HIV infection. 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 [NATIONALLY COMPLETED NAME] may still develop infections or other illnesses associated with HIV infection. You must keep in regular contact with your doctor.

People taking [NATIONALLY COMPLETED NAME] may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. Please contact your doctor whenever you develop a rash.

In patients taking [NATIONALLY COMPLETED NAME] and raltegravir (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.

[NATIONALLY COMPLETED NAME] 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 [NATIONALLY COMPLETED NAME].

Tell your doctor about your situation BEFORE and DURING your treatment
Make sure that you check the following points and tell your doctor if any of these apply to you.
- Tell your doctor if you have had **problems with your liver** before, including hepatitis B or C. Your doctor may evaluate how severe your liver disease is before deciding if you can take [NATIONALLY COMPLETED NAME].
- Tell your doctor if you have **diabetes**. [NATIONALLY COMPLETED NAME] might increase sugar levels in the blood.
- Tell your doctor immediately if you notice any **symptoms of infection** (for example enlarged lymph nodes and fever). In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. 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.
- 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 symptoms of infection or other 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, please inform your doctor immediately to seek necessary treatment.
- Tell your doctor if you **notice changes in body fat**. Redistribution, accumulation or loss of body fat may occur in patients receiving a combination of antiretroviral medicines.
- Tell your doctor if you have **haemophilia**. [NATIONALLY COMPLETED NAME] might increase the risk of bleeding.
- Tell your doctor if you are **allergic to sulphonamides** (e.g. used to treat certain infections).
- Tell your doctor if you notice any **musculoskeletal problems**. Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. 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 please inform your doctor.

Children and adolescents

[NATIONALLY COMPLETED NAME] 400 milligram is not for use in children younger than 3 years of age or weighing less than 15 kilograms.

[**[800 mg]:**
[NATIONALLY COMPLETED NAME] 800 milligram is not for use in children younger than 3 years of age or weighing less than 40 kilograms.]

Other medicines and [NATIONALLY COMPLETED NAME]
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 [NATIONALLY COMPLETED NAME]. These are mentioned above under the heading 'Do not combine [NATIONALLY COMPLETED NAME] with any of the following medicines:'

In most cases, [NATIONALLY COMPLETED NAME] can be combined with anti-HIV medicines belonging to another class [e.g. NRTIs (nucleoside reverse transcriptase inhibitors), NNRTIs (nonnucleoside reverse transcriptase inhibitors), CCR5 antagonists and FIs (fusion inhibitors)]. [NATIONALLY COMPLETED NAME] with cobicistat or ritonavir has not been tested with all PIs (protease inhibitors) and must not be used with other HIV PIs. 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.

The effects of [NATIONALLY COMPLETED NAME] might be reduced if you take any of the following products. Tell your doctor if you take:
- *Phenobarbital, phenytoin* (to prevent seizures)
- *Dexamethasone* (corticosteroid)
- *Efavirenz* (HIV infection)
- *Telaprevir, boceprevir* (hepatitis C virus infection)
- *Rifapentine, rifabutin* (medicines to treat some infections such as tuberculosis) - *Saquinavir* (HIV infection).

The effects of other medicines might be influenced if you take [NATIONALLY COMPLETED NAME]. Tell your doctor if you take:
- *Amlodipine, diltiazem, disopyramide, carvedilol, felodipine, flecainide, metoprolol, mexiletine,*

- *nifedipine, nicardipine*, *propafenone*, *timolol, verapamil* (for heart disease) as the therapeutic effect or side effects of these medicines may be increased.
  Apixaban, dabigatran etexilate, rivaroxaban, warfarin (to reduce clotting of the blood) as their therapeutic effect or side effects may be altered; your doctor may have to check your blood.
- Oestrogen-based hormonal contraceptives and hormonal replacement therapy. [NATIONALLY COMPLETED NAME] might reduce its effectiveness. When used for birth control, alternative methods of non-hormonal contraception are recommended.
- *Atorvastatin, pravastatin, rosuvastatin* (to lower cholesterol levels). The risk of muscle tissue disorder might be increased. Your doctor will evaluate which cholesterol lowering regimen is best for your specific situation.
- *Clarithromycin* (antibiotic)
- *Ciclosporin, everolimus, tacrolimus, sirolimus* (to treat 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.
- *Fluticasone, budesonide* (to control asthma). Its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.
- *Buprenorphine/naloxone* (medicines to treat opiate dependence)
- *Salmeterol* (medicine to treat asthma)
- *Artemether/lumefantrine* (a combination medicine to treat malaria).
- *Dasatinib, everolimus, nilotinib, vinblastine, vincristine* (to treat cancer)
- *Prednisone* (corticosteroid)
- *Sildenafil, tadalafil, vardenafil* (for erectile dysfunction or to treat a heart and lung disorder called pulmonary arterial hypertension).

The dosage of other medicines might need to be changed since either their own or [NATIONALLY COMPLETED NAME]'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)
- *Digoxin* (to treat certain heart disorders)
- *Clarithromycin* (antibiotic)
- *Ketoconazole, itraconazole, fluconazole, posaconazole, clotrimazole* (to treat fungal infections). Voriconazole should only be taken after medical evaluation.
- *Rifabutin* (against bacterial infections)
- *Sildenafil, vardenafil, tadalafil* (for erectile dysfunction or high blood pressure in the pulmonary circulation)
- *Amitriptyline, desipramine, imipramine, nortriptyline, paroxetine, sertraline, trazodone* (to treat depression and anxiety)
- *Maraviroc* (to treat HIV infection)
- *Methadone* (to treat opiate dependance)
- *Carbamazepine* (to prevent seizures or to treat certain types of nerve pain)
- *Colchicine* (to treat gout)
- *Bosentan* (to treat high blood pressure int the pulmonary circulation)
- *Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam that is not taken orally, zoldipem* (sedative agents)
- *Perphenazine, risperidone, thioridazine* (to treat psychiatric conditions) - *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.

[NATIONALLY COMPLETED NAME] with food and drink
See section 3 'How to take [NATIONALLY COMPLETED NAME].'

Pregnancy and breast-feeding
Tell your doctor immediately if you are pregnant or if you are breast-feeding. Pregnant or breastfeeding mothers must not take [NATIONALLY COMPLETED NAME] unless specifically directed by the doctor. It is recommended that HIV infected women must not breast-feed their infants because of both the possibility of your baby becoming infected with HIV through your breast milk and because of the unknown effects of the medicine on your baby.

Driving and using machines
Do not operate machines or drive if you feel dizzy after taking [NATIONALLY COMPLETED NAME].

[Only for 400 mg:]
[NATIONALLY COMPLETED NAME] tablets contain sunset yellow FCF (E110) which may cause allergic reactions.

3. How to take [NATIONALLY COMPLETED NAME]

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.
Even if you feel better, do not stop taking [NATIONALLY COMPLETED NAME] and cobicistat or ritonavir without talking to your doctor.

After therapy has been initiated, the dose or dosage form must not be changed or therapy must not be stopped without instruction of the doctor.

[NATIONALLY COMPLETED NAME] 400 milligram tablets are only to be used to construct the once daily 800 milligram regimen.
[**[800 mg]:**
[NATIONALLY COMPLETED NAME] 800 milligram tablets are intended for once daily use only.]

Dose for adults who have not taken antiretroviral medicines before (your doctor will determine this)
The usual dose of [NATIONALLY COMPLETED NAME] is 800 milligram (2 tablets containing 400 milligram of [NATIONALLY COMPLETED NAME] or 1 tablet containing 800 milligram of [NATIONALLY COMPLETED NAME]) once daily.
You must take [NATIONALLY COMPLETED NAME] every day and always in combination with 150 milligram of cobicistat or 100 milligram of ritonavir and with food. [NATIONALLY COMPLETED NAME] cannot work properly without cobicistat or ritonavir and food. You must eat a meal or a snack within 30 minutes prior to taking your [NATIONALLY COMPLETED NAME] and cobicistat or ritonavir. The type of food is not important. Even if you feel better, do not stop taking [NATIONALLY COMPLETED NAME] and cobicistat or ritonavir without talking to your doctor.

Instructions for adults
- Take two 400 milligram tablets at the same time, once a day, every day. [**[800 mg]:**
- Take one 800 milligram tablet at the same time, once a day, every day.]
- Take [NATIONALLY COMPLETED NAME] always together with 150 milligram of cobicistat or100 milligram of ritonavir.
- Take [NATIONALLY COMPLETED NAME] with food.
- Swallow the tablets with a drink such as water or milk. [**[800 mg]:**
- Swallow the tablet with a drink such as water or milk.]
- Take your other HIV medicines used in combination with [NATIONALLY COMPLETED NAME] and cobicistat or ritonavir as recommended by your doctor.
- Darunavir 100 milligram per milliliter oral suspension has been developed for use in children, but can also be used in adults in some cases.

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Dose for adults who have taken antiretroviral medicines before (your doctor will determine this)
The dose is either:
- 800 milligram [NATIONALLY COMPLETED NAME] (2 tablets containing 400 milligram of [NATIONALLY COMPLETED NAME] or 1 tablet containing 800 milligram of [NATIONALLY COMPLETED NAME]) together with 150 milligram cobicistat or 100 milligram ritonavir once daily.
  OR
  600 milligram [NATIONALLY COMPLETED NAME] (2 tablets containing 300 milligram of [NATIONALLY COMPLETED NAME] or 1 tablet containing 600 milligram of [NATIONALLY COMPLETED NAME]) together with 100 milligram ritonavir twice daily.

Please discuss with your doctor which dose is right for you.

Dose for children 3 years of age and above, weighing more than 40 kilograms who have not taken antiretroviral medicines before (your child's doctor will determine this)
- The usual dose of [NATIONALLY COMPLETED NAME] is 800 milligram (2 tablets containing 400 milligram of [NATIONALLY COMPLETED NAME] or 1 tablet containing 800 milligram of [NATIONALLY COMPLETED NAME]) together with 100 milligram ritonavir once daily.

Dose for children 3 years of age and above, weighing more than 40 kilograms who have taken antiretroviral medicines before (your child's doctor will determine this) The dose is either:
- 800 milligram [NATIONALLY COMPLETED NAME] (2 tablets containing 400 milligram of [NATIONALLY COMPLETED NAME] or 1 tablet containing 800 milligram of [NATIONALLY COMPLETED NAME]) together with 100 milligram ritonavir once daily. OR
- 600 milligram [NATIONALLY COMPLETED NAME] (2 tablets containing 300 milligram of [NATIONALLY COMPLETED NAME] or 1 tablet containing 600 milligram of [NATIONALLY COMPLETED NAME]) together with 100 milligram ritonavir twice daily.

Please discuss with your doctor which dose is right for you.

Instructions for children 3 years of age and above, weighing more than 40 kilograms
- Take 800 milligram [NATIONALLY COMPLETED NAME] (2 tablets containing 400 milligram of [NATIONALLY COMPLETED NAME] or 1 tablet containing 800 milligram of [NATIONALLY COMPLETED NAME]) at the same time, once a day, every day.
- Take [NATIONALLY COMPLETED NAME] always together with 100 milligram of ritonavir.
- Take [NATIONALLY COMPLETED NAME] with food.
- Swallow the tablets with a drink such as water or milk.
- Take your other HIV medicines used in combination with [NATIONALLY COMPLETED NAME] and ritonavir as recommended by your doctor.

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 [NATIONALLY COMPLETED NAME] than you should Contact your doctor, pharmacist or nurse immediately.

If you forget to take [NATIONALLY COMPLETED NAME]
If you notice **within 12 hours**, you must take the tablets immediately. Always take with cobicistat or ritonavir and food. If you notice **after 12 hours**, then skip the intake and take the next doses as usual. Do not take a double dose to make up for a forgotten dose.

Do not stop taking [NATIONALLY COMPLETED NAME] without talking to your doctor first
HIV therapy may increase your sense of well-being. Even when you feel better, do not stop taking [NATIONALLY COMPLETED NAME]. Talk to your doctor first.

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 prior to initiating [NATIONALLY COMPLETED NAME]. 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 colored) urine, pale colored stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on your right side below your ribs.

Skin rash (more often when used in combination with raltegravir), itching. The rash is usually mild to moderate. A skin rash might also be a symptom of a rare severe situation. It is therefore important to contact your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms or whether [NATIONALLY COMPLETED NAME] must be stopped.

Other clinically relevant severe side effects, reported at a common frequency, were diabetes, body changes associated with fat redistribution and increased blood fat levels. Those reported at an uncommon frequency were inflammation of the pancreas. **Very common side effects** (may affect more than 1 in 10 people) - diarrhoea.

Common side effects (may affect up to 1 in 10 people)
- vomiting, nausea, abdominal pain or distension, dyspepsia, flatulence
- headache, tiredness, dizziness, drowsiness, numbness, tingling or pain in hands or feet, loss of strength, difficulty falling asleep.

Uncommon side effects (may affect up to 1 in 100 people)
- chest pain, changes in electrocardiogram, rapid heart beating
- decreased or abnormal skin sensibility, pins and needles, attention disturbance, loss of memory, problems with your balance
- difficulty breathing, cough, nosebleed, throat irritation
- inflammation of the stomach or mouth, heartburn, retching, dry mouth, discomfort of the abdomen, constipation, belching
- kidney failure, kidney stones, difficult discharge of urine, frequent or excessive passage of urine, sometimes at night
- urticaria, severe swelling of the skin and other tissues (most often the lips or the eyes), eczema, excessive sweating, night sweats, hair loss, acne, scaly skin, colouration of nails - muscle pain, muscle cramps or weakness, pain in extremity, osteoporosis
- slowing down of the thyroid gland function. This can be seen in a blood test.
- high blood pressure, flushing

-
- red or dry eyes
- fever, swelling of lower limbs due to fluids, malaise, irritability, pain
- symptoms of infection, herpes simplex
- erectile dysfunction, enlargement of breasts
- sleeping problems, sleepiness, depression, anxiety, abnormal dreams, decrease in sexual drive
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood tests. Your doctor will explain these to you. Examples are: low white or red blood cell count, low blood platelet count, high sugar levels, high levels of insulin.

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]
  heart attack, slow heart beating, palpitations
- visual disturbance
- chills, feeling abnormal
- a feeling of confusion or disorientation, altered mood, restlessness
- fainting, epileptic fits, changes or loss of taste
- mouth sores, vomiting blood, inflamation of the lips, dry lips, coated tongue
- running nose
- skin lesions, dry skin
- stiffness of muscles or joints, joint pain with or without inflammation
- changes in some values of your blood cells or chemistry. These can be seen in the results of blood and/or urine tests. Your doctor will explain these to you. Examples are: increase in some white blood cells.

Some side effects are typical for anti-HIV medicines in the same family as [NATIONALLY COMPLETED NAME]. These are:
- raised blood sugar and worsening of diabetes.
- muscle pain, tenderness or weakness. On rare occasions, these muscle disorders have been serious.
- changes in body shape due to fat redistribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (buffalo hump). The cause and long-term health effects of these conditions are not known at this time.

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 [NATIONALLY COMPLETED NAME]

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

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

[NATIONALLY COMPLETED NAME] does not require any special storage conditions.

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

6. Contents of the pack and other information

What [NATIONALLY COMPLETED NAME] contains
- The active substance is darunavir. Each tablet contains 400 milligram [800 milligram] of darunavir.
- The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate. The film-coating contains poly(vinyl alcohol) - partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc, sunset yellow FCF (E110).

[800 mg]:
- The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate. The film-coating contains poly(vinyl alcohol) – partially hydrolysed, macrogol 3350, titanium dioxide (E171), talc, iron oxide red (E172).]

What [NATIONALLY COMPLETED NAME] looks like and contents of the pack
Light orange oval shaped film-coated tablet, debossed with ‘400’ on one side and plain on the other side.
60 tablets in a plastic bottle.
[NATIONALLY COMPLETED NAME] is also available as 75 milligram, 150 milligram, 300 milligram, 600 milligram and 800 milligram film-coated tablets.

[**[800 mg]:**
Dark red oval shaped film-coated tablet, debossed with ‘800’ on one side and plain on the other side.
30 tablets in a plastic bottle.

The [Nationally Completed Name] 800 milligram tablets are available in packs containing one bottle or three bottles per carton.
[NATIONALLY COMPLETED NAME] is also available as 75 milligram, 150 milligram, 300 milligram, 400 milligram and 600 milligram film-coated tablets.]

Not all pack sizes may be marketed

Marketing Authorisation Holder
[To be completed nationally]

Manufacturer
[To be completed nationally]

This leaflet was last revised in {MM/YYYY}.
[To be completed nationally]

6.3 Annex 3 – Worldwide marketing authorization by country (including EEA)

Table 6-1 A3.1 Licensing status in the EEA

Not yet authorized

Table 6-2 A3.2 Licensing status in the rest of the world Not yet authorized

6.4 Annex 4 – Synopsis of ongoing and completed clinical trial programme

None

6.5 Annex 5 – Synopsis of ongoing and completed pharmaco-epidemiological study programme

None

6.6 Annex 6 – Protocols for proposed and on-going studies in categories 1-3 of the section “Summary table of additional pharmacovigilance activities” in RMP Part III

None

6.7 Annex 7 – Specific adverse event follow up forms

None

6.8 Annex 8 – Protocols for proposed and on-going studies in RMP Part IV

None

6.9 Annex 9 – Newly available study reports for RMP Parts III & IV

None

6.10 Annex 10 - Details of proposed additional risk minimization activities (if applicable)

None

6.11 Annex 11 – Mock-up of proposed additional risk minimization measures (if applicable)

None

6.12 Annex 12 – Other supporting data (including referenced material)

External references

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