RISK MANAGEMENT PLAN

FOR

RITONAVIR

Active substance(s) (INN or common name):	Ritonavir
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, protease inhibitors (J05AE03)
Name of Marketing Authorisation Holder or Applicant:	Accord Healthcare Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Ritonavir Accord 100 mg Tablets

Data lock point for this RMP 20 July 2015 Version number 3

Date of final sign off 18 Aug 2015

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse drug event
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapies
CART	Combination Antiretroviral Therapy
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual recognition and Decentralised Procedures – Human
ECG	Electrocardiogram
EEA	European Economic Area
EU	European Union
EURD	European Reference Date
HIV-1	Human Immunodeficiency Virus 1
ICSR	Individual Case Safety Report
IRIS	Immune Reconstitution Inflammatory Syndrome
MAA	Marketing Authorization Applicant
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
OCs	Oral Contraceptives

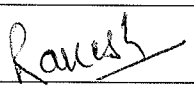
Abbreviation	Definition
PL	Package Leaflets
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTY	Patient Treatment Years
SmPC	Summary of Product Characteristics
WHOPAR	WHO Public Assessment Report

PART I: PRODUCT(S) OVERVIEW

Part	**Module/annex**	**Date last updated for submission (sign off date)**	***Version number of RMP when last submitted**
Part II Safety Specification	SV Post authorisation experience	18-Aug-2015	Version 2.0
	SVIII Summary of the safety concerns	18-Aug-2015	Version 2.0
Part III Pharmacovigilance Plan		18-Aug-2015	Version 2.0
Part IV Plan for post-authorisation efficacy studies		Notapplicable	Not applicable
Part V Risk Minimisation Measures		18-Aug-2015	Version 2.0
Part VI Summary of RMP		18-Aug-2015	Version 2.0
Part VII Annexes	ANNEX 1 Eudravigilance interface	Not applicable	Not applicable
	ANNEX 2 Proposed SmPC	18-Aug-2015	Version 2.0

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted
	ANNEX 3 Worldwide marketing status by country	18-Aug-2015	Version 2.0
	ANNEX 4 Synopsis of on-going and completed clinical trial programme	Not applicable	Not applicable
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	Not applicable	Not applicable
	ANNEX 6 Protocols for proposed and on-going studies in Part III	Not applicable	Not applicable
	ANNEX 7 Specific adverse event follow-up forms	Not applicable	Not applicable
	ANNEX 8 Protocols for studies in Part IV	Not applicable	Not applicable
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	Not applicable	Not applicable
	ANNEX 10 Details of proposed additional risk minimisation activities	Not applicable	Not applicable

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted
	ANNEX 11 Mock up examples	Not applicable	Not applicable
	ANNEX 12 Other supporting data	18-Aug-2015	Version 2.0

QPPV name	Rakesh Barmy
QPPV signature	
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Overview of versions:

Version number of last agreed RMP:	Not applicable
Version number:	Not applicable

Current RMP versions under evaluation:

RMP Version number	Submitted on	Submitted within
Version 2.0	26-Jun-2015	NL/H/3149/01-02/DC NL/H/3150/01/02/DC

Invented name(s) in the European Economic Area (EEA)	Ritonavir
Authorisation procedure	De-Centralised procedure
Brief description of the product including: • chemical class • summary of mode of action • important information about its composition	Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors <u>*Ritonavir dosed as a pharmacokinetic enhancer*</u> Pharmacokinetic enhancement by ritonavir is based on ritonavir's activity as a potent inhibitor of CYP3A-mediated metabolism. The degree of enhancement is related to the metabolic pathway of the co-administered protease inhibitor (PI) and the impact of the co-administered protease inhibitor on the metabolism of ritonavir. Maximal inhibition of metabolism of the co-administered PI is generally achieved with ritonavir doses of 100 mg daily to 200 mg twice daily, and is dependent on the co- administered PI. For additional information on the effect of ritonavir on co-administered PI metabolism.[1] <u>*Ritonavir dosed as an antiretroviral agent*</u> Ritonavir is an orally active peptidomimetic inhibitor of the HIV-1 and HIV-2 aspartyl proteases. Inhibition of HIV protease renders the enzyme incapable of processing the *gag-pol* polyprotein precursor which leads to the production of HIV particles with immature morphology that is unable to initiate new rounds of infection. Ritonavir has selective affinity for the HIV protease and has little inhibitory activity against human aspartyl proteases.[1] Each film-coated tablet contains 100 mg ritonavir. The

	inactive ingredients are copovidone(K-30), sorbitanlaurate(E493), silica colloidal anhydrous(E551), calcium hydrogen phosphate anhydrous, sodium stearyl fumarate. Excipients used for film coating are hypromellose(E464), titanium dioxide (E171), macrogol/PEG MW 400 (E1521) / macrogol/peg mw3350 (E1521), hydroxypropyl cellulose(E463), talc(E553b), silica colloidal anhydrous(E551), polysorbate 80(E433). [1]
Indication(s) in the EEA Proposed	Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children of 2 years of age and older). [1]
Posology and route of administration in the EEA Proposed	Ritonavir should be administered by physicians who are experienced in the treatment of HIV infection. Ritonavir film-coated tablets are administered orally and should be ingested with food. Ritonavir film-coated tablets should be swallowed whole and not chewed, broken or crushed. ***Ritonavir dosed as a pharmacokinetic enhancer*** The following HIV-1 protease inhibitors have been approved for use with ritonavir as a pharmacokinetic enhancer at the noted doses. *Adult use:* • Amprenavir 600 mg twice daily with ritonavir 100 mg twice daily • Atazanavir 300 mg once daily with ritonavir 100 mg once daily • Fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily

	• Lopinavir co-formulated with ritonavir (lopinavir/ritonavir 400 mg/100 mg or 800 mg/200 mg) • Saquinavir 1000 mg twice daily with ritonavir 100 mg twice daily in ART experienced patients. Initiate treatment with saquinavir 500 mg twice daily with ritonavir 100 mg twice daily for the first 7 days, then saquinavir 1000 mg twice daily with ritonavir 100 mg twice daily in ART-naive patients. • Tipranavir 500 mg twice daily with ritonavir 200 mg twice daily. (Tipranavir with ritonavir should not be used in treatment-naive patients). • Darunavir 600 mg twice daily with ritonavir 100 mg twice daily in antiretroviral treatment (ART) experienced patients. Darunavir 800 mg once daily with ritonavir 100 mg once daily may be used in some ART experienced patients. • Darunavir 800mg once daily with ritonavir 100 mg once daily in ART-naïve patients *Paediatric use:* Ritonavir is recommended for children 2 years of age and older. Ritonavir is not recommended in children below 2 years of age due to lack of data on safety and efficacy. *Renal impairment:* As ritonavir is primarily metabolised by the liver, ritonavir may be appropriate for use with caution as a pharmacokinetic enhancer in patients with renal insufficiency depending on the specific protease inhibitor with which it is co-administered. However, since the renal clearance of ritonavir is negligible, the decrease in the total body clearance is not expected in

	patients with renal impairment. *Hepatic impairment:* Ritonavir should not be given as a pharmacokinetic enhancer to patients with decompensated liver disease. In the absence of pharmacokinetic studies in patients with stable severe hepatic impairment (Child Pugh Grade C) without decompensation, caution should be exercised when ritonavir is used as a pharmacokinetic enhancer as increased levels of the co-administered PI may occur. Specific recommendations for use of ritonavir as a pharmacokinetic enhancer in patients with hepatic impairment are dependent on the protease inhibitor with which it is co-administered. ***Ritonavir dosed as an antiretroviral agent*** *Adult use:* The recommended dose of ritonavir film-coated tablets is 600 mg (6 tablets) twice daily (total of 1200 mg per day) by mouth. Gradually increasing the dose of ritonavir when initiating therapy may help to improve tolerance. Treatment should be initiated at 300 mg (3 tablets) twice daily for a period of three days and increased by 100 mg (1 tablet) twice daily increments up to 600 mg twice daily over a period of no longer than 14 days. Patients should not remain on 300 mg twice daily for more than 3 days. *Paediatric use (2 years of age and above):* The recommended dosage of ritonavir in children is 350 mg/m^2 by mouth twice daily and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m^2 and increased at 2 to 3 day intervals by 50

	mg/m^2 twice daily. For older children it may be feasible to substitute tablets for the maintenance dose of the oral solution. Ritonavir is not recommended in children below 2 years of age due to lack of data on safety and efficacy. *Renal impairment:* Currently, there are no data specific to this patient population and therefore specific dosage recommendations cannot be made. The renal clearance of ritonavir is negligible; therefore, a decrease in the total body clearance is not expected in patients with renal impairment. Because ritonavir is highly protein bound it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis. *Hepatic impairment:* Ritonavir is principally metabolised and eliminated by the liver. Pharmacokinetic data indicate that no dose adjustment is necessary in patients with mild to moderate hepatic impairment. Ritonavir should not be given to patients with severe hepatic impairment. *Older people:* Pharmacokinetic data indicated that no dose adjustment is necessary for older patients. [1]
Pharmaceutical form(s) and strengths Proposed	100 mg film-coated tablet

Country and date of first authorisation worldwide	Not yet Authorised
Country and date of first launch worldwide	Not Applicable
Country and date of first authorisation in the EEA	Not Applicable

Is the product subject to additional monitoring in the EU? Yes ☐ No ☑

PART II: SAFETY SPECIFICATION

Module SV - Post-authorisation experience

SV.1 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons:

There have been no marketing authorisation restrictions on distribution, clinical trial suspensions, dosage modification, changes in target populations or indications, or formulation changes to Accord ritonavir, for any safety reasons.

SV.2 Non-study post-authorisation exposure

Ritonavir is not authorized worldwide by MAH till the data lock point of this RMP.

SV.3 Post-authorisation use in special populations

Not applicable.

SV.4 Post-authorisation off-label use

Not applicable.

SV.5 Epidemiological study exposure (if applicable)

Not applicable

Module SVIII - Summary of the safety concerns

Table 1 Summary of safety concerns

Important identified risk (s)	• Toxicity of ritonavir oral solution in preterm neonates • PR Prolongation[1] • Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease) [1]
Important potential risk (s)	• Drug-drug interactions with HCV products[1] • Risk of bleeding[1] • Osteonecrosis[1]
Missing information	• Severe hepatic impairment[1] • Severe renal impairment[1] • Use during pregnancy and lactation[1] • Limited experience with the 100 mg Tablet in HIV-1-infected children less than 2 years of age[1] • Geriatric population[1]

[1] Proposed SPC of Ritonavir Accord 100 mg Tablets

Part III: PHARMACOVIGILANCE PLAN

Routine pharmacovigilance system at Accord

[redacted]The following list summarizes Accord's activities for conducting routine global pharmacovigilance:

- Management of adverse drug event reporting training for MAA employees likely to have an interface with customers and/or regulatory authorities
- Generation of safety data exchange agreement covering different business arrangements (like co-marketing, co-distribution, out-licensing etc.)
- Handling of product quality complaints associated with ADE/ADR including lack of efficacy
- Global case processing (spontaneous, literature and regulatory authority cases)
- Follow up of safety reports for missing information and for information on the progress and outcome of the cases
- Generation of PSURs with cumulative analysis of data from all sources
- Management of cases with exposure to medicinal products during pregnancy
- Handling of customer communications/medical inquiries
- Periodic signal detection activity
- Conducting literature searches on weekly basis
- Identification of duplicate individual case safety reports (ICSRs) in pharmacovigilance database

Routine processing of ICSRs includes a medical evaluation of ICSRs. Risk benefit assessment for individual products is undertaken as part of Safety Data Review Group meetings are held

at predetermined timepoints. Appropriate actions as determined during such meetings are addressed in accordance to the strength of evidence.

III.1 Safety concerns and overview of planned pharmacovigilance actions

Table 2: Important identified risk: Toxicity of ritonavir oral solution in preterm neonates

Safety concern: Toxicity of ritonavir oral solution in preterm neonates		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activities will be carried out as stated in part III (Routine pharmacovigilance system at Accord)	To ensure that the risk benefit balance of ritonavir remains positive and to evaluate and further characterize the risk of ritonavir oral solution in preterm neonates in terms of demographic profile of population at risk and establish relationship with the administered dose, duration etc.

Table 3: Important identified risk: PR prolongation

Safety concern: PR prolongation		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**

Safety concern: PR prolongation		
None	Routine pharmacovigilance activities will be carried out as stated in part III (Routine pharmacovigilance system at Accord)	To ensure that the risk benefit balance of ritonavir remains positive and to evaluate and further characterize the risk of PR interval prolongation with ritonavir in terms of demographic profile of population at risk and establish relationship with the administered dose, duration etc.

Table 4: Important identified risk: Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease)

Safety concern: Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease)		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activities will be carried out as stated in part III (Routine pharmacovigilance system at Accord)	To ensure that the risk benefit balance of ritonavir remains positive and to evaluate and further characterize the risk of Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease) with ritonavir in terms of

		demographic profile of population at risk and establish relationship with the administered dose, duration etc.

Table 5: Important potential risk: Drug-drug interactions with HCV products

Safety concern: Drug-drug interactions with HCV products		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activities will be carried out as stated in part III (Routine pharmacovigilance system at Accord)	To ensure that the risk benefit balance of ritonavir remains positive and to evaluate and further characterize the risk of ritonavir interaction with HCV products in terms of demographic profile of population at risk and establish relationship with the administered dose, duration etc.

Table 6: Important potential risk: Risk of bleeding

Safety concern: Risk of bleeding		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**

None	Routine pharmacovigilance activities will be carried out as stated in part III (Routine pharmacovigilance system at Accord)	To ensure that the risk benefit balance of ritonavir remains positive and to evaluate and further characterize the risk of bleeding with ritonavir in terms of demographic profile of population at risk and establish relationship with the administered dose, duration etc.

Table 7: Important potential risk: Osteonecrosis

Safety concern: Osteonecrosis		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activities will be carried out as stated in part III (Routine pharmacovigilance system at Accord)	To ensure that the risk benefit balance of ritonavir remains positive and to evaluate and further characterize the risk of osteonecrosis with ritonavir in terms of demographic profile of population at risk and establish relationship with the administered dose, duration etc.

Table 8: Missing information: Severe hepatic impairment

Safety concern: **Severe hepatic impairment**		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Confirmation of the incidence and nature of adverse reactions following exposure to ritonavir.	Routine pharmacovigilance activities will be carried out as stated in part III (Routine pharmacovigilance system at Accord)	To investigate the possibility of use of ritonavir in patients with severe hepatic impairment or to provide reassurance about the absence of a risk after exposure to ritonavir.

Table 9: Missing information: Severe renal impairment

Safety concern: **Severe renal impairment**		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Confirmation of the incidence and nature of adverse reactions following exposure to ritonavir.	Routine pharmacovigilance activities will be carried out as stated in part III (Routine pharmacovigilance system at Accord)	To investigate the possibility of use of ritonavir in patients with severe renal impairment or to provide reassurance about the absence of a risk after exposure to ritonavir.

Table 10: Missing information: Use during pregnancy and lactation

Safety concern: **Use during pregnancy and lactation**		
Areas requiring	**Proposed routine and**	**Objectives**

confirmation or further investigation	**additional PhV activities**	
Confirmation of the incidence and nature of adverse reactions following exposure of ritonavir to pregnant or lactating women.	Routine pharmacovigilance activities will be carried out as stated in part III (Routine pharmacovigilance system at Accord)	To investigate the possibility of a risk in pregnant women or infant following use in pregnancy and lactation or to provide reassurance about the absence of a risk after exposure to ritonavir.

Table 11: Missing information: Limited experience with the 100 mg tablet in HIV-1-infected children less than 2 years of age

Safety concern: Limited experience with the 100 mg tablet in HIV-1-infected childrenless than 2 years of age		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Confirmation of the incidence and nature of adverse reactions following exposure of ritonavir to the children less than 2 years of age.	Routine pharmacovigilance activities will be carried out as stated in part III (Routine pharmacovigilance system at Accord)	To investigate the possibility of risk in children less than 2 years of age.

Table 12: Missing information: Geriatric population

Safety concern: Geriatric population		
Areas requiring confirmation or further	**Proposed routine and additional PhV activities**	**Objectives**

investigation		
Confirmation of the incidence and nature of adverse reactions following exposure of ritonavir to geriatric patients.	Routine pharmacovigilance activities will be carried out as stated in part III (Routine pharmacovigilance system at Accord)	To investigate the possibility of a risk in geriatric population or to provide reassurance about the absence of a risk after exposure to ritonavir.

III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

No additional pharmacovigilance activities other than discussed in part III (Routine pharmacovigilance system at Accord) are warranted.

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

None

III.4 Details of outstanding additional pharmacovigilance activities

There are no outstanding additional pharmacovigilance activities in EU.

III.5 Summary of the Pharmacovigilance Plan

Not applicable

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable

PART V: RISK MINIMISATION MEASURES

V.1 Risk minimisation measures by safety concern

Table 13: Important identified risk: Toxicity of ritonavir oral solution in preterm neonates

Safety concern	**Toxicity of ritonavir oral solution in preterm neonates**
Objective(s) of the risk minimisation measures	None
Routine risk minimisation measures	None proposed
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessment	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	-

Table 14: Important identified risk: PR prolongation

Safety concern	**PR prolongation**
Objective(s) of the risk minimisation measures	To minimise the occurrence of adverse reaction associated with the exposure to the medicinal product by preparing and updating controlled and standardised format of the product information that provides up to date information to healthcare practitioners about the safe use of the medicinal product.
Routine risk minimisation measures	Section 4.4 and 5.1 of Accord ritonavir SmPC has information on this safety concern.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities as stated in part III will help in identifying any change in the frequency, severity or characteristic of a safety issue or identification of a new at risk group.
Criteria for judging the success of the proposed risk minimisation measures	Decrease in severity, specificity, or frequency of risk
Planned dates for assessment	During PSUR preparation (if applicable) as per the EURD list and periodic signal detection activity.
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	If new information leads to a change in the benefit-risk balance of this drug, Health Authorities will be notified immediately and the RMP shall be reviewed and updated.

	Moreover, the safety section of the Product Information shall be updated and communicated, as required.
Comment	-

Table 15: Important identified risk: Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease)

Safety concern	**Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease)**
Objective(s) of the risk minimisation measures	To minimise the occurrence of adverse reaction associated with the exposure to the medicinal product by preparing and updating controlled and standardised format of the product information that provides up to date information to healthcare practitioners about the safe use of the medicinal product.
Routine risk minimisation measures	Section 4.4 and 4.8 of Accord ritonavir SmPC has information on this safety concern.
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities as stated in part III will help in identifying any change in the frequency, severity or characteristic of a safety issue or identification of a new at risk group.

Criteria for judging the success of the proposed risk minimisation measures	Decrease in severity, specificity, or frequency of risk
Planned dates for assessment	During PSUR preparation (if applicable) as per the EURD list and periodic signal detection activity.
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	If new information leads to a change in the benefit-risk balance of this drug, Health Authorities will be notified immediately and the RMP shall be reviewed and updated. Moreover, the safety section of the Product Information shall be updated and communicated, as required.
Comment	-

Table 16: Important potential risk: Drug-drug interactions with HCV products

Safety concern	**Drug-drug interactions with HCV products**
Objective(s) of the risk minimisation measures	To minimise the occurrence of adverse reaction associated with the exposure to the medicinal product by preparing and updating controlled and standardised format of the product information that provides up to date information to healthcare practitioners about the safe use of the medicinal product.
Routine risk minimisation measures	Section 4.4 and 4.5 of Accord ritonavir SmPC has information on this safety concern.

Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities as stated in part III will help in identifying any change in the frequency, severity or characteristic of a safety issue or identification of a new at risk group.
Criteria for judging the success of the proposed risk minimisation measures	Decrease in severity of risk
Planned dates for assessment	During PSUR preparation (if applicable) as per the EURD list and periodic signal detection activity.
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	If new information leads to a change in the benefit-risk balance of this drug, Health Authorities will be notified immediately and the RMP shall be reviewed and updated. Moreover, the safety section of the Product Information shall be updated and communicated, as required.
Comment	-

Table 17: Important potential risk: Risk of bleeding

Safety concern	**Risk of bleeding**
Objective(s) of the risk minimisation measures	To minimise the occurrence of adverse reaction associated with the exposure to the

	medicinal product by preparing and updating controlled and standardised format of product information that provides up to date information to healthcare practitioners about the safe use of medicinal product.
Routine risk minimisation measures	Section 4.4 and 4.5 of Accord ritonavir SmPC has information on this safety concern
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities as stated in part III will help in identifying any change in the frequency, severity or characteristic of a safety issue or identification of a new at risk group.
Criteria for judging the success of the proposed risk minimisation measures	Decrease in severity, specificity, or frequency of risk
Planned dates for assessment	During PSUR preparation (if applicable) as per the EURD list and periodic signal detection activity.
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	If new information leads to a change in the benefit-risk balance of this drug, Health Authorities will be notified immediately and the RMP shall be reviewed and updated. Moreover, the safety section of the Product Information shall be updated and communicated, as required.

Comment	-

Table 18: Important potential risk: Osteonecrosis

Safety concern	**Osteonecrosis**
Objective(s) of the risk minimisation measures	To minimise the occurrence of adverse reaction associated with the exposure to the medicinal product by preparing and updating controlled and standardised format of product information that provides up to date information to healthcare practitioners about the safe use of medicinal product.
Routine risk minimisation measures	Section 4.4 and 4.8 of Accord ritonavir SmPC has information on this safety concern
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities as stated in part III will help in identifying any change in the frequency, severity or characteristic of a safety issue or identification of a new at risk group.
Criteria for judging the success of the proposed risk minimisation measures	Decrease in severity, specificity, or frequency of risk
Planned dates for assessment	During PSUR preparation (if applicable) as per the EURD list and periodic signal detection activity.
Results of effectiveness measurement	Not applicable

Impact of risk minimisation	If new information leads to a change in the benefit-risk balance of this drug, Health Authorities will be notified immediately and the RMP shall be reviewed and updated. Moreover, the safety section of the Product Information shall be updated and communicated, as required.
Comment	-

Table 19: Missing information: Severe hepatic impairment

Safety concern	**Severe hepatic impairment**
Objective(s) of the risk minimisation measures	To investigate the presence or absence of risk.
Routine risk minimisation measures	Section 4.2, 4.3 and 4.4 of Accord ritonavir SmPC has information on this safety concern
Additional risk minimisation measure(s)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities as stated in part III will help in identifying any change in the frequency, severity or characteristic of a safety issue or identification of a new at risk group.
Criteria for judging the success of the proposed risk minimisation measures	Identification of sever hepatic impairment event associated with the drug use.

Planned dates for assessment	During PSUR preparation (if applicable) as per the EURD list and periodic signal detection activity
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	If new information leads to a change in the benefit-risk balance of this drug, Health Authorities will be notified immediately and the RMP shall be reviewed and updated. Moreover, the safety section of the Product Information shall be updated and communicated, as required.
Comment	-

Table 20: Missing information: Severe renal impairment

Safety concern	**Severe renal impairment**
Objective(s) of the risk minimisation measures	To investigate the presence or absence of risk.
Routine risk minimisation measures	Section 4.2, 4.4, 4.5, 4.8 and 5.2 of Accord ritonavir SmPC has information on this safety concern
Additional risk minimisation measure(s)	None proposed

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities as stated in part III will help in identifying any change in the frequency, severity or characteristic of a safety issue or identification of a new at risk group.
Criteria for judging the success of the proposed risk minimisation measures	Identification of sever renal impairment event associated with the drug use.
Planned dates for assessment	During PSUR preparation (if applicable) as per the EURD list and periodic signal detection activity
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	If new information leads to a change in the benefit-risk balance of this drug, Health Authorities will be notified immediately and the RMP shall be reviewed and updated. Moreover, the safety section of the Product Information shall be updated and communicated, as required.
Comment	-

Table 21: Missing information: Use during pregnancy and lactation

Safety concern	**Use during pregnancy and lactation**
Objective(s) of the risk minimisation measures	To investigate the presence or absence of risk in pregnant women and their infants.

Routine risk minimisation measures	Section 4.6 and 5.3 of Accord ritonavir SmPC has information on this safety concern
Additional risk minimisation measure(s)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities as stated in part III will help in identifying any change in the frequency, severity or characteristic of a safety issue or identification of a new at risk group.
Criteria for judging the success of the proposed risk minimisation measures	Identification of any adverse events associated with drug exposure during pregnancy and lactation.
Planned dates for assessment	During PSUR preparation (if applicable) as per the EURD list and periodic signal detection activity
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	If new information leads to a change in the benefit-risk balance of this drug, Health Authorities will be notified immediately and the RMP shall be reviewed and updated. Moreover, the safety section of the Product Information shall be updated and communicated, as required.
Comment	-

Table 22: Missing information: Limited experience with the 100 mg Tablet in HIV-1-infected childrenless than 2 years of age

Safety concern	**Limited experience with the 100 mg Tablet in HIV-1-infected childrenless than 2 years of age**
Objective(s) of the risk minimisation measures	To investigate the presence or absence of risk in children less than 2 years of age.
Routine risk minimisation measures	Section 4.2 and 5.2 of Accord ritonavir SmPC has information on this safety concern
Additional risk minimisation measure(s)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities as stated in part III will help in identifying any change in the frequency, severity or characteristic of a safety issue or identification of a new at risk group.
Criteria for judging the success of the proposed risk minimisation measures	Identification of any adverse events associated with drug exposure in children less than 2 years of age.
Planned dates for assessment	During PSUR preparation (if applicable) as per the EURD list and periodic signal detection activity
Results of effectiveness measurement	Not applicable

Impact of risk minimisation	If new information leads to a change in the benefit-risk balance of this drug, Health Authorities will be notified immediately and the RMP shall be reviewed and updated. Moreover, the safety section of the Product Information shall be updated and communicated, as required.
Comment	-

Table 23: Missing information: Geriatric population

Safety concern	**Geriatric population**
Objective(s) of the risk minimisation measures	To investigate the presence or absence of risk in while using the medicinal product in geriatric patients.
Routine risk minimisation measures	Section 4.2 and 5.2 of Accord ritonavir SmPC has information on this safety concern
Additional risk minimisation measure(s)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities as stated in part III will help in identifying any change in the frequency, severity or characteristic of a safety issue or identification of a new at risk group.

Criteria for judging the success of the proposed risk minimisation measures	Identification of any adverse events associated with drug exposure to geriatric patients.
Planned dates for assessment	During PSUR preparation (if applicable) as per the EURD list and periodic signal detection activity
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	If new information leads to a change in the benefit-risk balance of this drug, Health Authorities will be notified immediately and the RMP shall be reviewed and updated. Moreover, the safety section of the Product Information shall be updated and communicated, as required.
Comment	-

V.2 Risk minimisation measure failure (if applicable)

Not applicable.

V.3 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks: Toxicity of ritonavir oral solution in preterm	None proposed.	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
neonates		
Important identified risks: PR prolongation	Proposed product information for Accord ritonavir includes following information on this safety concern: Section 4.4: *PR interval prolongation:* Ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd or 3rd degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicinal products known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving ritonavir. Ritonavir should be used with caution in such patients. Section 5.1: Modest prolongation of the PR interval was also noted in subjects receiving ritonavir in the study on Day 3. The mean changes from baseline in PR interval ranged from 11.0 to 24.0 msec in the 12 hour interval post dose. Maximum PR interval was 252 msec and no second or third degree heart block was observed.	Currently available data does not support the need for additional risk minimization activities.
Important identified risks: Immune	Proposed product information for Accordritonavir includes following information on this safety concern:	Currently available data does not support

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease)	Section 4.4: *Immune Reactivation Syndrome*: in HIV-infected patients with severe immune deficiency at the time of institution ofcombination antiretroviral therapy (CART), an inflammatory reaction to asymtomatic or residual opportunisticpathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactionshave been observed within the first few weeks or months of initiation of CART. Relevant examples arecytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis jiroveci pneumonia.Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immunereactivation; however, the reported time to onset is more variable and can occur many months after initiation oftreatment. Section 4.8: 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. Autoimmunedisorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variableand can occur many months after initiation of treatment.	the need for additional risk minimization activities.

<table>
<tr><th>Safety concern</th><th>Routine risk minimisation measures</th><th>Additional risk minimisation measures</th></tr>
<tr><td>Important potential risks: Drug-drug interactions with HCV products</td><td>Proposed product information for Accordritonavir includes following information on this safety concern:
Section 4.4:
Patients with chronichepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentiallyfatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C,please refer to therelevant product information for these medicinal products.
Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liverfunction abnormalities during combination antiretroviral therapy and should be monitored according to standardpractice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatmentmust be considered.
Section 4.5:
<table><tr><th colspan="5">Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products</th></tr><tr><th>Co-administered Medicinal Products</th><th>Dose of Coadministered Medicinal Products (mg)</th><th>Dose of Ritonavir (mg)</th><th>Effect on Coadministered Medicinal Products AUC</th><th>Effect on Coadministered Medicinal Products C_{max}</th></tr><tr><td colspan="5">HCV Protease Inhibitor</td></tr><tr><td>Simeprevir</td><td>200 qd</td><td>100d12h</td><td>↑7.2-fold</td><td>↑4.7-fold</td></tr><tr><td></td><td colspan="4">Ritonavir increases plasma concentrations of simeprevir as a result of CYP3A4 inhibition. It</td></tr></table></td><td>Currently available data does not support the need for additional risk minimization activities.</td></tr>
</table>

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	is not recommended to co-administer ritonavir with simeprevir.	
Important potential risks: Risk of bleeding	Proposed product information for Accordritonavir includes following information on this safety concern: Section 4.4: *Haemophilia*: there have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than a half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding. *Interactions with other medicinal products* Rivaroxaban: It is not recommended to use ritonavir in patients receiving rivaroxaban, due to the risk of increased bleeding. Section 4.5: *Medicinal products that are affected by the use of ritonavir* Ritonavir effects on Non-antiretroviral anticoagulant (Rivaroxaban)	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban.	
Important potential risks: Osteonecrosis	Proposed product information for Accordritonavir includes following information on this safety concern: Section 4.4: *Osteonecrosis:* Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported 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. Section 4.8: 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.	Currently available data does not support the need for additional risk minimization activities.
Missing information:	Proposed product information for Accordritonavir includes following information on this safety	Currently available data

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Severe hepatic impairment	concern: Section 4.2: *Hepatic impairment:* Ritonavir should not be given as a pharmacokinetic enhancer to patients with decompensated liver disease. In the absence of pharmacokinetic studies in patients with stable severe hepatic impairment (Child Pugh Grade C) without decompensation, caution should be exercised when ritonavir is used as a pharmacokinetic enhancer as increased levels of the co-administered PI may occur. Specific recommendations for use of ritonavir as a pharmacokinetic enhancer in patients with hepatic impairment are dependent on the protease inhibitor with which it is co-administered. Section 4.3: Ritonavir should not be given as a pharmacokinetic enhancer or as an antiretroviral agent to patients with decompensated liver disease. Section 4.4: *Liver disease:* Ritonavir should not be given to patients with decompensated liver disease. For patients with stable severe hepatic impairment (Child Pugh Grade C) without decompensation. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Patients with pre-existing liver dysfunction including	does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.	
Missing information: Severe renal impairment	Proposed product information for Accordritonavir includes following information on this safety concern: Section 4.2: *Renal impairment:* As ritonavir is primarily metabolised by the liver, ritonavir may be appropriate for use with caution as a pharmacokinetic enhancer in patients with renal insufficiency depending on the specific protease inhibitor with which it is co-administered. However, since the renal clearance of ritonavir is negligible, the decrease in the total body clearance is not expected in patients with renal impairment. Currently, there are no data specific to this patient population and therefore specific dosage recommendations cannot be made. The renal clearance of ritonavir is negligible, therefore, a decrease in the total body clearance is not expected in patients with renal impairment. Because ritonavir is highly protein bound it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.	Currently available data does not support the need for additional risk minimization activities.

<table>
<tr><th>Safety concern</th><th>Routine risk minimisation measures</th><th>Additional risk minimisation measures</th></tr>
<tr><td></td><td>
Section 4.4:

Renal disease: Since the renal clearance of ritonavir is negligible, the decrease in the total body clearance is not expected in patients with renal impairment.

Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovirdisoproxil fumarate in clinical practice.

Section 4.5:

<table>
<tr><th colspan="5">Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products</th></tr>
<tr><th>Co-administered Medicinal Products</th><th>Dose of Coadministered Medicinal Products (mg)</th><th>Dose of Ritonavir (mg)</th><th>Effect on Coadministered Medicinal Products AUC</th><th>Effect on Coadministered Medicinal Products C_{max}</th></tr>
<tr><td colspan="5">Anti-infectives</td></tr>
<tr><td>Clarithromycin</td><td>500 q12h</td><td>200 q8h</td><td>↑77%</td><td>↑31%</td></tr>
<tr><td>14-OH clarithromycin metabolite</td><td></td><td></td><td>↓100%</td><td>↓ 99%</td></tr>
<tr><td></td><td colspan="4">Due to the large therapeutic window of clarithromycin no dose reduction should be necessary in patients with normal renal function. Clarithromycin doses greater than 1 g per day should not be co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. For patients with renal impairment, a clarithromycin dose</td></tr>
</table>
</td><td></td></tr>
</table>

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	reduction should be considered: for patients with creatinine clearance of 30 to 60 ml/min the dose should be reduced by 50%, for patients with creatinine clearance less than 30 ml/min the dose should be reduced by 75%. Section 4.8: *Renal and urinary disorders:* Common: renal impairment (e.g. oliguria, elevated creatinine) Section 5.2: *Patients with impaired renal function:* Ritonavir pharmacokinetic parameters have not been studied in patients with renal impairment. However, since the renal clearance of ritonavir is negligible, no changes in the total body clearance are expected in patients with renal impairment.	
Missing information: Use during pregnancy and lactation	Proposed product information for Accord ritonavir includes following information on this safety concern: Section 4.6: A limited number (> 800) of pregnant women were exposed to ritonavir during pregnancy; a very limited number (< 300) were exposed during the first trimester. These data largely refer to exposures where ritonavir was used in combination therapy and not at therapeutic ritonavir doses but at lower doses as a pharmacokinetic enhancer for other PIs. These	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	limited data indicate no increase in the rate of birth defects compared to rates observed in population-based birth defect surveillance systems. Animal data have shown reproductive toxicity. The use of ritonavir may be considered in pregnancy only when the benefits outweigh the risk to the foetus. Ritonavir adversely interacts with oral contraceptives (OCs). Therefore, an alternative, effective and safe method of contraception should be used during treatment. It is not known whether this medicine is excreted in human milk. Milk excretion has not been measured in the animal studies, however a study in rats showed some effects on offspring development during lactation which are compatible with excretion of ritonavir in milk in that species. HIV infected women should not breast-feed their infants under any circumstances to avoid transmission of HIV. Section 5.3: Developmental toxicity observed in rats (embryolethality, decreased foetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dosage. Developmental toxicity in rabbits (embryolethality,decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage.	
Missing	Proposed product information for Accord ritonavir	Currently

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
information: Limited experience with the 100 mg Tablet in HIV-1-infectedchildrenless than 2 years of age	includes following information on this safety concern: Section 4.2: *Paediatric use:* Ritonavir is not recommended in children below 2 years of age due to lack of data on safety and efficacy. Section 5.2: *Paediatric patients:* Ritonavir steady-state pharmacokinetic parameters were evaluated in HIV infected children less than 2 years of age receiving doses ranging from 350 to 450 mg/m² twice daily. Ritonavir concentrations in this study were highly variable and somewhat lower than those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice daily. Across dose groups, ritonavir oral clearance (CL/F/m^2) declined with age with median values of 9.0 L/h/m^2 in children less than 3 months of age, 7.8 L/h/m^2 in children between 3 and 6 months of age and 4.4 L/h/m^2 in children between 6 and 24 months of age.	available data does not support the need for additional risk minimization activities.
Missing information: Geriatric population	Proposed product information for Accord ritonavir includes following information on this safety concern: Section 4.2: *Older people:*Pharmacokinetic data indicated that no dose adjustment is necessary for older patients. Section 5.2:	Currently available data does not support the need for additional risk minimization activities.

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	Ritonavir plasma exposures in patients 50 – 70 years of age when dosed 100 mg in combination with lopinaviror at higher doses in the absence of other protease inhibitors is similar to thatobserved in younger adults.	

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Important identified risk (s)	• Toxicity of ritonavir oral solution in preterm neonates • PR prolongation • Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease)
Important potential risk (s)	• Drug-drug interactions with HCV products • Risk of bleeding • Osteonecrosis
Missing information	• Severe hepatic impairment • Severe renal impairment • Use during pregnancy and lactation • Limited experience with the 100 mg Tablet in HIV-1-infected childrenless than 2 years of age • Geriatric population

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: Toxicity of ritonavir oral solution in preterm neonates	None proposed.	None proposed.
Important identified risks: PR prolongation	Proposed product information for Accord ritonavir includes following information on this safety concern: Section 4.4: *PR interval prolongation:* Ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd or 3rd degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicinal products known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving ritonavir. Ritonavir should be used with caution in such patients. Section 5.1: Modest prolongation of the PR interval was also noted in subjects receiving ritonavir in the study on Day 3. The mean changes from baseline in PR	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	interval ranged from 11.0 to 24.0 msec in the 12 hour interval post dose. Maximum PR interval was 252 msec and no second or third degree heart block was observed.	
Important identified risks: Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease)	Proposed product information for Accordritonavir includes following information on this safety concern: Section 4.4: *Immune Reactivation Syndrome*: in HIV-infected patients with severe immune deficiency at the time of institution ofcombination antiretroviral therapy (CART), an inflammatory reaction to asymtomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples arecytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis jiroveci pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. 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 can occur many months after initiation of treatment. Section 4.8: In HIV-infected patients with severe immune	Currently available data does not support the need for additional risk minimization activities.

<table>
<tr><th>Safety concern</th><th>Routine risk minimisation measures</th><th>Additional risk minimisation measures</th></tr>
<tr><td></td><td>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 can occur many months after initiation of treatment.</td><td></td></tr>
<tr><td>Important potential risks: Drug-drug interactions with HCV products</td><td>Proposed product information for Accordritonavir includes following information on this safety concern:
Section 4.4:
Patients with chronichepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentiallyfatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C,please refer to therelevant product information for these medicinal products.
Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liverfunction abnormalities during combination antiretroviral therapy and should be monitored according to standardpractice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatmentmust be considered.
Section 4.5:
<table><tr><th colspan="5">Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products</th></tr><tr><th>Co-administered</th><th>Dose of Coadminist</th><th>Dose of</th><th>Effect on Coadminis</th><th>Effect on Coadminis</th></tr></table></td><td>Currently available data does not support the need for additional risk minimization activities.</td></tr>
</table>

<table>
<tr><th>Safety concern</th><th>Routine risk minimisation measures</th><th>Additional risk minimisation measures</th></tr>
<tr><td></td><td>
<table>
<tr><th>Medicinal Products</th><th>ered Medicinal Products (mg)</th><th>Ritonavir (mg)</th><th>tered Medicinal Products AUC</th><th>tered Medicinal Products C_{max}</th></tr>
<tr><td colspan="5">HCV Protease Inhibitor</td></tr>
<tr><td>Simeprevir</td><td>200 qd</td><td>100d12h</td><td>↑7.2-fold</td><td>↑4.7-fold</td></tr>
<tr><td colspan="5">Ritonavir increases plasma concentrations of simeprevir as a result of CYP3A4 inhibition. It is not recommended to co-administer ritonavir with simeprevir.</td></tr>
</table>
</td><td></td></tr>
<tr><td>Important potential risks: Risk of bleeding</td><td>Proposed product information for Accordritonavir includes following information on this safety concern:

Section 4.4:

Haemophilia: there have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than a half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Interactions with other medicinal products

Rivaroxaban: It is not recommended to use ritonavir in patients receiving rivaroxaban, due to the risk of</td><td>Currently available data does not support the need for additional risk minimization activities.</td></tr>
</table>

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	increased bleeding. Section 4.5: *Medicinal products that are affected by the use of ritonavir* <u>Ritonavir effects on Non-antiretroviral anticoagulant (Rivaroxaban)</u> Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban.	
Important potential risks: Osteonecrosis	Proposed product information for Accordritonavir includes following information on this safety concern: Section 4.4: *Osteonecrosis:* Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported 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. Section 4.8: Cases of osteonecrosis have been reported,	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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.	
Missing information: Severe hepatic impairment	Proposed product information for Accordritonavir includes following information on this safety concern: Section 4.2: *Hepatic impairment:* Ritonavir should not be given as a pharmacokinetic enhancer to patients with decompensated liver disease. In the absence of pharmacokinetic studies in patients with stable severe hepatic impairment (Child Pugh Grade C) without decompensation, caution should be exercised when ritonavir is used as a pharmacokinetic enhancer as increased levels of the co-administered PI may occur. Specific recommendations for use of ritonavir as a pharmacokinetic enhancer in patients with hepatic impairment are dependent on the protease inhibitor with which it is co-administered. Section 4.3: Ritonavir should not be given as a pharmacokinetic enhancer or as an antiretroviral agent to patients with decompensated liver disease. Section 4.4: *Liver disease:* Ritonavir should not be given to patients with decompensated liver disease. For	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	patients with stable severe hepatic impairment (Child Pugh Grade C) without decompensation. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.	
Missing information: Severe renal impairment	Proposed product information for Accordritonavir includes following information on this safety concern: Section 4.2: *Renal impairment:* As ritonavir is primarily metabolised by the liver, ritonavir may be appropriate for use with caution as a pharmacokinetic enhancer in patients with renal insufficiency depending on the specific protease inhibitor with which it is co-administered. However, since the renal clearance of ritonavir is negligible, the decrease in the total body clearance is not expected in patients with renal impairment. Currently, there are no data specific to this patient population and therefore specific dosage	Currently available data does not support the need for additional risk minimization activities.

<table>
<tr><th>Safety concern</th><th>Routine risk minimisation measures</th><th>Additional risk minimisation measures</th></tr>
<tr><td></td><td>
recommendations cannot be made. The renal clearance of ritonavir is negligible, therefore, a decrease in the total body clearance is not expected in patients with renal impairment. Because ritonavir is highly protein bound it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

Section 4.4:

Renal disease: Since the renal clearance of ritonavir is negligible, the decrease in the total body clearance is not expected in patients with renal impairment.

Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovirdisoproxil fumarate in clinical practice.

Section 4.5:

<table>
<tr><th colspan="5">Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products</th></tr>
<tr><th>Co-administered Medicinal Products</th><th>Dose of Coadministered Medicinal Products (mg)</th><th>Dose of Ritonavir (mg)</th><th>Effect on Coadministered Medicinal Products AUC</th><th>Effect on Coadministered Medicinal Products C_{max}</th></tr>
<tr><td colspan="5">Anti-infectives</td></tr>
<tr><td>Clarithromycin</td><td>500 q12h</td><td>200 q8h</td><td>↑77%</td><td>↑31%</td></tr>
</table>
</td><td></td></tr>
</table>

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	14-OH clarithromycin metabolite ↓100% ↓ 99% Due to the large therapeutic window of clarithromycin no dose reduction should be necessary in patients with normal renal function. Clarithromycin doses greater than 1 g per day should not be co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. For patients with renal impairment, a clarithromycin dose reduction should be considered: for patients with creatinine clearance of 30 to 60 ml/min the dose should be reduced by 50%, for patients with creatinine clearance less than 30 ml/min the dose should be reduced by 75%. Section 4.8: *Renal and urinary disorders:* Common: renal impairment (e.g. oliguria, elevated creatinine) Section 5.2: *Patients with impaired renal function:* Ritonavir pharmacokinetic parameters have not been studied in patients with renal impairment. However, since the renal clearance of ritonavir is negligible, no changes in the total body clearance are expected in patients with renal impairment.	
Missing information: Use	Proposed product information for Accord ritonavir includes following information on this safety	Currently available data

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
during pregnancy and lactation	concern: Section 4.6: A limited number (> 800) of pregnant women were exposed to ritonavir during pregnancy; a very limited number (< 300) were exposed during the first trimester. These data largely refer to exposures where ritonavir was used in combination therapy and not at therapeutic ritonavir doses but at lower doses as a pharmacokinetic enhancer for other PIs. These limited data indicate no increase in the rate of birth defects compared to rates observed in population-based birth defect surveillance systems. Animal data have shown reproductive toxicity. The use of ritonavir may be considered in pregnancy only when the benefits outweigh the risk to the foetus. Ritonavir adversely interacts with oral contraceptives (OCs). Therefore, an alternative, effective and safe method of contraception should be used during treatment. It is not known whether this medicine is excreted in human milk. Milk excretion has not been measured in the animal studies, however a study in rats showed some effects on offspring development during lactation which are compatible with excretion of ritonavir in milk in that species. HIV infected women should not breast-feed their infants under any circumstances to avoid transmission of HIV. Section 5.3:	does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Developmental toxicity observed in rats (embryolethality, decreased foetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dosage. Developmental toxicity in rabbits (embryolethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage.	
Missing information: Limited experience with the 100 mg Tablet in HIV-1-infected childrenless than 2 years of age	Proposed product information for Accord ritonavir includes following information on this safety concern: Section 4.2: *Paediatric use:* Ritonavir is not recommended in children below 2 years of age due to lack of data on safety and efficacy. Section 5.2: *Paediatric patients:* Ritonavir steady-state pharmacokinetic parameters were evaluated in HIV infected children less than 2 years of age receiving doses ranging from 350 to 450 mg/m² twice daily. Ritonavir concentrations in this study were highly variable and somewhat lower than those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice daily. Across dose groups, ritonavir oral clearance (CL/F/m^2) declined with age with median values of 9.0 L/h/m^2 in children less than 3 months of age, 7.8 L/h/m^2 in children between 3 and 6 months of age and 4.4	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	L/h/m^2 in children between 6 and 24 months of age.	
Missing information: Geriatric population	Proposed product information for Accord ritonavir includes following information on this safety concern: Section 4.2: *Older people:* Pharmacokinetic data indicated that no dose adjustment is necessary for older patients. Section 5.2: Ritonavir plasma exposures in patients 50 – 70 years of age when dosed 100 mg in combination with lopinaviror at higher doses in the absence of other protease inhibitors is similar to thatobserved in younger adults.	Currently available data does not support the need for additional risk minimization activities.

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

In 1981, the Centers for Disease Control and Prevention reported unusual clusters of pneumonia caused by fungus (*Pneumocystis carinii*pneumonia) and cancer (Kaposi's sarcoma) in gay men in parts of the US. These were the first reported cases of Acquired Immune Deficiency Syndrome (AIDS). Twenty years later, the global HIV/AIDS epidemic has killed an estimated 21.8 million people and another 36.1 million are living with HIV infection. Around 95% of these people live in non-industrialised countries with few financial resources to deal with the HIV/AIDS epidemic. Over 90% of people living with HIV/AIDS do not know they are infected and even if they did antiretroviral therapies (ART) are not at present an option for them. Most people living with HIV/AIDS are in the economically productive age-group supporting children and elderly relatives and most will receive minimal

care when they finally develop AIDS-related illness. From many aspects the global HIV/AIDS epidemic is an enormous tragedy for humankind. [4]

VI.2.2 Summary of treatment benefits

Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children of 2 years of age and older).

In a study ritonavir was used as add-on therapy with other drug (i.e. zidovudine, stavudine, didanosine and zalcitabine etc.) in HIV-1 infected patients. The results indicated decrease in mortality and AIDS related events.

In another study, HIV-1 infected patients without previous anti-viral therapy were treated with ritonavir in combination with zidovudine or alone and showed beneficial effect.

In one study, HIV infected children showed good response in favour of a triple drug therapy of ritonavir, zidovudine and lamivudine for 48 weeks.

In a study 50 HIV-1 infected children age 4 weeks to 2 years received ritonavir 350 or 450 mg/m^2 every 12 hours along with zidovudine 160 mg/m^2 every 8 hours and lamivudine 4 mg/kg every 12 hours. Response was similar in both dosing regimens and across patient age.

In a study, 76 HIV-1 infected children aged 6 months to 12 years who were received ritonavir 350 or 450 mg/m^2 every 12 hours co-administered with lamivudine and stavudine. Favorable response was achieved at week 48.

However, these studies were conducted for the reference product (Norvir, AbbVie Ltd., UK) and no studies were performed for Accord ritonavir to evaluate the expected benefit, considering its similarity to the reference product.

VI.2.3 Unknowns relating to treatment benefits

Data on use of ritonavir 100 mg tabletin liver disease patients, kidney disease patients, use during pregnancy and breast feeding as well as use in elderly patients andchildren below 2 years of age is not available.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Toxicity of ritonavir oral solution in preterm neonates	None	None
Abnormal ECG (PR interval prolongation)	Ritonavir has been shown to cause abnormal ECG (modest asymptomatic prolongation of the PR interval) in some healthy adult subjects. Rare reports heart block (2^{nd} or 3^{rd} degree atrioventricular block) in patients with underlying heart disease or in patients receiving medicinal products for abnormal ECG (known to prolong the PR interval) have been reported when receiving ritonavir.	Yes. During the treatment, doctor should monitor the patient's ECG on regular interval.
Disorder in which a person's immune system attacks parts of his or her own body (Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders (such as	Disorder in which a person's immune system attacks parts of his or her own body (Graves disease) has been reported.	Yes. Patients should inform to their doctor for occurrenceof any immune disorder during the treatment.

Risk	What is known	Preventability
Graves' disease))		

Important potential risks

Risk	What is known
Drug-drug interactions with HCV products	Patients with hepatitis and treated with combination antiviral therapy are at an increased risk of life-threateningliver disease.
Risk of bleeding	There have been reports of increased bleeding in patients with impaired ability to control blood clotting or coagulation (haemophilia) who are taking this protease inhibitors medicine.
Destruction of bone (Osteonecrosis)	Cases for destruction of bone (osteonecrosis) have been reported in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy.

Missing information

Risk	What is known
Severe liver disease (hepatic impairment)	The safety of ritonavir has not been studied in the patient with severe liver disease (hepatic impairment).
Severe kidney disease (renal impairment)	Kidney disease (acute renal failure) has been reported in patient taking ritonavir.
Use during pregnancy and breast feeding (lactation)	There is a limited data on use of ritonavir in pregnant and breast feeding (lactating) women.
Limited experience with the 100 mg Tablet in HIV-1-	The safety or efficacy of ritonavir has not been studied in the

Risk	What is known
infected childrenless than 2 years of age	patient less than 2 years of age.
Elderly (Geriatric) population	Data on study of what the body does to the drug indicated that no dose adjustment is necessary for older patients.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No studies planned

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concern	Comment
3.0	18-Aug-2015	Following safety concerns are added: **Important identified risk**: • Toxicity of ritonavir oral solution in preterm neonates **Missing information:** • Geriatric population	Safety concerns have been updated based on RMS Day 120 Draft Preliminary Assessment Report of Ritonavir 100 mg tablets (NL/H/3149/01-02/DC and NL/H/3150/01-02/DC) by The Netherland,

Version	Date	Safety Concern	Comment
			dated 10 July 2015.
2.0	25-Jun-2015	Following safety concerns are added: **Important identified risk**: • Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease) **Important potential risk:** • Drug-drug interactions with HCV products Following safety concerns are removed: **Important identified risk**: • Pancreatitis • Diabetes/Hyperglycemia **Important potential risk:** • Lipodystrophy • Nephrolithiasis with combination with other protease inhibitors and ritonavir	Safety concerns have been updated based on RMS Day 70 PreliminaryAssessment Report of Ritonavir Accord/Sandoz 100 mg tablets (NL/H/3149/01-02/DC and NL/H/3150/01-02/DC) by The Netherland, dated 05 August 2014.

Version	Date	Safety Concern	Comment
		• Stevens Johnson syndrome • Drug interaction between ritonavir and quetiapine • Drug interaction between ritonavir and fluticasonepropionate The important potential risk PR interval prolongation has been upgraded to important identified risk.	

PART VII: ANNEXES

Annex 1 – EudraVigilance Interface

Not applicable

Annex 2 - SmPC& Package Leaflet

SmPC of Accord Ritonavir 100 mg film coated tablets

SUMMARY OFPRODUCTCHARACTERISTICS

1 NAME OFTHE MEDICINALPRODUCT

[Product name] 100 mgfilm-coatedtablets

2 QUALITATIVEAND QUANTITATIVE COMPOSITION

Each film-coated tablets contains 100 mg of ritonavir.

Excipient with known effect:

Each film-coated tablet contains 6.15 mg of sodium stearyl fumarate equivalent to 0.362 mg of sodium. For the Full list of excipients, see section 6.1.

3 PHARMACEUTICALFORM

Film-coatedtablet.

White to off white, capsule shaped, film-coated tablets, with a dimension of approx. 17.1 mm in length and 9.1 mm in width, debossed with 'H' on one side and 'R9' on other side.

4 CLINICALPARTICULARS

4.1 Therapeutic indications

Ritonaviris indicatedin combinationwithotherantiretroviralagentsforthetreatment of HIV-1infected patients(adultsandchildrenof2yearsofageandolder).

4.2 Posology and method ofadministration

Ritonavir shouldbe administered byphysicianswhoareexperiencedinthetreatmentof HIVinfection.
Ritonavir film-coated tablets are administered orally and should be ingested with food (see section 5.2).
[Product name] film-coated tablets should be swallowed whole and not chewed, broken or crushed.

Ritonavir dosed asa pharmacokineticenhancer

Whenritonavirisused asapharmacokineticenhancerwithotherproteaseinhibitors(PIs) theSummaryofProductCharacteristics(SmPC)fortheparticularprotease inhibitor mustbeconsulted.

ThefollowingHIV-1proteaseinhibitorshavebeen approvedforusewith ritonavirasa pharmacokineticenhancerat the noteddoses.

Adults:

Amprenavir 600 mgtwice dailywith ritonavir 100mgtwice daily

Atazanavir 300 mgoncedailywith ritonavir 100mgonce daily

Fosamprenavir 700 mgtwice dailywith ritonavir100 mgtwice daily

Lopinavirco-formulatedwith ritonavir (lopinavir/ritonavir) 400 mg/100 mgor 800 mg/200 mg

Saquinavir 1000 mgtwice dailywith ritonavir 100mgtwice dailyin ART experienced patients.Initiate treatment with saquinavir 500 mgtwice daily with ritonavir 100 mgtwice dailyfor thefirst 7 days, then saquinavir 1000mg twice dailywith ritonavir100 mgtwice dailyin ART-naïve patients.

Tipranavir 500 mgtwicedailywith ritonavir 200mgtwice daily.(Tipranavir with ritonavir should not be usedin treatment-naïvepatients).

Darunavir 600 mgtwicedailywithritonavir 100mgtwice dailyin antiretroviral treatment (ART) experienced patients. Darunavir 800 mgonce dailywith ritonavir 100mgonce dailymaybe used in some ART experienced patients. Refer to the darunavir SmPCfor furtherinformation on once daily dosingin ART experienced patients.

Darunavir 800 mgonce dailywith ritonavir 100 mgonce dailyin ART-naïve patients

Paediatric use: Ritonavir is recommendedfor children 2years ofage and older. Forfurther dosagerecommendations, refer to the product information of other Protease Inhibitorsapprovedfor co-administration with ritonavir. [Product name]is not recommended inchildrenbelow 2years ofage dueto lack of data on safetyand efficacy.

Renal impairment: As ritonavir is primarilymetabolised bythe liver,ritonavir may be appropriate for use with caution as a pharmacokinetic enhancer in patients with renal insufficiencydependingon thespecificprotease inhibitorwith which it is co-administered. However, since therenalclearance of ritonavir is negligible, the decrease inthe total bodyclearanceis not expected in patients with renal impairment.For specific dosinginformation in patients with renal impairment, refer to theSummary of Product Characteristics (SPC) of the co-administered protease inhibitor.

Hepaticimpairment: Ritonavir should not be givenas a pharmacokineticenhancer to patients with decompensated liver disease (seesection 4.3).In the absence of pharmacokinetic studies in patients with stableseverehepaticimpairment (Child Pugh Grade C) without decompensation, caution should be exercised whenritonavir is used as a pharmacokinetic enhanceras increased levels of the co-administered PImayoccur. Specificrecommendations for use of ritonavir as a pharmacokinetic enhancer in patients withhepatic impairment are dependent on theprotease inhibitorwithwhich it is co-administered. The SmPC of the co-administered PIshould be reviewed for specific dosinginformation in this patient population.

Ritonavir dosed as an antiretroviral agent

*Adult use:*Therecommended doseof [Product name] film-coated tablet is 600 mg(6 tablets) twice daily(totalof 1200 mgper day)bymouth.

Graduallyincreasingthedoseof ritonavir when initiatingtherapymayhelpto improve tolerance. Treatment should be initiated at 300 mg(3 tablets) twice daily for a period of three daysand increased by100 mg(1 tablet) twice dailyincrements up to 600 mgtwice dailyover a period of no longerthan 14 days. Patients should not remain on 300 mgtwice dailyfor morethan 3days.

Paediatric use (2 years of age and above): the recommended dosage of ritonavir in children is 350 mg/m^2 by mouth twice daily and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m^2 and increased at 2 to 3 day intervals by 50 mg/m^2 twice daily (Other

pharmaceutical forms/strengths may be more appropriate for administration to this population).

For olderchildren it maybefeasibleto substitutetablets for themaintenancedose of the oral solution.

Ritonavir is not recommended in children below 2years ofage due to lack ofdata on safetyandefficacy.

Renal impairment: Currently, thereare no data specific to this patient population and therefore specific dosage recommendations cannot be made. The renal clearanceof ritonaviris negligible,therefore,adecreasein thetotal bodyclearance is not expected in patients with renalimpairment.Because ritonavir is highly protein bound it is unlikelythat it will be significantlyremoved byhaemodialysis or peritoneal dialysis.

Hepaticimpairment: Ritonavir is principallymetabolised and eliminated bytheliver. Pharmacokinetic data indicate that no doseadjustment is necessaryin patients with mild to moderate hepatic impairment (see section 5.2). Ritonavir should not be given to patients with severe hepatic impairment (see section 4.3).

Older people: Pharmacokinetic dataindicated that no dose adjustment is necessaryfor older patients (seesection 5.2).

4.3 Contraindications

Hypersensitivityto theactivesubstanceor toanyof the excipients listed insection 6.1.

When ritonavir is used as a pharmacokineticenhancer of other protease inhibitors (PIs),consult the SummaryofProduct Characteristics (SmPC) of the co- administered protease inhibitorfor contraindications.

Ritonavir should not be givenas a pharmacokinetic enhancer oras anantiretroviral agent to patients with decompensated liverdisease.

In vitro and *in vivo*studies have demonstrated that ritonavir is a potent inhibitor of CYP3A- and CYP2D6-mediated biotransformations. The followingmedicines are contraindicatedwhen used with ritonavir and, unless otherwise noted, the contraindication is basedonthepotential for ritonavir to inhibit metabolismof the co-administered medicinalproduct, resultingin increased exposure to the co- administered medicinal productand risk ofclinicallysignificant adverseeffects.

The enzyme-modulating effect of ritonavir maybedose dependent. For some products, contraindications maybemore relevantwhen ritonavir is used asan antiretroviral agent thanwhen ritonavir is used asa pharmacokinetic enhancer (e.g. rifabutin and voriconazole):

Medicinal Product Class	Medicinal Products withinClass	Rationale
Concomitantmedicinal product levels increasedor decreased		
α1-Adrenoreceptor Antagonist	Alfuzosin	Increased plasmaconcentrations of alfuzosinwhich maylead to severehypotension (see

		section 4.5).
Analgesics	Pethidine, piroxicam, propoxyphene	Increased plasmaconcentrations of norpethidine, piroxicam and propoxyphene. Thereby,increasingthe risk of serious respiratorydepression or haematologic abnormalities, or other serious adverse effectsfrom these agents.
Antiarrthymics	Amiodarone, bepridil,encainide, flecanide, propafenone, quinidine	Increased plasmaconcentrations of amiodarone, bepridil, encainide, flecanide, propafenone, quinidine. Thereby, increasingthe risk of arrhythmias or other serious adverse effects from theseagents.
Antibiotic	Fusidic Acid	Increased plasmaconcentrations of fusidic acid and ritonavir.
Antifungal	Voriconazole	Concomitant use of ritonavir (400 mg twice dailyand more) and voriconazole is contraindicated due to a reduction in voriconazole plasma concentrations and possible loss of effect (seesection 4.5)
Antihistamines	Astemizole, terfenadine	Increased plasmaconcentrations of astemizole and terfenadine. Thereby, increasingthe risk of serious arrhythmias from these agents.
Antimycobacterial	Rifabutin	Concomitant useof ritonavir dosed asan antiretroviral agent (600mgtwice daily) and rifabutin due to an increase of rifabutin serum concentrations and risk of adversereactions, includinguveitis (see section 4.4). Recommendations regarding use of ritonavir dosedasa pharmacokineticenhancer with rifabutin are noted in section 4.5
Antipsychotics/Neuroleptics	Clozapine, pimozide	Increased plasmaconcentrations of clozapine and pimozide. Thereby, increasingthe risk of serious haematologic abnormalities, or other serious adverse effectsfrom these agents.
	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is

		contraindicated (see section 4.5).
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasmaconcentrations of ergot derivatives leadingto acute ergot toxicity, includingvasospasm and ischaemia.
GImotilityagent	Cisapride	Increased plasmaconcentrations of cisapride. Thereby, increasingtherisk of serious arrhythmias from this agent
HMG Co-A Reductase Inhibitor	Lovastatin, simvastatin	Increased plasmaconcentrations of lovastatin and simvastatin, thereby, increasingthe risk of myopathyincluding rhabdomyolysis (see section 4.5).
PDE5 inhibitor	Avanafil	Increased plasma concentrations of avanafil (see section 4.4. and 4.5).
	Sildenafil	Contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) only. Increased plasma concentrations of sildenafil. Thereby, increasing the potential for sildenafil-associated adverse events (which include hypotension and syncope). See section 4.4 and section 4.5 for co-administration of sildenafil in patients with erectile dysfunction.
	Vardenafil	Increased plasma concentrations of vardenafil (see section 4.4. and 4.5).
Sedatives/hypnotics	Clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam	Increased plasmaconcentrations of clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam. Thereby, increasingtherisk of extreme sedation and respiratory depression from these agents. (For caution on parenterallyadministered midazolam, see section 4.5).
Ritonavir medicinal product level decreased		
Herbal Preparation	St.John's Wort	Herbal preparations containing St. John's wort (*Hypericum perforatum*) due to the risk of decreased plasma concentrations and reduced clinical effects of ritonavir (see section 4.5).

4.4 Special warnings andprecautions for use

Ritonavir is not a cure for HIV-1 infection or AIDS. Patients receiving ritonavir or anyother antiretroviral therapymaycontinue to develop opportunistic infections and other complicationsof HIV-1 infection.

Patients should be advised thatcurrentantiretroviral therapyhas not been proven to prevent the risk of transmission of HIV to others through blood or sexual contact. Appropriate precautions should continue to be used.

When ritonavir is used as a pharmacokineticenhancer with other protease inhibitors (PIs),full details on thewarnings and precautions relevant to that particularPI should be considered, therefore the Summaryof Product Characteristics (SmPC) for the particular PImust beconsulted.

Ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer

Patients with chronic diarrhoea or malabsorption:Extramonitoringis recommendedwhen diarrhoea occurs. Therelativelyhigh frequencyofdiarrhoea duringtreatment with ritonavir maycompromisethe absorption and efficacy(dueto decreasedcompliance) ofritonavir or otherconcurrent medicinal products. Serious persistent vomitingand/ordiarrhoea associated with ritonavir usemight also compromise renalfunction.It is advisable tomonitor renal function in patients with renal function impairment.

Haemophilia: there havebeen reports of increasedbleeding, includingspontaneous skin haematomas and haemarthroses, inhaemophiliac patients typeA andBtreated with protease inhibitors. In some patients additional factor VIII was given. In more than a half of the reported cases, treatment with protease inhibitors wascontinued or reintroduced if treatment had been discontinued. Acausal relationship has been evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should thereforebemade awareof thepossibilityofincreased bleeding.

Diabetes mellitus and hyperglycaemia: New onsetdiabetes mellitus, hyperglycaemiaor exacerbation of existingdiabetes mellitus has been reported in patients receivingprotease inhibitors.Insomeof thesethehyperglycaemiawas severe andin some cases also associated with ketoacidosis. Manypatients had confoundingmedical conditions, some of which required therapywith agents that havebeen associated with thedevelopment ofdiabetes mellitus or hyperglycaemia.

Lipodystrophy: Combination antiretroviral therapyhas been associated with redistribution of bodyfat(lipodystrophy)in HIVpatients. The long-term consequences of these events arecurrentlyunknown. Knowledgeabout the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitorsand lipoatrophyand nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophyhas been associated with individual factors suchas olderage,and with medicinal product relatedfactors such as longer duration of antiretroviraltreatment and associatedmetabolic disturbances.Clinical examination should include evaluation forphysical signs of fatredistribution. Consideration should be given to measurement offastingserum lipids and blood glucose.Lipid disordersshould be managedasclinicallyappropriate(seesection4.8).

Pancreatitis: Pancreatitis should beconsidered ifclinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratoryvalues(such as increased serum lipase or amylasevalues) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and [Product name] therapyshould be discontinued if a diagnosis of pancreatitis is made (see section4.8).

Immune Reactivation Syndrome: in HIV-infected patients with severeimmune deficiencyat thetimeofinstitution of combination antiretroviral therapy(CART), an inflammatoryreactionto asymptomaticor residual opportunistic pathogens may arise andcause serious clinical conditions, or aggravation of symptoms. Typically,such reactions havebeenobserved within thefirstfew weeks or months of initiation of CART. Relevant examples arecytomegalovirusretinitis, generalised and/or focal mycobacterial infections,and Pneumocystis jiroveci pneumonia. Anyinflammatory symptoms should be evaluated and treatment instituted when necessary.

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 can occur many months after initiation of treatment.

Liver disease: Ritonavirshould not be given topatients with decompensated liver disease. For patients withstable severehepatic impairment (Child Pugh Grade C) without decompensation see section 4.2. Patientswith chronic hepatitis Bor C and treated with combinationantiretroviral therapyareat an increased risk for severe and potentiallyfatal hepatic adversereactions.In caseof concomitant antiviral therapyfor hepatitis BorC, please referto therelevant product information for these medicinal products.

Patients with pre-existingliverdysfunction includingchronicactivehepatitis have an increased frequencyofliverfunction abnormalities duringcombination antiretroviral therapyandshould be monitored accordingto standard practice.If thereis evidenceof worseningliverdiseasein such patients, interruption or discontinuation of treatment must be considered.

Renal disease: Since therenal clearance of ritonavir is negligible, thedecreasein the total bodyclearance is not expected in patients with renal impairment. For specificdosinginformation in patients with renal impairment, refer to theSummary of Product Characteristics (SPC) of the co-administered protease inhibitor. See also section 4.2.

Renal failure,renal impairment, elevatedcreatinine, hypophosphataemiaand proximal tubulopathy(including Fanconi syndrome) have beenreportedwith the use of tenofovir disoproxilfumarate in clinical practice (seesection 4.8).

Osteonecrosis: Althoughthe etiologyis considered to bemultifactorial (including corticosteroid use,alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported 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 theyexperience joint aches and pain, joint stiffness or difficultyin movement.

PR interval prolongation: ritonavir has been shown tocause modest asymptomatic prolongation of the PR interval in some healthyadult subjects. Rare reports of 2nd or3rd degreeatrioventricularblock in patients with underlyingstructural heartdisease and pre-existingconduction system abnormalities or in patients receivingmedicinal products known to prolongthe PR interval (suchas verapamil or atazanavir) have been reported in patientsreceivingritonavir. [Product name] should be used with caution in such patients (see section 5.1).

Interactions with other medicinal products

Ritonavir dosed as an antiretroviral agent

The followingWarningsand Precautions should beconsidered whenritonavir is used as an antiretroviralagent. Whenritonavir is used as a pharmacokinetic enhancer at the 100 mgand 200 mglevelit cannot be assumed that the following warnings and precautions will also apply. When ritonavir is used as a pharmacokineticenhancer, fulldetails on the warnings and precautions relevant to that particular PImust beconsidered, therefore theSummary of Product Characteristics, section 4.4, for the particularPImust be consulted to determineif the information below is applicable.

PDE5 inhibitors: Particular caution should be usedwhen prescribingsildenafil, tadalafil or vardenafil for thetreatment oferectiledysfunction in patients receiving ritonavir. Co-administration of ritonavir with thesemedicinal products is expected to substantiallyincreasetheir concentrations andmayresult in associatedadverse reactions suchas hypotension andprolonged erection (see section 4.5).

Concomitant use of avanafil or vardenafil with ritonavir is contraindicated. Concomitant useof sildenafil with ritonavir is contraindicated in pulmonaryarterial hypertension patients (seesection 4.3).

*HMG-CoA reductase inhibitors:*TheHMG-CoA reductaseinhibitors simvastatin and lovastatin arehighlydependent on CYP3A for metabolism, thus concomitant use of ritonavir with simvastatin or lovastatin is not recommended due to an increased risk of myopathyincludingrhabdomyolysis. Caution must also be exercised and reduced doses should be consideredif ritonavir is used concurrently with atorvastatin, which is metabolised to alesserextent byCYP3A. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir co-administration. The mechanism of this interaction is not clear, but maybe the result of transporter inhibition. When used with ritonavir dosed as apharmacokineticenhanceror as anantiretroviral agent, thelowest doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin andfluvastatinis not dependent ofCYP3A, and interactionsare not expected with ritonavir.If treatment with an HMG-CoA reductaseinhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).

Digoxin: Particular caution should be used whenprescribingritonavir in patients takingdigoxin since co-administration ofritonavir with digoxin is expected to increase digoxin levels. The increased digoxin levels maylessen over time(see section 4.5).

In patients who are alreadytakingdigoxin when ritonavir is introduced, the digoxin dose should be reduced to one-half of thepatients'normal dose and patients need to befollowed morecloselythan usual for several weeks after initiatingco- administration of ritonavir and digoxin.

In patients who are alreadytakingritonavirwhendigoxin is introduced, digoxin should be introduced moregraduallythan usual.Digoxin levels should be monitored more intensivelythan usual duringthis period, with dose adjustments made, as necessary, based on clinical,electrocardiographic and digoxin level findings.

Ethinyl estradiol: Barrieror other non-hormonalmethods of contraception should be considered whenadministeringritonavirat therapeutic or low dosesas ritonaviris likelytoreduce the effect and changethe uterine bleedingprofilewhen co- administered with estradiol-containingcontraceptives.

Glucocorticoids: Concomitant useof ritonavir and fluticasoneor other glucocorticoids that aremetabolised byCYP3A4is not recommended unless the potential benefit of treatmentoutweighs therisk of systemiccorticosteroid effects, includingCushing's syndrome and adrenal suppression (see section 4.5).

Trazodone: Particular caution should be used when prescribingritonavir inpatients usingtrazodone. Trazodone is a CYP3A4substrate and co-administration of ritonavir is expected to increase trazodonelevels. Adversereactions of nausea, dizziness, hypotension and syncope havebeen observed in single dose interaction studies in healthyvolunteers (see section 4.5)

Rivaroxaban:It is not recommended to use ritonavir in patients receiving rivaroxaban, due to the risk of increased bleeding (see section 4.5).

Ritonavir dosed as a pharmacokinetic enhancer

Theinteraction profiles ofHIV-proteaseinhibitors, co-administered with low dose ritonavir, are dependent on the specificco-administered PI.

For adescription of themechanisms and potential mechanisms contributingto the interaction profile ofthePIs, see section 4.5. Please also reviewthe Summary of Product Characteristicsfor the particular boosted PI.

Saquinavir: Doses of ritonavir higher than 100mg twice dailyshould not be used. Higherdoses ofritonavirhave been shown to be associated with an increased incidence ofadverse reactions. Co-administrationof saquinavir andritonavir has led to severeadverse reactions, mainlydiabetic ketoacidosis and liver disorders, especiallyin patients with pre-existingliverdisease.

Saquinavir/ritonavir should notbe given togetherwith rifampicin, due to the risk of severehepatotoxicity(presenting as increased hepatictransaminases) if thethree medicines aregiven together (see section 4.5).

*Tipranavir:*co-administered with 200 mgofritonavir has been associatedwith reports of clinical hepatitis and hepaticdecompensation includingsomefatalities. Extravigilanceis warranted in patients with chronichepatitis Bor hepatitis C co- infection, as these patients have an increased riskof hepatotoxicity.

Doses of ritonavir lowerthan 200 mgtwice dailyshould not be used as theymight alter theefficacyprofileof the combination.

Fosamprenavir: Co-administration of fosamprenavir with ritonavir in doses greater than 100 mgtwice dailyhas not been clinicallyevaluated. The use of higher ritonavir doses might alter the safetyprofileof thecombination and therefore is not recommended.

Atazanavir: Co-administration of atazanavir withritonavir at doses greater than 100 mgonce dailyhas not been clinicallyevaluated. The use of higherritonavirdoses mayalter thesafetyprofileof atazanavir(cardiaceffects, hyperbilirubinemia) and therefore is not recommended. Onlywhen atazanavir with ritonavir is co- administered with efavirenz, a dose increase of ritonavir to 200 mgonce dailycould be considered.In this instance, closeclinical monitoringis warranted. Refer to the Reyataz SmPCfor further details.

4.5 Interaction with other medicinal products andother forms ofinteraction

Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent

Ritonavir has a highaffinityfor several cytochromeP450 (CYP) isoforms and may inhibit oxidation with thefollowingranked order:CYP3A4 > CYP2D6. Co- administration of [Product name]and medicinalproducts primarilymetabolised by CYP3A mayresult in increased plasmaconcentrations of the other medicinal product, which could increase orprolongits therapeutic and adverseeffects. For select medicinal products (e.g. alprazolam) the inhibitoryeffects ofritonavir on CYP3A4 maydecreaseovertime. Ritonavir also has ahighaffinityfor P- glycoprotein and mayinhibit this transporter.Theinhibitoryeffect ofritonavir (with or without other protease inhibitors) on P-gp activitymaydecrease over time (e.g. digoxin and fexofenadine-see table'Ritonavir effects on non-antiretroviralmedicinal products' below). Ritonavir mayinduceglucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 therebyincreasingthe biotransformation of somemedicinal products metabolised bythese pathways, and mayresult in decreased systemic exposure to suchmedicinal products, which could decease or shorten their therapeuticeffect.

Important information regardingmedicinal product interactions whenritonavir is used as a pharmacokinetic enhancer is also contained in the SummaryofProduct Characteristics (SPC) of the co-administered proteaseinhibitor (PI).

Medicinal products that affect ritonavir levels

Serum levels of ritonavircan bereduced byconcomitant useof herbal preparations containingSt John's wort (*Hypericum perforatum).* This is due to the induction of medicinal product metabolisingenzymes bySt John's wort. Herbal preparations containingSt John's wort must not be used in combination with ritonavir.Ifa patient is alreadytaking StJohn's wort,stop StJohn's wort and if possiblecheck viral levels. Ritonavir levels mayincrease on stoppingSt John's wort. The dose of ritonavir mayneedadjusting. The inducingeffectmaypersist for at least 2 weeks aftercessation of treatment with StJohn's wort (see section 4.3).

Serum levels of ritonavirmaybeaffected byselectco-administered medicinal products (e.g. delavirdine, efavirenz, phenytoin and rifampicin). These interactions are noted in the medicinal product interaction tables below.

Medicinal products that are affected by the use ofritonavir

Interactions betweenritonavir and PIs, antiretroviral agents other than PIsand other non-antiretroviral medicinal products are listed in the tables below.

Medicinal Product Interactions – Ritonavir with Protease Inhibitors (PIs)

Co-Administered Medicinal Product	Dose of Co-administered Medicinal Product (mg)	Dose of Ritonavir (mg)	Medicinal Product Assessed	AUC	C_{min}

Amprenavir	600 q12h	100 q12h	Amprenavir[2]	↑ 64%	↑ 5 fold
	Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition.Clinical trials confirmed the safety and efficacy of 600 mg amprenavir twice daily withritonavir 100 mg twice daily. Ritonavir oral solution should not be co-administered withamprenavir oral solution to children due to the risk of toxicity from excipients in the twoformulations. For further information, physicians should refer to the Agenerase SmPC.				
Atazanavir	300 q24h	100 q24h	Atazanavir	↑86%	↑11 fold
			Atazanavir[1]	↑2 fold	↑3-7fold
	Ritonavir increases the serum levels of atazanaviras a result of CYP3A4 inhibition. Clinical trials confirmedthe safetyandefficacyof300 mgatazanavir oncedailywith ritonavir 100 mgonce dailyin treatment experienced patients. For further information, physicians should refer to the ReyatazSmPC.				
Darunavir	600, single	100 q12h	Darunavir	↑14 fold	
	Ritonavir increases the serum levels of darunaviras a result of CYP3A inhibition. Darunavir must begivenwith ritonavir to ensureits therapeuticeffect. Ritonavir doses higher than 100 mgtwicedailyhavenot been studied with darunavir.For further information, refer to theSmPC for Prezista.				
Fosamprenavir	700 q12h	100 q12h	Amprenavir	↑ 2.4 fold	↑11 fold
	Ritonavir increases the serum levels of amprenavir(from fosamprenavir) as a result of CYP3A4 inhibition. Fosamprenavir must begivenwith ritonavir to ensure its therapeutic effect.Clinicaltrials confirmed the safetyandefficacyoffosamprenavir 700 mgtwice dailywith ritonavir 100 mgtwice daily. Ritonavirdoses higherthan100 mgtwice dailyhave not been studied with fosamprenavir.Forfurther information,physicians should refer to theTelzir SmPC				
Indinavir	800 q12h	100 q12h	Indinavir[3]	↑178%	ND
			Ritonavir	↑72%	ND
	400 q12h	400 q12h	Indinavir[3]	↔	↑4 fold
			Ritonavir	↔	↔
	Ritonavir increases the serum levels of indinaviras a result of CYP3A4 inhibition.Appropriate doses for this combination, withrespect to efficacyand safety, have notbeen established. Minimal benefit of ritonavir-mediated pharmacokinetic enhancement is achievedwith doses higher than 100 mgtwice daily.Incases ofco-administration of ritonavir (100 mgtwice daily)and indinavir (800mgtwice daily)caution is warranted as therisk of nephrolithiasis maybeincreased.				

Nelfinavir	1250 q12h	100 q12h	Nelfinavir	↑20 to39%	ND
	750, single	500 q12h	Nelfinavir	↑152%	ND
			Ritonavir	↔	↔
	Ritonavir increases the serum levels of nelfinavir as a result of CYP3A4 inhibition. Appropriate doses for this combination, with respect to efficacy and safety, have notbeen established. Minimal benefit of ritonavir-mediated pharmacokinetic enhancement is achieved with doses higher than 100 mg twice daily.				
Saquinavir	1000 q12h	100 q12h	Saquinavir[4]	↑ 15-fold	↑ 5-fold
			Ritonavir	↔	↔
	400 q12h	400 q12h	Saquinavir[4]	↑ 17-fold	ND
			Ritonavir	↔	↔
	Ritonavir increases the serum levels of saquinavir as a result of CYP3A4 inhibition. Saquinavir should only be given in combination with ritonavir. Ritonavir 100 mg twice daily with saquinavir 1000 mg twice daily provides saquinavir systemic exposure over 24 hours similar to or greater than those achieved with saquinavir 1200 mg three times daily without ritonavir. In a clinical study investigating the interaction of rifampicin 600 mg once daily and saquinavir 1000 mg with ritonavir 100 mg twice daily in healthy volunteers, severe hepatocellular toxicity with transaminase elevations up to > 20-fold the upper limit of normal after 1 to 5 days of co-administration was noted. Due to the risk of severe hepatoxicity, saquinavir/ritonavir should not be given together with rifampicin. For further information, physicians should refer to the Invirase or Fortovase SmPC.				
Tipranavir	500 q12h	200 q12h	Tipranavir	↑ 11 fold	↑ 29 fold
			Ritonavir	↓ 40%	ND
	Ritonavir increases the serum levels of tipranavir as a result of CYP3A inhibition. Tipranavir must be given with low dose ritonavir to ensure its therapeutic effect. Doses of ritonavir less than 200 mg twice daily should not be used with tipranavir as they might alter the efficacy of the combination. For further information, physicians should refer to the Aptivus SmPC.				
	ND: Not determined.				

1. Based on cross-study comparison to 400 mg atazanavir once daily alone.

2. Based on cross-study comparison to 1200 mg amprenavir twice daily alone.

3. Based on cross-study comparison to 800 mg indinavir three times daily alone.

4. Based on cross-study comparison to 600 mg saquinavir three times daily alone.

Medicinal Product Interactions – Ritonavir with Antiretroviral Agents Other ThanProtease Inhibitors (PIs)

Co-Administered Medicinal Product	Dose of Co-administered Medicinal Product (mg)	Dose of Ritonavir (mg)	Medicinal Product Assessed	AUC	C_{min}
Didanosine	200 q12h	600 q12h 2 h later	Didanosine	↓ 13%	↔
	As ritonavir is recommended to be taken with food and didanosine should be taken on anempty stomach, dosing should be separated by 2.5 h. Dose alterations should not be necessary.				
Delavirdine	400 q8h	600 q12h	Delavirdine[1]	↔	↔
			Ritonavir	↑ 50%	↑ 75%
	Based on comparison to historical data, the pharmacokinetics of delavirdine did not appear to be affected by ritonavir. When used in combination with delavirdine, dose reduction of ritonavir may be considered.				
Efavirenz	600 q24h	500 q12h	Efavirenz	↑ 21%	
			Ritonavir	↑ 17%	
	A higher frequency of adverse reactions (eg, dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) have been observed when efavirenz is co-administered with ritonavir dosed as an antiretroviral agent.				
Maraviroc	100 q12h	100 q12h	Maraviroc	↑ 161%	↑ 28%
	Ritonavir increases the serum levels of maraviroc as a result of CYP3A inhibition.Maraviroc may be given with ritonavir to increase the maraviroc exposure. For further information, refer to the SmPC for Celsentri.				
Nevirapine	200 q12h	600 q12h	Nevirapine	↔	↔

			Ritonavir	↔	↔
	Co-administration of ritonavir with nevirapine does not lead to clinically relevant changesin the pharmacokinetics of either nevirapine or ritonavir.				
Raltegravir	400 single	100 q12h	Raltegravir	↓ 16%	↓ 1%
	Co-administration of ritonavir and Raltegravir results in a minor reduction in Raltegravirlevels.				
Zidovudine	200 q8h	300 q6h	Zidovudine	↓ 25%	ND
	Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreasedlevels of zidovudine. Dose alterations should not be necessary.				
	ND: Not determined 1.Based on parallel group comparison.				

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	**Dose of Coadministered Medicinal Products (mg)**	**Dose of Ritonavir (mg)**	**Effect on Coadministered Medicinal Products AUC**	**Effect on Coadministered Medicinal Products C_{max}**
Alpha1-Adrenoreceptor Antagonist				
Alfuzosin	Ritonavir co-administration is likely to result in increased plasma concentrations of alfuzosin and is therefore **contraindicated** (see section 4.3).			
Amphetamine Derivatives				
Amphetamine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).			
Analgesics				
Buprenorphine Norbuprenorphine	16 q24h	100 q12h	↑ 57%	↑ 77%

Glucuronide metabolites			↑ 33% ↔	↑ 108% ↔
	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamics changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine or ritonavir may therefore not be necessary when the two are dosed together. When ritonavir is usedin combination with another PI and buprenorphine, the SmPC of the co-administered PI should be reviewed for specific dosing information.			
Pethidine, piroxicam, propoxyphene	Ritonavir co-administration is likely to result in increased plasmaconcentrations of pethidine, piroxicam, and propoxyphene and istherefore **contraindicated** (see section 4.3).			
Fentanyl	Ritonavir dosed as a pharmacokinetic enhancer or as anantiretroviral agent inhibits CYP3A4 and as a result is expected toincrease the plasma concentrations of fentanyl. Careful monitoringof therapeutic and adverse effects (including respiratorydepression) is recommended when fentanyl is concomitantlyadministered with ritonavir.			
Methadone[1]		500 q12h	↓ 36%	↓ 38%
	5, single dose			
	Increased methadone dose may be necessary when concomitantlyadministered with ritonavir dosed as an antiretroviral agent or as apharmacokinetic enhancer due to induction of glucuronidation.Dose adjustment should be considered based on the patient'sclinical response to methadone therapy.			
Morphine	Morphine levels may be decreased due to induction ofglucuronidation by co-administered ritonavir dosed as anantiretroviral agent or as a pharmacokinetic enhancer.			
Antiarrthymics				
Amiodarone, bepridil, encainide, flecanide, propafenone, quinidine	Ritonavir co-administration is likely to result in increased plasmaconcentrations of amiodarone, bepridil, encainide, flecanide,propafenone, and quinidine and is therefore **contraindicated** (seesection 4.3).			
Digoxin	0.5 single IV dose	300 q12h, 3 days	↑ 86%	ND
	0.4 single oraldose	200 q12h, 13 days	↑ 22%	↔
	This interaction may be due to modification of P-glycoproteinmediated digoxin efflux by ritonavir dosed as an antriretroviralagent or as a pharmacokinetic			

	enhancer. Increased digoxin levelsobserved in patients receiving ritonavir may lessen over time asinduction develops (see section 4.4).			
Antiasthmatic				
Theophylline[1]	3 mg/kg q8h	500 q12h	↓ 43%	↓ 32%
	An increased dose of theophyline may be required when coadministeredwith ritonavir, due to induction of CYP1A2.			
Anticancer agents				
Dasatinib, nilotinib, vincristine, vinblastine	Serum concentrations may be increased when co-administeredwith ritonavir resulting in the potential for increased incidence ofadverse reactions.			
Anticoagulant				
Rivaroxaban	10, single dose	600 q12h	↑ 153%	↑ 55%
	Inhibition of CYP3A and P-gp lead to increased plasma levels andpharmacodynamics effects of rivaroxaban which may lead to anincreased bleeding risk. Therefore, the use of ritonavir is notrecommended in patients receiving rivaroxaban.			
Warfarin	5, single dose	400 q12h	↑ 9%	↓ 9%
S-Warfarin				
R-Warfarin			↓ 33%	↔
	Induction of CYP1A2 and CYP2C9 lead to decreased levels of Rwarfarinwhile little pharmacokinetic effect is noted on S- warfarinwhen co-administered with ritonavir. Decreased R-warfarin levelsmay lead to reduced anticoagulation, therefore it is recommendedthat anticoagulation parameters are monitored when warfarin isco-administered with ritonavir dosed as an antiretroviral agent oras a pharmacokinetic enhancer.			
Anticonvulsants				
Carbamazepine	Ritonavir dosed as a pharmacokinetic enhancer or as anantiretroviral agent inhibits CYP3A4 and as a result is expected toincrease the plasma concentrations of carbamazepine. Carefulmonitoring of therapeutic and adverse effects is recommendedwhen carbamazepine is concomitantly administered with ritonavir.			
Divalproex, lamotrigine, phenytoin	Ritonavir dosed as a pharmacokinetic enhancer or as anantiretroviral agent induces oxidation by CYP2C9 andglucuronidation and as a result is expected to decrease the plasmaconcentrations of anticonvulsants. Careful monitoring of serumlevels or therapeutic effects is recommended when thesemedicines are concomitantly administered with ritonavir.Phenytoin may decrease serum levels			

of ritonavir.

Antidepressants				
Amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline	Ritonavir dosed as an antiretroviral agent is likely to inhibitCYP2D6 and as a result is expected to increase concentrations ofdesipramine, imipramine, amitriptyline, nortriptyline, fluoxetine,paroxetine or sertraline. Careful monitoring of therapeutic andadverse effects is recommended when these medicines areconcomitantly administered with antiretroviral doses of ritonavir(see section 4.4).			
Desipramine	100, single oraldose	500 q12h	↑ 145%	↑ 22%
	The AUC and Cmax of the 2-hydroxy metabolite were decreased15 and 67%, respectively. Dosage reduction of desipramine isrecommended when co-administered with ritonavir dosed as anantiretroviral agent.			
Trazodone	50, single dose	200 q12h	↑ 2.4-fold	↑ 34%
	An increase in the incidence in trazodone-related adverse reactionswas noted when co-administered with ritonavir dosed as anantiretroviral agent or as a pharmacokinetic enhancer. If trazodoneis co-administered with ritonavir, the combination should be usedwith caution, initiating trazodone at the lowest dosage andmonitoring for clinical response and tolerability.			
Anti-gout treatments				
Colchicine	Concentrations of colchicine are expected to increase when coadministered with ritonavir.			
Antihistamines				
Astemizole, terfenadine	Ritonavir co-administration is likely to result in increased plasmaconcentrations of astemizole and terfenadine and is therefore**contraindicated** (see section 4.3).			
Fexofenadine	Ritonavir may modify P-glycoprotein mediated fexofenadineefflux when dosed as an antriretroviral agent or as apharmacokinetic enhancer resulting in increased concentrations offexofenadine. Increased fexofenadine levels may lessen over timeas induction develops.			
Loratadine	Ritonavir dosed as a pharmacokinetic enhancer or as anantiretroviral agent inhibits CYP3A and as a result is expected toincrease the plasma concentrations of loratadine. Carefulmonitoring of therapeutic and adverse effects is recommendedwhen loratidine is concomitantly administered with ritonavir.			

Anti-infectives

Fusidic Acid	Ritonavir co-administration is likely to result in increased plasmaconcentrations of both fusidic acid and ritonavir and is therefore**contraindicated** (see section 4.3).			
Rifabutin[1]	150 daily	500 q12h	↑ 4-fold	↑ 2.5-fold
25-*O*-desacetyl rifabutin metabolite			↑ 38-fold	↑ 16-fold
	Due to the large increase in rifabutin AUC, the concomitant use ofrifabutin with ritonavir dosed as an antiretroviral agent is**contraindicated** (see section 4.3). The reduction of the rifabutindose to 150 mg 3 times per week may be indicated for select PIswhen co-administered with ritonavir as a pharmacokineticenhancer. The SmPC of the co-administered PI should beconsulted for specific recommendations. Consideration should begiven to official guidance on the appropriate treatment oftuberculosis in HIV-infected patients.			
Rifampicin	Although rifampicin may induce metabolism of ritonavir, limiteddata indicate that when high doses of ritonavir (600 mg twicedaily) is co-administered with rifampicin, the additional inducingeffect of rifampicin (next to that of ritonavir itself) is small andmay have no clinical relevant effect on ritonavir levels in highdoseritonavir therapy. The effect of ritonavir on rifampicin is notknown.			
Voriconazole	200 q12h	400 q12h	↓ 82%	↓ 66%
	200 q12h	100 q12h	↓ 39%	↓ 24%
	Concomitant use of ritonavir dosed as an antiretroviral agent andvoriconazole is **contraindicated** due to reduction in voriconazoleconcentrations (see section 4.3). Co-administration ofvoriconazole and ritonavir dosed as a pharmacokinetic enhancershould be avoided, unless an assessment of the benefit/risk to thepatient justifies the use of voriconazole.			
Atovaquone	Ritonavir dosed as a pharmacokinetic enhancer or as anantiretroviral agent induces glucuronidation and as a result isexpected to decrease the plasma concentrations of atovaquone.Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is concomitantly administeredwith ritonavir.			
Clarithromycin	500 q12h	200 q8h	↑ 77%	↑ 31%
14-OH clarithromycin metabolite			↓ 100%	↓ 99%

	Due to the large therapeutic window of clarithromycin no dosereduction should be necessary in patients with normal renalfunction. Clarithromycin doses greater than 1 g per day should notbe co-administered with ritonavir dosed as an antiretroviral agentor as a pharmacokinetic enhancer. For patients with renalimpairment, a clarithromycin dose reduction should be considered:for patients with creatinine clearance of 30 to 60 ml/min the doseshould be reduced by 50%, for patients with creatinine clearanceless than 30 ml/min the dose should be reduced by 75%.			
Erythromycin, itraconazole	Ritonavir dosed as a pharmacokinetic enhancer or as anantiretroviral agent inhibits CYP3A4 and as a result is expected toincrease the plasma concentrations of erythromycin anditraconazole. Careful monitoring of therapeutic and adverse effectsis recommended when erythromycin or itraconazole is usedconcomitantly administered with ritonavir.			
Ketoconazole	200 daily	500q12h	↑ 3.4-fold	↑ 55%
	Ritonavir inhibits CYP3A-mediated metabolism of ketoconazole.Due to an increased incidence of gastrointestinal and hepaticadverse reactions, a dose reduction of ketoconazole should beconsidered when co-administered with ritonavir dosed as anantiretroviral agent or as a pharmacokinetic enhancer.			
Sulfamethoxazole/	800/160,	500q12h	↓ 20% /	↔
Trimethoprim[2]	single dose		↑ 20%	
	Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.			
Antipsychotics/Neuroleptics				
Clozapine, pimozide	Ritonavir co-administration is likely to result in increased plasmaconcentrations of clozapine or pimozide and is therefore**contraindicated** (see section 4.3).			
Haloperidol, risperidone, thioridazine	Ritonavir dosed as an antiretroviral agent is likely to inhibitCYP2D6 and as a result is expected to increase concentrations ofhaloperidol, risperidone and thioridazine. Careful monitoring oftherapeutic and adverse effects is recommended when thesemedicines are concomitantly administered with antiretroviraldoses of ritonavir (see section 4.3).			
Quetiapine	Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Concomitant administration of ritonavir and quetiapine is contraindicated as it may increase quetiapine-related toxicity.			
ß2-agonist (long acting)				
Salmeterol	Ritonavir inhibits CYP3A4 and as a result a pronounced increasein the plasma concentrations of salmetarol is expected. Thereforeconcomitant use is not recommended.			

Calcium channel antagonists

Amlodipine, diltiazem, nifedipine	Ritonavir dosed as a pharmacokinetic enhancer or as anantiretroviral agent inhibits CYP3A4 and as a result is expected toincrease the plasma concentrations of calcium channel antagonists.Careful monitoring of therapeutic and adverse effects isrecommended when these medicines are concomitantlyadministered with ritonavir.
Endothelin antagonists	
Bosentan	Co-administration of bosentan and ritonavir may increase steadystate bosentan maximum concentrations (Cmax) and area underthe curve (AUC)
Ergot Derivatives	
Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Ritonavir co-administration is likely to result in increased plasma concentrations of ergot derivatives and is therefore**contraindicated** (see section 4.3).
GI motility agent	
Cisapride	Ritonavir co-administration is likely to result in increased plasmaconcentrations of cisapride and is therefore **contraindicated** (seesection 4.3).

HCV Protease Inhibitor				
Simeprevir	200 qd	100d12h	↑ 7.2-fold	↑ 4.7-fold
	Ritonavir increases plasma concentrations of simeprevir as a result of CYP3A4 inhibition. It is not recommended to co-administer ritonavir with simeprevir.			

HMG Co-A Reductase Inhibitors	
Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin	HMG-CoA reductase inhibitors which are highly dependent onCYP3A metabolism, such as lovastatin and simvastatin, areexpected to have markedly increased plasma concentrations whenco-administered with ritonavir dosed as an antiretroviral agent or asa pharmacokinetic enhancer. Since increased concentrations oflovastatin and simvastatin may predispose patients to myopathies,including rhabdomyolysis, the combination of these medicinalproducts with ritonavir is **contraindicated** (see section 4.3).Atorvastatin is less dependent on CYP3A for metabolism. Whilerosuvastatin elimination is not dependent on CYP3A, an elevationof rosuvastatin exposure has been reported with ritonavir coadministration.The mechanism of this interaction is not clear, butmay be the result of transporter inhibition. When used withritonavir dosed as a pharmacokinetic enhancer or as anantiretroviral agent, the lowest possible doses of atorvastatin orrosuvastatin should be administered. The metabolism of pravastatinand fluvastatin is not

	dependent on CYP3A, and interactions arenot expected with ritonavir. If treatment with an HMG-CoAreductase inhibitor is indicated, pravastatin or fluvastatin isrecommended.			
Hormonal contraceptive				
Ethinyl estradiol	50 µg, single dose	500 q12h	↓ 40%	↓ 32%
	Due to reductions in ethinyl oestradiol concentrations, barrier orother non-hormonal methods of contraception should be consideredwith concomitant ritonavir use when dosed as an antiretroviralagent or as a pharmacokinetic enhancer. Ritonavir is likely tochange the uterine bleeding profile and reduce the effectiveness ofoestradiol-containing contraceptives (see section 4.4).			
Immunosuppressants				
Cyclosporine, tacrolimus, everolimus	Ritonavir dosed as a pharmacokinetic enhancer or as anantiretroviral agent inhibits CYP3A4 and as a result is expected toincrease the plasma concentrations of cyclosporine, tacrolimus oreverolimus. Careful monitoring of therapeutic and adverse effectsis recommended when these medicines are concomitantlyadministered with ritonavir.			
Phosphodiesterase inhibitors				
Avanafil	50, single dose	600 q12h	↑ 13-fold	↑ 2.4-fold
	Concomitant use of avanafil with ritonavir is contraindicated (see section 4.3).			
Sildenafil	100, single dose	500 q12h	↑ 11-fold	↑ 4-fold
	Concomitant use of sildenafil for the treatment of erectiledysfunction, with ritonavir dosed as an antiretroviral agent or as apharmacokinetic enhancer should be done with caution and in noinstance should sildenafil doses exceed 25 mg in 48 hours (see alsosection 4.4). Concomitant use of sildenafil with ritonavir is**contraindicated** in pulmonary arterial hypertension patients (seesection 4.3).			
Tadalafil	20, singledose	200 q12h	↑ 124%	↔
	The concomitant use of tadalafil for the treatment of erectiledysfunction with ritonavir dosed as an antiretroviral agent or as apharmacokinetic enhancer should be with caution at reduced dosesof no more than 10 mg tadalafil every 72 hours with increasedmonitoring for adverse reactions (see section 4.4).When tadalafil is used concurrently with ritonavir in patients withpulmonary arterial hypertension, refer to the tadalafil SmPC orprescribing information			
Vardenafil	5, single dose	600 q12h	↑ 49-fold	↑ 13-fold

	Concomitant use of vardenafil with ritonavir is **contraindicated** (see section4.3).			
Sedatives/hynoptics				
Clorazepate, diazepam, estazolam, flurazepam, oral and parenteral midazolam and triazolam	Ritonavir co-administration is likely to result in increased plasmaconcentrations of clorazepate, diazepam, estazolam andflurazepam and is therefore **contraindicated** (see section 4.3).Midazolam is extensively metabolised by CYP3A4. Coadministrationwith ritonavir may cause a large increase in theconcentration of this benzodiazepine. No medicinal productinteraction study has been performed for the co-administration ofritonavir with benzodiazepines. Based on data for other CYP3A4inhibitors, plasma concentrations of midazolam are expected to besignificantly higher when midazolam is given orally. Therefore,ritonavir should not be co-administered with orally administeredmidazolam (see section 4.3), whereas caution should be used withco-administration of ritonavir and parenteral midazolam. Datafrom concomitant use of parenteral midazolam with other PIssuggest a possible 3 – 4 fold increase in midazolam plasma levels.If ritonavir is co-administered with parenteral midazolam, itshould be done in an intensive care unit (ICU) or similar settingwhich ensures close clinical monitoring and appropriate medicalmanagement in case of respiratory depression and/or prolongedsedation. Dosage adjustment for midazolam should be considered,especially if more than a single dose of midazolam isadministered.			
Triazolam	0.125, singledose	200, 4 doses	↑ >20 fold	↑ 87%
	Ritonavir co-administration is likely to result in increased plasmaconcentrations of triazolam and is therefore **contraindicated** (seesection 4.3).			
Pethidine	50, oral single dose	500 q12h	↓ 62%	↓ 59%
Norpethidine metabolite			↑ 47%	↑ 87%
	The use of pethidine and ritonavir is **contraindicated** due to theincreased concentrations of the metabolite, norpethidine, whichhas both analgesic and CNS stimulant activity. Elevatednorpethidine concentrations may increase the risk of CNS effects(eg, seizures), see section 4.3.			
Alprazolam	1, single dose	200 q12h, 2 days	↑ 2.5 fold	↔
		500 q12h, 10 days	↓ 12%	↓ 16%

	Alprazolam metabolism was inhibited following the introductionof ritonavir. After ritonavir use for 10 days, no inhibitory effect ofritonavir was observed. Caution is warranted during the firstseveral days when alprazolam is co-administered with ritonavirdosed as an antiretroviral agent or as a pharmacokinetic enhancer,before induction of alprazolam metabolism develops.			
Buspirone	Ritonavir dosed as a pharmacokinetic enhancer or as anantiretroviral agent inhibits CYP3A and as a result is expected toincrease the plasma concentrations of buspirone. Carefulmonitoring of therapeutic and adverse effects is recommendedwhen buspirone concomitantly administered with ritonavir.			
Sleeping agent				
Zolpidem	5	200, 4 doses	↑ 28%	↑ 22%
	Zolpidem and ritonavir may be co-administered with carefulmonitoring for excessive sedative effects.			
Smoke cessation				
Bupropion	150	100 q12h	↓ 22%	↓ 21%
	150	600 q12h	↓ 66%	↓ 62%
	Bupropion is primarily metabolised by CYP2B6. Concurrentadministration of bupropion with repeated doses of ritonavir isexpected to decrease bupropion levels. These effects are thought torepresent induction of bupropion metabolism. However, becauseritonavir has also been shown to inhibit CYP2B6 in vitro, therecommended dose of bupropion should not be exceeded. Incontrast to long-term administration of ritonavir, there was nosignificant interaction with bupropion after short-termadministration of low doses of ritonavir (200 mg twice daily for 2days), suggesting reductions in bupropion concentrations mayhave onset several days after initiation of ritonavir coadministration.			
Steroids				
Fluticasone propionate aqueous nasal spray	200 µg qd	100 q12h	↑ ~ 350-fold	↑ ~ 25-fold
	Systemic corticosteroid effects including Cushing's syndrome andadrenal suppression (plasma cortisol levels were noted to bedecreased 86% in the above study) have been reported in patientsreceiving ritonavir and inhaled or intranasal fluticasonepropionate; similar effects could also occur with othercorticosteroids metabolised by CYP3A eg, budesonide.Consequently,			

	concomitant administration of ritonavir dosed as anantiretroviral agent or as a pharmacokinetic enhancer and theseglucocorticoids is not recommended unless the potential benefit oftreatment outweighs the risk of systemic corticosteroid effects (seesection 4.4). A dose reduction of the glucocorticoid should beconsidered with close monitoring of local and systemic effects or aswitch to a glucocorticoid, which is not a substrate for CYP3A4(eg, beclomethasone). Moreover, in case of withdrawal ofglucocorticoids progressive dose reduction may be required over alonger period.			
Dexamethasone	Ritonavir dosed as a pharmacokinetic enhancer or as anantiretroviral agent inhibits CYP3A and as a result is expected toincrease the plasma concentrations of dexamethasone. Carefulmonitoring of therapeutic and adverse effects is recommendedwhen dexamethasone is concomitantly administered with ritonavir.			
Prednisolone	20	200 q12h	↑ 28%	↑ 9%
	Careful monitoring of therapeutic and adverse effects isrecommended when prednisolone is concomitantly administeredwith ritonavir. The AUC of the metabolite prednisolone increasedby 37 and 28% after 4 and 14 days ritonavir, respectively.			
	ND: Not determined 1. Based on a parallel group comparison 2. Sulfamethoxazole was co-administered with trimethoprim.			

Cardiac and neurologic events have been reported when ritonavir has been coadministeredwith disopyramide, mexiletine or nefazadone. The possibility of medicinal product interaction cannot be excluded.

In addition to the interactions listed above, as ritonavir is highly protein bound, the possibility of increased therapeutic and toxic effects due to protein binding displacement of concomitant medicinal products should be considered.

Ritonavir dosed as a pharmacokinetic enhancer

Important information regarding medicinal product interactions when ritonavir is used a pharmacokinetic enhancer is also contained in the Summary of Product Characteristics of the co-administered protease inhibitor.

Proton pump inhibitors and H_2-receptor antagonists*:* proton pump inhibitors and H_2-receptor antagonists (e.g. omeprazole or ranitidine) may reduce concentrations for co-administered protease inhibitors. For specific information regarding the impact of coadministration of acid reducing agents, refer to the SmPC of the co-administered protease inhibitor.
Based on interaction studies with the ritonavir boosted protease inhibitors (lopinavir/ritonavir,atazanavir), concurrent administration of omeprazole or ranitidine does not significantly modify ritonavir efficacy as a pharmacokinetic enhancer despite a slight change of exposure (about 6 - 18%).

4.6 Fertility, pregnancy and lactation

A limited number (> 800) ofpregnantwomen were exposedto ritonavir duringpregnancy; averylimitednumber(<300)wereexposedduringthefirsttrimester.Thesedatalargely referto exposures where ritonavir wasusedincombinationtherapyandnotattherapeutic ritonavirdosesbutatlowerdosesasapharmacokineticenhancerforotherprotease inhibitors(PIs).These limited data indicatenoincreasein the rateofbirth defectscompared to rates observed in population-based birth defectsurveillance systems. Animal data have shown reproductivetoxicity(see section5.3).The useof [Product name]maybe consideredin pregnancyonlywhen thebenefits outweigh the riskto the foetus.

Ritonavir adverselyinteractswithoralcontraceptives(OCs).Therefore,analternative, effective andsafemethod ofcontraception shouldbe used duringtreatment.

Itisnotknownwhetherthismedicineisexcretedinhumanmilk.Milkexcretionhasnot been measured in the animal studies, however a studyin rats showed someeffectson offspringdevelopment duringlactation which arecompatiblewith excretion ofritonavirin milkin thatspecies.HIV infectedwomen shouldnotbreast-feedtheirinfantsunderany circumstances to avoidtransmission ofHIV.

4.7 Effects on ability to drive and use machines

No studieson the effects onthe abilityto drive and usemachines havebeen performed. As somnolenceand dizziness are known undesirable effects, this should betaken intoaccount when drivingor usingmachinery.

4.8 Undesirable effects

Ritonavir dosed as a pharmacokinetic enhancer

Adversereactions associated with the use of ritonavir as a pharmacokinetic enhancer are dependent on the specificco-administered protease inhibitor (PI).For information on adverse reactions refer tothe SmPCof the specificco-administered PI.

Ritonavir dosed as an antiretroviral agent

Adverse reactions from clinical trials and post-marketing experience in adult patients

The most frequentlyreported adverse drug reactions amongpatients receiving ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (includingdiarrhoea, nausea, vomiting, abdominal pain (upper and lower)), neurological disturbances(includingparaesthesia and oral paraesthesia) and fatigue/asthenia.

The following adverse reactions of moderate to severe intensitywith possible or probable relationship to ritonavir havebeen reported. Within each frequency grouping, undesirable effects are presented in order of decreasingseriousness: very common (> 1/10); common (> 1/100 to < 1/10); uncommon (> 1/1000 to <1/100); rare(> 1/10,000 to < 1/1,000); not known (cannotbe estimated from theavailable data).

Events noted as havingafrequencynot known were identified via post-marketing surveillance

Adversereactions in clinical studies and post-marketing in adultpatients

SystemOrder Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Common	Decreased WBC, decreased haemoglobin, decreased neutrophils, increased

		eosinophils, thrombocytopenia
	Uncommon	Increased neutrophils
Immune system disorders	Common	Hypersensitivity, includingurticariaand faceedema
	Rare	Anaphylaxis
Metabolism and nutrition disorders	Common	Hypercholesterolaemia,hypertriglyceridaemia,gout, lipodystrophyacquired,oedema and peripheral oedema, dehydration (usually associated withgastrointestinal symptoms)
	Uncommon	Diabetes mellitus
	Rare	Hyperglycaemia
Nervous system disorders	Verycommon	Dysgeusia, oraland peripheral paresthesia, headache, dizziness, peripheral neuropathy
	Common	Insomnia,anxiety, confusion, disturbance in attention, syncope, seizure
Eye disorders	Common	Blurred vision
Cardiac disorders	Uncommon	Myocardial infarction
Vascular disorders	Common	Hypertension, hypotension including orthostatic hypotension,peripheral coldness
Respiratory, thoracic and mediastinal disorders	Verycommon	Pharyngitis, oropharyngeal pain, cough
Gastrointestinal disorders	Verycommon	Abdominal pain (upperand lower),nausea, diarrhoea (includingsevere with electrolyteimbalance), vomiting, dyspepsia
	Common	Anorexia, flatulence, mouth ulcer, gastrointestinal haemorrhage, gastroesophageal reflux disease, pancreatitis
Hepatobiliarydisorders	Common	Hepatitis (includingincreased AST, ALT,GGT), blood bilirubin increased(includingjaundice)

Skin and subcutaneous tissue disorders	Verycommon Common Rare	Pruritus, rash (including erythematous and maculopapular) Acne Stevens Johnson syndrome, Toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	Verycommon Common	Arthralgia and back pain Myositis, rhabdomyolysis, myalgia, myopathy/CPK increased
Renal and urinarydisorders	Common Uncommon	Increased urination, renal impairment (e.g. oliguria, elevated creatinine) Acute renal failure
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Very common Common	Fatigue including asthenia, flushing, feeling hot Fever, weight loss
Investigations	Common Uncommon	Increased amylase, decreased free and total thyroxin Increased glucose, increased magnesium, increased alkaline phosphatase

Hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis, and jaundicehaveoccurred in patients receivingritonavir aloneor in combination with other antiretrovirals.

Combination antiretroviral therapyhas beenassociated with redistribution of body fat (lipodystrophy)in HIV patients includingthe loss of peripheral and facial subcutaneous fat, increased intra-abdominaland visceral fat, breast hypertrophyand dorsocervical fataccumulation (buffalo hump).

Combination antiretroviral therapyhas beenassociated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

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 can occur many months after initiation of treatment (see section 4.4).

Pancreatitis has been observed in patients receivingritonavir therapy, including thosewho developed hypertriglyceridemia.In some casesfatalities havebeen observed. Patients with advanced HIV disease maybeat risk of elevated triglycerides and pancreatitis (see section 4.4).

Cases of osteonecrosishave been reported, particularlyin patients withgenerally acknowledged risk factors, advanced HIV diseaseor long-term exposure to combination antiretroviral therapy(CART). Thefrequencyof this is unknown (see section 4.4).

Reportingof suspected adverse reactions

Reportingsuspected adverse reactions afterauthorisation of the medicinalproduct is important.It allows continued monitoringof thebenefit/risk balanceofthe medicinal product. Healthcare professionalsareasked to report anysuspected adversereactions via thenational reportingsystem[to be completed nationally].

4.9 Overdose

Human experienceofacuteoverdosewithritonavirislimited.Onepatientin clinicaltrials tookritonavir1500 mg/day fortwo daysand reportedparaesthesia, whichresolved afterthe dose wasdecreased. Acaseof renal failurewith eosinophilia has beenreported.

Thesignsoftoxicityobservedinanimals(miceandrats)includeddecreasedactivity, ataxia, dyspnoea and tremors.

Thereis no specificantidote foroverdose with ritonavir.Treatment ofoverdose with ritonavirshouldconsistof generalsupportivemeasuresincludingmonitoringofvitalsigns andobservationoftheclinicalstatusofthepatient.Duetothesolubilitycharacteristicsand possibilityoftransintestinalelimination,itisproposedthatmanagementofoverdosecould entailgastriclavageandadministrationofactivatedcharcoal.Sinceritonavirisextensively metabolisedbytheliverandishighlyproteinbound, dialysisisunlikelytobebeneficialin significantremoval of themedicine.

5 PHARMACOLOGICALPROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeuticgroup: antivirals for systemicuse, protease inhibitorsATC code:J05AE03

Ritonavir dosed as a pharmacokinetic enhancer

Pharmacokinetic enhancement byritonavir is based on ritonavir's activityas a potent inhibitor of CYP3A- mediated metabolism.The degree ofenhancement is related to themetabolicpathwayof theco-administered proteaseinhibitor (PI)and theimpact of the co-administered protease inhibitoron themetabolism of ritonavir. Maximal inhibition of metabolismof the co-administered PIis generallyachieved with ritonavir doses of 100 mgdailyto 200 mgtwice daily, and is dependent onthe co- administered PI.Foradditional information on the effect of ritonavir onco- administered PImetabolism, see Section 4.5 and refer to the SummaryofProduct Characteristics (SmPC) of theparticular co-administered PIs.

Ritonavir dosed as an antiretroviral agent

Ritonavir is an orallyactivepeptidomimeticinhibitor of theHIV-1 and HIV-2 aspartyl proteases.Inhibition of HIV protease renders the enzymeincapableof processingthe *gag-pol* polyprotein precursorwhich leads to the production of HIV particles with immaturemorphologythat are unable to initiate new roundsof infection. Ritonavir has selective affinityfor the HIVprotease and has little inhibitoryactivityagainst human aspartyl proteases.

Ritonavir was the first protease inhibitor(approved in 1996) forwhich efficacywas proven in a studywith clinical endpoints. However,due toritonavir's metabolic inhibitory properties its use as a pharmacokineticenhancerof otherPIs is the prevalent use of ritonavir in clinical practice (seesection 4.2).

Effects on the Electrocardiogram

QTcFinterval wasevaluated in a randomised, placebo andactive (moxifloxacin 400 mgonce daily)controlled crossoverstudyin 45 healthyadults, with 10 measurements over 12 hours on Day3. The maximum mean (95% upperconfidence bound) difference in QTcFfrom placebo was 5.5 (7.6) for 400 mgtwice daily ritonavir. The Day3ritonavir exposure wasapproximately1.5 fold higherthan that observed with the 600 mgtwice dailydose atsteadystate.No subject experiencedan increase in QTcFof≥60 msec from baseline ora QTcFinterval exceedingthe potentiallyclinicallyrelevant threshold of 500 msec.

Modest prolongation of the PR interval was also noted in subjects receiving ritonavir in the same studyon Day3. The mean changes from baseline in PR interval ranged from 11.0to 24.0 msec in the 12 hour interval post dose. Maximum PR interval was 252 msec and no second or thirddegree heart block was observed (see section 4.4).

Resistance

Ritonavir-resistant isolates ofHIV-1 have been selected*in vitro* and isolated from patients treated with therapeutic doses ofritonavir.

Reduction in the antiretroviral activityofritonavir is primarilyassociatedwith the protease mutations V82A/F/T/S andI84V. Accumulation of other mutations in the proteasegene (including at positions20, 33, 36, 46, 54, 71, and 90) can also contribute to ritonavir resistance.Ingeneral,as mutations associated with ritonavir resistanceaccumulate, susceptibilityto select other PIs maydecrease due to cross-resistance. The Summary of Product Characteristics of other protease inhibitorsor official continuous updates should be consulted for specificinformation regardingproteasemutations associatedwith reducedresponse to these agents.

Clinical pharmacodynamic data

The effects ofritonavir (alone or combined with other antiretroviral agents) on biological markers of disease activitysuchas CD4 cell count and viral RNA were evaluated in several studies involvingHIV-1 infected patients. The following studies are the most important.

Adult Use

A controlled studycompleted in 1996 with ritonavir as add-on therapyin HIV-1 infected patients extensivelypre-treated with nucleoside analoguesand baseline CD4 cell counts ≤ 100 cells/μ l showed a reduction in mortalityand AIDS defining events. The mean average change from

baseline over 16 weeks for HIV RNA levelswas -0.79 log_{10} (maximum mean decrease: 1.29 log_{10}) in the ritonavir group versus -0.01 log10 in the control group. The most frequently used nucleosides in this studywere zidovudine, stavudine, didanosine and zalcitabine.

Ina studycompleted in 1996 recruitingless advanced HIV-1 infected patients (CD4 200-500 cells/µ l) without previous antiretroviral therapy, ritonavir incombination with zidovudine or alone reduced viral load in plasma and increased CD4 count. The mean average change from baseline over 48 weeks for HIV RNA levels was -0.88 log_{10}in the ritonavir group versus -0.66 log10 in the ritonavir + zidovudine group versus -0.42 log_{10} in the zidovudine group.

The continuation of ritonavir therapyshouldbeevaluated byviral load because of the possibilityof theemergence ofresistance as described under section 4.1Therapeutic indications.

Paediatric Use

In an open label trial completed in 1998 in HIV infected, clinically stable children there was a significant difference (p = 0.03) in the detectable RNA levels in favour of a triple regimen (ritonavir, zidovudine and lamivudine) following 48 weeks treatment.

In a study completed in 2003, 50 HIV-1 infected, PI and lamivudine naïve children age 4 weeks to 2 years received ritonavir 350 or 450 mg/m^2 every 12 hours co- administered with zidovudine 160 mg/m^2 every 8 hours and lamivudine 4 mg/kg every 12 hours. In intent to treat analyses, 72% and 36% of patients achieved reduction in plasma HIV-1 RNA of ≤ 400 copies/ml at Week 16 and 104, respectively. Response was similar in both dosing regimens and across patient age.

In a study completed in 2000, 76 HIV-1 infected children aged 6 months to 12 years who were PI naive and naive to lamivudine and/or stavudine received ritonavir 350 or 450 mg/m^2 every 12 hours co-administered with lamivudine and stavudine. In intent to treat analyses, 50% and 57% of patients in the 350 and 450 mg/ m^2 dose groups, respectively, achieved reduction in plasma HIV-1 RNA to ≤ 400 copies/mlat Week 48.

5.2 Pharmacokinetic properties

Absorption

There is no parenteral formulation of ritonavir, therefore the extent of absorption and absolute bioavailabilityhave not been determined. The pharmacokinetics of ritonavir duringmultipledose regimens were studied in non-fastingHIV-infectedadult volunteers. Upon multiple dosing, ritonavir accumulation is slightlyless than predicted from asingledosedueto atime and dose-related increasein apparent clearance(Cl/F). Trough concentrations of ritonavir decreaseovertime, possibly due to enzyme induction,but appeared to stabilise bytheend of 2 weeks. The time to maximum concentration (T_{max}) remained constant at approximately4 hours with increasingdose. Renal clearanceaveraged less than 0.1 l/h and was relatively constant throughout the dosage range.

The pharmacokinetic parameters observed with various dosingschemes of ritonavir alone are shown in the table below. Plasma concentrations of ritonavir after administration of a single 100 mgdose tabletare similar to the 100 mgsoftgelatine capsule under fedconditions.

	Ritonavir Dosing Regimen				
	100 mgoncedail	100 mg twicedaily[1]	200 mg oncedaily	200 mg twicedaily	600 mg twicedaily
C_{max} (µg/ml)	0.84 ± 0.39	0.89	3.4 ± 1.3	4.5 ± 1.3	11.2 ± 3.6
C_{trough}	0.08 ± 0.04	0.22	0.16 ± 0.10	0.6 ± 0.2	3.7 ± 2.6
$AUC_{12 \text{ or } 24}$ (µg·h/ml)	6.6 ± 2.4	6.2	20.0 ± 5.6	21.92 ± 6.48	77.5 ± 31.5
$t_{1/2}$ (h)	~5	~5	~4	~8	~3 to 5
Cl/F (L/h)	17.2 ± 6.6	16.1	10.8 ± 3.1	10.0 ± 3.2	8.8 ± 3.2

[1]Values expressed as geometric means. Note: ritonavir was dosedafter ameal for all listed regimens.

Effects of food on oral absorption

Food slightlydecreases the bioavailabilityof the ritonavir film-coated tablets. Administration of a single100 mgdose of ritonavir film-coated tablets with a moderate fat meal (857 kcal, 31% caloriesfromfat) or a high fat meal (907kcal,52% caloriesfrom fat) was associatedwith a mean decrease of 20-23% inritonavirAUC and C_{max}.

Distribution

The apparent volume of distribution (VB/F) of ritonavir is approximately 20 - 40 l after a single 600 mg dose. The protein binding of ritonavir in human plasma is approximately 98 - 99% and is constant over the concentration range of 1.0 – 100µ g /ml. Ritonavir binds to both human alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA) with comparable affinities.
Tissue distribution studies with^{14}C-labelled ritonavir in rats showed the liver, adrenals, pancreas, kidneys and thyroid to have the highest concentrations of ritonavir. Tissue to plasma ratios of approximately 1 measured in rat lymph nodes suggests that ritonavir distributes into lymphatic tissues. Ritonavir penetrates minimally into the brain.

Metabolism

Ritonavir was noted to be extensivelymetabolised bythe hepatic cytochrome P450 system, primarilybytheCYP3A isozymefamilyand to alesserextent bythe CYP2D6 isoform. Animal studies as well as in vitro experiments with human hepatic microsomes indicated that ritonavir primarilyunderwent oxidativemetabolism. Four ritonavir metabolites havebeenidentified in man. The isopropylthiazoleoxidation metabolite(M-2) is themajor metabolite and has antiviral activitysimilar to that of parentcompound. However, the AUC ofthe M-2 metabolite was approximately3%of theAUC ofparent compound.

Low doses of ritonavir have shown profound effects on the pharmacokinetics of other protease inhibitors (PIs)and other productsmetabolised byCYP3A4) and other PIs mayinfluence the pharmacokinetics of ritonavir (see section 4.5).

Elimination

Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarilyviathehepatobiliarysystem; approximately86% of radiolabel wasrecoveredfrom stool, partof whichis expected to be unabsorbed ritonavir.In these studiesrenal elimination was not found to be a major route of elimination of ritonavir. This was consistent with theobservations in animal studies.

Special Populations
No clinicallysignificant differences in AUC or C_{max}were noted betweenmales and females. Ritonavir pharmacokineticparameters werenot statisticallysignificantly associated with bodyweight or lean bodymass. Ritonavir plasma exposures in patients 50 – 70years ofage when dosed 100mgin combination with lopinavir or at higher doses in the absenceof other PIs is similar to that observed inyounger adults.

Patients with impaired liver function
After multiple dosingofritonavir to healthyvolunteers (500 mgtwice daily)and subjects with mild to moderate hepatic impairment (Child Pugh Class A and B, 400 mgtwice daily)exposureto ritonavir after dose normalisation was not significantly different between the two groups.

Patients with impaired renal function
Ritonavir pharmacokinetic parameters havenot been studied in patients with renal impairment. However, since the renal clearance ofritonavir is negligible, no changes in the total bodyclearanceare expected in patients with renal impairment.

Paediatricpatients
Ritonavir steady-state pharmacokineticparameters wereevaluated in HIVinfected children above 2years ofage receivingdoses rangingfrom 250 mg/m² twice dailyto 400 mg/m² twice daily. Ritonavir concentrations obtained after 350 to 400 mg/m² twicedailyin paediatricpatients werecomparable to thoseobtained in adults receiving600 mg(approximately330 mg/m²) twice daily. Across dosegroups, ritonavir oral clearance (CL/F/m²) wasapproximately1.5 to 1.7 times faster in paediatric patients above2years ofage than in adult subjects.

Ritonavir steady-state pharmacokineticparameters wereevaluated in HIVinfected children less than 2yearsof age receivingdosesrangingfrom 350 to 450 mg/m² twice daily. Ritonavir concentrations inthis studywere highlyvariable and somewhat lower than those obtained in adults receiving600 mg (approximately330 mg/m²) twice daily. Across dose groups,ritonaviroral clearance (CL/F/m²)declined with age with median values of 9.0L/h/m² in children less than 3 months ofage, 7.8L/h/m² in children between 3 and 6 months of ageand 4.4L/h/m² in children between 6and 24 months of age.

5.3 Preclinical safety data

Repeated dosetoxicitystudies in animals identified major target organs as theliver, retina, thyroidgland andkidney. Hepaticchangesinvolved hepatocellular,biliary and phagocyticelementsand wereaccompanied byincreases in hepaticenzymes. Hyperplasiaoftheretinalpigment epithelium (RPE) and retinal degeneration have been seen inall of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidencesuggests that theseretinal changes maybe secondaryto phospholipidosis. However,clinical trials revealed no evidenceof medicinal product-induced ocularchangesin humans. All thyroid changeswere reversible upon discontinuation of ritonavir. Clinical

investigation in humans has revealed no clinicallysignificant alterationin thyroid function tests. Renal changes includingtubular degeneration, chronic inflammation and proteinureawerenoted in rats and are felt to be attributable tospecies-specific spontaneous disease. Furthermore, no clinicallysignificant renal abnormalities werenoted in clinical trials.

Developmental toxicityobserved in rats(embryolethality, decreased foetal body weightand ossification delaysand visceral changes, includingdelayed testicular descent)occurred mainlyat a maternallytoxic dosage. Developmental toxicityin rabbits (embryolethality,decreased litter size anddecreased foetal weights) occurred at a maternallytoxic dosage.

Ritonavir was not found to be mutagenic orclastogenic in a batteryofin vitro and in vivo assays includingthe Ames bacterial reverse mutation assayusing *Salmonella typhimurium* and *Escherichia coli*, themouse lymphoma assay,the mouse micronucleus testand chromosomal aberration assays in human lymphocytes.

Longterm carcinogenicitystudies of ritonavir inmice and rats revealed tumourigenicpotential specific for these species, but are regarded as of no relevance for humans.

6 PHARMACEUTICALPARTICULARS

6.1 List ofexcipients

Tablet:
Copovidone(K-30)
Sorbitan laureate (E493)
Silica,colloidal anhydrous(E551)
Calcium Hydrogen Phosphate, anhydrous
Sodiumstearylfumarate

Film-coating:
Hypromellose(E464)
Titanium dioxide (E171)
Macrogol/PEG MW 400 (E1521)/ Macrogol/PEG MW3350 (E1521)
Hydroxypropyl cellulose (E463)
Talc (E553b)
Silica, colloidal anhydrous (E551)
Polysorbate 80 (E433)

6.2 Incompatibilities

Notapplicable.

6.3 Shelflife

30 months.

6.4 Special precautions forstorage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents ofcontainer

White high density polyethylene (HDPE) bottles closed with white child resistant polypropylene caps.
Packsizes: 30 and 120 tablets.

Notallpacksizesmaybemarketed.

6.6 Specialprecautionsfordisposal

Nospecial 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

Date of first authorisation: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Packageleaflet:Informationforthepatient

[Product name]100 mgfilm-coatedtablets
ritonavir

Read allofthisleafletcarefully beforeyoustarttaking thismedicinebecauseitcontains important informationforyou.
- Keep thisleaflet. You may needto readitagain.
- Ifyou haveanyfurtherquestions,ask yourdoctororpharmacist.
- Thismedicinehasbeen prescribedforyou only. Do notpassitonto others.Itmayharmthem, even iftheirsignsof illnessarethesameasyours.
- Ifyou getanyof thesideeffects,talkto yourdoctororpharmacist.Thisincludes anypossible sideeffectsnotlisted inthis leaflet.Seesection 4.

In thisleaflet:

1. What[Product name]isandwhatitisusedfor

[Product name] contains the active substance ritonavir. Ritonavirisaprotease inhibitorused to controlHIV infection. Ritonavir is used in combination with otheranti-HIV medicines (antiretrovirals) to control yourHIV infection.

[Product name] is used by children 2 years of age or older, adolescents and adults who are infected with HIV, the virus which causes AIDS. [Product name] should not be administered to children younger than 2 years of age unless specifically directed by their doctor.

[Product name] can beused at fulldoseon its own, or at lowerdoses (called boosterdoses)with other medicines. Yourdoctor willdiscusswith you thebestcombination of medicines foryou.

2. Whatyouneedto knowbeforeyoutake[Product name]

Do not take[Product name]

- ifyou areallergicto ritonaviroranyoftheotheringredientsofthismedicine(listed insection6).
- ifyou haveseverelіverdisease.
- ifyou arecurrentlytakinganyof thefollowing medicines:
  - astemizoleorterfenadine (commonlyused to treatallergysymptoms– thesemedicines maybeavailablewithoutprescription);
  - amiodarone,bepridil,encainide,flecainide, propafenone, quinidine(used to correct irregularheartbeats);
  - dihydroergotamine, ergotamine (usedtotreatmigraineheadache);
  - ergonovine, methylergonovine(used tostop excessivebleedingthatmayoccur following childbirth oran abortion);

- clorazepate, diazepam, estazolam, flurazepam, triazolamororal(taken bymouth) midazolam(used to help you sleep and/orrelieveanxiety);
- clozapine, pimozide, (usedto treatabnormalthoughtsor feelings);
- pethidine,piroxicam, propoxyphene (usedto relievepain);
- cisapride(used torelievecertain stomach problems);
- rifabutin(used to prevent/treatcertain infections)*;
- voriconazole (usedto treatfungalinfections)*;
- simvastatin,lovastatin(used tolowerblood cholesterol);
- alfuzosin(usedtotreatenlarged prostategland);
- fusidicacid (usedtotreatbacterialinfections);
- sildenafilifyou sufferfroma lungdiseasecalled pulmonaryarterialhypertensionthat makesbreathingdifficult. Patientswithout thisdiseasemayusesildenafilforimpotence (erectiledysfunction)undertheirdoctor'ssupervision (seethesectionon**Othermedicinesand [Product** name]);
- avanafil or vardenafil (used to treat erectile dysfunction);
- productscontainingStJohn'swort (*Hypericumperforatum*)as thismaystop [Product name]fromworkingproperly. StJohn'swortisoften usedinherbalmedicinesthatyou can buy yourself.

* Yourdoctormaydecidethatyou cantakerifabutin and/orvoriconazolewithabooster(lower dose) of[Product name]buta fulldoseof[Product name]mustnotbetaken togetherwiththesetwomedicines.

Ifyou arecurrentlytakinganyof thesemedicines, ask yourdoctoraboutswitchingto adifferent medicinewhile you aretaking[Product name]. Often, thereareothermedicinesyou cantake instead.

Also readthelistofmedicinesin 'Othermedicines and [Product name]'forusewith certain othermedicines whichrequirespecialcare.

Warningsand precautions
Talk to your doctor before taking [Product name].

Important information

- If[Product name]istaken in combination with otherantiretroviralmedicines, itis importantthatyou alsocarefullyreadtheleafletsthatareprovided withtheseothermedicines.Theremaybe additionalinformation inthoseleafletsaboutsituationswhen [Product name]should beavoided. If you haveanyfurtherquestionsabout[Product name]ortheothermedicinesprescribed, pleaseask yourdoctororpharmacist.
- [Product name]isnotacureforHIVinfectionorAIDS.
- Peopletaking[Product name]maystilldevelop infectionsorotherillnessesassociatedwith HIV infectionorAIDS.It is therefore importantthatyou remain underthesupervisionofyour doctor whiletaking[Product name].
- 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.

Tell your doctor if you have/had:

- Ahistoryof**liverdisease.**

- **HepatitisBorC**and arebeingtreated with acombinationofantiretroviralagents,asyou are atagreaterriskofasevereand potentiallylife threateningreaction becauseoftheeffecton theliver. Regularbloodtestsmaybe required to check your liverisworkingproperly.

- **Haemophilia**, as therehavebeenreportsof increasedbleedingin patientswith haemophiliawho aretakingthis typeofmedicine(proteaseinhibitors).Thereason forthis is notknown. You mayneed additionalmedicineto help yourbloodclot(factorVIII), in orderto control anybleeding.

- **ErectileDysfunction,** asthemedicinesused to treaterectiledysfunction can cause hypotension and prolongederection.

- **Diabetes**, as therehavebeen reportsofworseningofor thedevelopmentofdiabetes (diabetes mellitus)in somepatientstakingproteaseinhibitors.

- **Kidney (renal)disease,**sinceyourdoctormayneed to checkthedoseofyourother medicines(such asproteaseinhibitors).

Tellyourdoctorifyou experience:

- **Changes inthedistribution ofthefat**on yourbody, orabuild uporlossofbodyfat (see section4**Possibleside effects**).

- **Diarrhoea orvomiting**that isnotimproving(persistent),asthismayreducehowwellthe medicinesyou aretakingwork.

- **Feeling sick**(nausea), **vomiting** orhave**stomach pain**, becausethesemaybesignsof inflammation ofthepancreas (pancreatitis). Somepatientstaking[Product name]can develop seriousproblemswiththeirpancreas.Tellyourdoctorassoon aspossibleifthisappliesto you.

- **Symptoms of infection** –informyourdoctorimmediately. Somepatientswith advanced HIV infection(AIDS)who thenstartanti-HIVtreatmentmaydevelop thesymptomsof infections theyhavehadin thepasteven if theydidn’tknowtheyhad hadthem. It isbelievedthat this happensbecause thebody'simmune responseimprovesand helps thebodytofight these infections.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.

- **Jointstiffness, achesandpains**(especiallyofthehip, kneeand shoulder)anddifficulty moving, tellyourdoctor, asthismaybeasign ofaproblemthatcan destroybone (osteonecrosis). Somepatientstakinganumberofantiretroviralmedicinesmaydevelop this disease.

- **Musclepain, tenderness orweakness**, particularlyincombination with antiretroviraltherapy includingproteaseinhibitorsand nucleosideanalogues.On rareoccasionsthesemuscle disordershavebeen serious. (Seesection 4**Possiblesideeffects**)

- **Dizziness, light-headedness,faintingspellsorabnormalheartbeat.** Somepatientstaking [Product name]mayexperiencechanges intheelectrocardiogram(ECG). Tellyourdoctorifyou haveaheartdefectorconduction defect.

- Ifyou haveanyotherhealth concerns, discussthesewith yourdoctorassoon as you can.

[Product name]isnot recommended inchildren below2 yearsofage.

Othermedicinesand [Product name]

Therearesomemedicinesyou cannottakeatallwith[Product name].Thesearelistedearlierinsection 2, under‘Do nottake[Product name]’.Therearesomeothermedicines thatcan onlybeused undercertain circumstancesasdescribedbelow. Pleasetellyourdoctororpharmacistifyou aretakingorhave recentlytaken anyothermedicines,includingmedicinesobtained withoutaprescription.

Thefollowingwarningsapplywhen [Product name]istakenasafulldose. However,thesewarningsmay alsoapplywhen [Product name]isusedinlowerdoses(abooster)withothermedicines.

Tellyourdoctororpharmacist ifyou aretaking, haverecentlytaken ormight take any of the medicineslistedbelow, asspecialcareshould betaken:

- **Sildenafil or tadalafil**forimpotence(erectiledysfunction). Thedoseand/orfrequencyofuseofthesemedicinesmayneed tobereduced to avoid hypotension and prolongederection. You mustnottake[Product name]with sildenafilifyou suffer frompulmonaryarterialhypertension(seealso‘**Before you take[Product name]**’).Tellyourdoctorif you aretakingtadalafilforpulmonaryarterialhypertension.

- **Digoxin** (heartmedicine).Yourdoctormayneed to adjust thedoseof digoxin and monitoryou whileyou aretakingdigoxin and [Product name]inordertoavoid heartproblems.
- **Hormonalcontraceptives**containingethinyloestradiolas[Product name]mayreducethe effectivenessofthesemedicines. It isrecommended thatacondomorothernon-hormonal method ofcontraceptionisusedinstead.You mayalso noticeirregularuterinebleedingifyou aretakingthis typeofhormonalcontraceptivewith [Product name].

- **Atorvastatin orrosuvastatin**(forhigh cholesterol)as[Product name]mayraisetheblood levelsof thesemedicines.Talkto yourdoctorbefore you takeanycholesterol-reducingmedicineswith [Product name](seealso ‘**Do nottake[Product name]**’ above).

- **Steroids**(e.g. dexamethasone, fluticasonepropionate,prednisolone)as[Product name]mayraisethe bloodlevelsofthesemedicineswhich mayleadto Cushing’ssyndrome (developmentofa rounded face)andreduceproduction ofthehormonecortisol. Yourdoctormaywish toreduce thesteroid doseormonitoryoursideeffectsmoreclosely.

- **Trazodone**(amedicinefordepression)asan increaseofunwantedeffectslikenausea, dizziness,lowblood pressureand faintingcanoccurwhen taken with [Product name].

- **Rifampicin andsaquinavir**(used fortuberculosisandHIV, respectively)asseriousliver damagecan occurwhen taken with [Product name].

- **Bosentan**(used forpulmonaryarterialhypertension)as ritonavirmayincreasethebloodlevels of thismedicine.

Therearemedicinesthat maynotmix with [Product name]becausetheireffectscouldincreaseordecrease when takentogether. In somecasesyourdoctormay needto performcertaintests, changethedoseor monitoryou

regularly.Thisiswhy you shouldtellyourdoctorifyou aretakingany medicines, includingthoseyou haveboughtyourselforherbalproducts, butitisespeciallyimportantto mention these:

- amphetamineoramphetaminederivatives;
- antibiotics(e.g. erythromycin, clarithromycin);
- anticancertreatments(e.g.dasatinib, nilotinib, vincristine, vinblastine);
- anticoagulants (e.g. rivaroxaban, warfarin);
- antidepressants(e.g. amitriptyline,desipramine, fluoxetine,imipramine, nortriptyline, paroxetine,sertraline,trazodone);
- antifungals(e.g. ketoconazole,itraconazole);
- antihistamines(e.g. loratadine, fexofenadine);
- antiretroviralmedicinesincludingHIV-proteaseinhibitorsand Non-nucleosidereverse transcriptaseinhibitors(NNRTI);
- antiviral medicine used to treat chronic hepatitis C virus (HCV) infection in adults (simeprevir);
- anxietymedicine,buspirone;
- asthmamedicine, theophylline, salmeterol;
- atovaquone, amedicineused totreatacertaintypeofpneumoniaand malaria;
- buprenorphine,amedicineusedforthetreatmentofchronicpain;
- bupropion,amedicineusedto help you stop smoking;
- epilepsymedicines(e.g. carbamazepine, divalproex,lamotrigine, phenytoin);
- heartmedicines(e.g. digoxin, disopyramide, mexiletineand calciumchannelantagonistssuch as amlodipine, diltiazemand nifedipine);
- immunesystem(e.g. cyclosporine, tacrolimus, everolimus);
- morphineand morphine-likemedicinesused to treatseverepain (e.g. methadone,fentanyl);
- sleepingpills(e.g. alprazolam,zolpidem)andalso midazolamadministered byinjection;
- tranquillisers(e.g. haloperidol, risperidone, thioridazine);
- colchicine,atreatment forgout

Therearesomemedicinesyou cannottakeatallwith[Product name].Thesearelistedearlierin section 2 under‘Do nottake[Product name]’.

[Product name]withfood and drink

[Product name] 100 mgfilm-coatedtabletsshould betaken withfood.

Pregnancyand breast-feeding

Ifyouthinkyou arepregnantoryou areplanningto becomepregnant,itisveryimportant that you discussthiswith yourdoctor.

Thereisverylittleinformation ontheuseofritonavir(theactive ingredient in[Product name])during pregnancy. Ingeneral,thepregnantmothersreceived ritonavirafter thefirstthreemonthsof pregnancyata lowerdose(booster)alongwith otherproteaseinhibitors. [Product name]did notappear to increasethechanceofdevelopingbirth defectscompared tothegeneralpopulation.

It isnotknown if[Product name]passesintobreastmilk. Toavoid transmittingthe infection, motherswith HIVshould notbreastfeedtheirbabies.

Driving and usingmachines

[Product name]can causesleepinessand dizziness. Ifyou areaffecteddo notdriveorusemachinery.

[Product name]containssodium
Thismedicinecontains 0.362mgsodiumper tablet.To betaken into consideration bypatientson a controlledsodiumdiet.

3. Howtotake[Product name]

Always take thismedicineexactlyasyourdoctorhas told you. You should checkwith yourdoctor orpharmacistifyou arenotsure.It is taken bymouth usuallytwo timeseveryday. [Product name]film-coatedtabletsshould betaken with food as thiscanaffect thewayin which [Product name]isabsorbed into yourbody.

Itisimportantthat[Product name]tabletsare swallowedwholeand notchewed, broken orcrushed.

Recommended dosesof[Product name]are:

- if[Product name]isused to boosttheeffectsofcertainotheranti-HIVmedicinesthe typicaldose for adultsis1to 2tabletsonceor twicedaily. For more detailed dose recommendations, including those for children, see the Package Leaflet of the anti-HIV medicines [Product name] is given in combination with.

- ifyourdoctorprescribesafulldose,adultsmaybestarted on adoseof3tabletsinthemorningand 3 tablets12 hourslater, graduallyincreasingoveraperiodofupto 14 days tothe fulldoseof6 tabletstwicedaily(totaling1,200 mgperday). Children(2 – 12 yearsofage)willstartwith adosesmaller thanthisandcontinueupto themaximumallowed for theirsize.

Yourdoctor willadviseyou on thedosage to be taken.

Likeallanti-HIVmedicines, [Product name]should betaken everydayto helpcontrolyour HIV, no matter howmuch betteryou feel. Ifasideeffectispreventing you fromtaking[Product name] asdirected,tellyour doctorstraightaway. Duringepisodesofdiarrhoeayourdoctormaydecidethatextramonitoringis needed.

Alwayskeep enough [Product name]on handso you don't run out. When you travelorneed tostay in thehospital, makesureyou haveenough [Product name]to lastuntilyou can getanewsupply.

Ifyoutakemore[Product name] than youshould

Numbness, tingling, ora“pinsand needles”sensationmayoccurifyou take toomuch [Product name]. If you realiseyou havetakenmore [Product name]than you weresupposedto, contactyourdoctororthe Accidentand EmergencyDepartmentofyournearesthospitalstraightaway.

Ifyouforgetto take[Product name]

Ifyoumissadose,take the missed doseassoon aspossible. If itisnearlytime forthenextdose,just take thatone. Do nottakeadoubledose to makeup fora forgottendose.

Ifyoustoptaking[Product name]

Even ifyou feelbetter,donotstoptaking[Product name]withouttalkingto yourdoctor.Taking[Product name] as recommended should giveyou thebestchanceofdelayingresistanceto themedicines.

4. Possibleside effects

Likeallmedicines,thismedicine can causesideeffects, although noteverybodygetsthem.Also,thesideeffectsofritonavirwhen used withotherantiretroviralmedicinesaredependenton the othermedicines. Soit isimportantthatyou carefullyread thesideeffectssection of the leafletsthat areprovided withtheseothermedicines.

The frequency of possible side effects listed below is defined using the following convention:

very common	affects more than 1 user in 10
common	affects 1 to 10 users in 100
uncommon	affects 1 to 10 users in 1,000
rare	affects 1 to 10 users in 10,000
very rare	affects less than 1 user in 10,000
not known	frequency cannot be estimated from the available data.

Very common side effects:

- upperandlowerstomach ache
- vomiting
- diarrhoea(maybesevere)
- feelingsick(nausea)
- flushing, feelinghot
- headache
- dizziness
- paininthethroat
- cough
- upsetstomach orindigestion
- a tinglingsensation ornumbnessinthehands,feetoraroundthelipsand mouth
- feelingweak/tired
- badtaste inthemouth
- damage to thenerves thatcan causeweaknessandpain
- itching
- rash
- jointpainand backpain

Commonside effects

- allergicreactionsincludingskin rashes(maybe red, raised, itchy),severeswellingof theskin and othertissues
- changesin fatdistribution (see**Sideeffectsassociatedwith combination antiretroviral therapy**below)
- increasein cholesterol
- inabilitytosleep (insomnia)

- increasein triglycerides
- anxiety
- gout
- stomach bleeding
- inflammation of the liver and yellowing of the skin or whites of the eyes
- increasein urination
- reduced kidneyfunction
- seizures(fits)
- lowlevelsofblood platelets
- thirst (dehydration)
- abnormallyheavyperiods
- wind (flatulence)
- lossofappetite
- mouth ulcer
- muscleaches(pain),tendernessorweakness
- fever
- weight loss
- laboratorytestresults:changes in blood test results(such asbloodchemistryandbloodcount)
- confusion
- difficultypayingattention
- fainting
- blurred vision
- swellingofthehandsand feet
- high bloodpressure
- lowblood pressureandfeelingfaintwhen gettingup
- coldnessinthehandsand feet
- acne

Uncommonside effects
- heartattack
- diabetes
- kidneyfailure

Rareside effects
- severe or life threatening skin reaction including blisters (Stevens Johnson syndrome, toxic epidermal necrolysis)
- serious allergic reaction (anaphylaxis)
- highlevels ofsugar in the blood

Tell your doctor if you feel sick (nauseous), are vomiting, or have stomach pain, because these may be signs of an inflamed pancreas. Also tell your doctor if you experience joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty moving, as this may be a sign of osteonecrosis. See also section 2 **Before you take [Product name].**

Sideeffectsassociatedwith combination antiretroviraltherapy maycausechanges in bodyshape due tochangesinfatdistribution.Thesemayincludelossoffatfromlegs, armsand face, increased fat in theabdomen (belly)andinternalorgans, breastenlargementand fattylumpson thebackoftheneck (“buffalo hump”).Thecauseandlong-termhealth effectsoftheseconditionsarenotknown.

Combinationantiretroviraltherapymayalso causeraised lacticacidandsugar intheblood, increased fats intheblood andresistanceto insulin(insulin willnotworkaseffectively).

In patientswith haemophilia typeAand B,therehavebeenreportsofincreased bleedingwhiletaking thistreatmentoranotherproteaseinhibitor. Should thishappen to you, seekimmediateadvicefrom yourdoctor.

Casesofdiabetesmellitus or increasedblood sugarshavebeen reported in patients receiving[Product name]r orotherprotease inhibitors.

Abnormal liverfunctiontests, hepatitis(inflammationof theliver),andrarelyjaundice, havebeen reported inpatientstaking[Product name]. Somepeoplehadotherillnessesorweretakingothermedicines. Peoplewith liverdiseaseorhepatitismayhaveworseningof liverdisease.

Therehavebeenreportsofmusclepain, tendernessor weakness, particularlywhen takingmedicines to lowercholesterolin combination with antiretroviraltherapy, includingproteaseinhibitorsand nucleosideanalogues. On rareoccasionsthesemuscledisordershavebeen serious(rhabdomyolysis). In theeventofunexplainedorcontinualmusclepain,tenderness, weaknessor cramps, stop takingthe medicine, contactyourdoctorassoonaspossibleorgoto theAccidentand EmergencyDepartmentof yournearesthospital.

Inform your doctor as soon as possible if you experience any symptoms that suggest an allergic reaction after taking [Product name] such as rash, hives or breathing difficulties.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, contact your doctor, pharmacist, Accident and Emergency department or if it is urgent get immediate medical help.

Reporting of side effects

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

5. Howtostore[Product name]

Keep outofthesightand reach ofchildren.

Do notusethismedicineaftertheexpirydateonthelabel.Theexpirydaterefersto thelastdayof that month.

This medicinal product does not require any special storage conditions.

Do notthrowawayany medicinesviawastewaterorhousehold waste. Ask yourpharmacisthow to throwawaymedicinesyouno longeruse.Thesemeasureswillhelp protecttheenvironment.

6. Contentsof thepack andotherinformation

What[Product name]contains

- Theactivesubstanceisritonavir. Each film-coatedtabletcontains100 mgritonavir.

- Theothertablet ingredientsare:copovidone,sorbitanlaurate (E493), silica colloidal anhydrous (E551), Calcium Hydrogen Phosphate anhydrous, sodium stearylfumarate.

- Thetabletcoatingiscomposed of:hypromellose (E464),titaniumdioxide(E171), macrogol(E1521), hydroxypropylcellulose (E463),talc (E553b),silicacolloidalanhydrous (E551), polysorbate80 (E433).

What[Product name] looks likeand contents of thepack

[Product name]100 mg tablets are white to off white, capsule shaped, film-coated tablets debossed with 'H' on one side and 'R9' on other side.

[Product name] 100 mg film-coated tablets are available in white HDPE bottles with child resistant polypropylene caps of30 and 120 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

<{Name of the Member State}><{Name of the medicinal product}>
<{Name of the Member State}><{Name of the medicinal product}>

This leaflet was last revised in <{month YYYY}>.

[To be completed nationally]

Annex 3 - Worldwide marketing authorisation by country (including EEA)

A3.1 Licensing status in the EEA

Country	Current Licence status	Date of licence action	Date first marketed in country	Trade name	Comment
No authorisation					

A3.2 Licensing status in the rest of the world

Country	Current Licence status	Date of licence action	Date first marketed in country	Trade name	Comment
No authorisation					

Annex 4 - Synopsis of on-going and completed clinical trial programme

None

Annex 5 - Synopsis of on-going and completed pharmacoepidemiological study programme

None

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

Annex 7 - Specific adverse event follow-up forms

None

Annex 8 - Protocols for proposed and on-going studies in RMP part IV

None

Annex 9 - Newly available study reports for RMP parts III & IV

None

Annex 10 - Details of proposed additional risk minimisation measures (if applicable)

None

Annex 11 - Mock-up of proposed additional risk minimisation measures (if applicable)

None

Annex 12 - Other supporting data (including referenced material)

References:

1. Accord SmPC of Ritonavir 100 mg film coated tablets
2. WHO Public Assessment Report (WHOPAR) of Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets dated January 2013.
3. Pharmacovigilance Risk Assessment Committee (PRAC), Minutes of the 8-11 July 2013 meeting dated 05 September 2013
4. Morison L. The global epidemiology of HIV/AIDS. Br Med Bull. 2001;58:7-18..