Core Risk Management Plan for Norvir® (Ritonavir)

AbbVie Inc. (AbbVie)

RMP version to be assessed as part of this application:

RMP Version Number: 8.2

Data lock point for this RMP: 30 November 2024

Date of final sign off: November 2025

Rationale for submitting an updated RMP:

The RMP was revised to update Part I: Product(s) Overview section to align with the approved Summary of Product Characteristics (Section 4.2 Posology and method of administration) following the conclusion of procedure EMA/VR/0000249795. This includes removing Amprenavir and Saquinavir (no longer marketed in EU) and adding back tipranavir and removing the phrases *"Ritonavir is no longer recommended in clinical practice at the antiretroviral dose of 1200 mg (600 mg twice daily). Ritonavir's use as a pharmacokinetic enhancer of other protease inhibitors is the prevalent use in clinical practice. Ritonavir's Product Information has been updated to reflect its common use as a pharmacokinetic enhancer of concomitantly administered antiviral agents. Previous information that was generated when used as an antiretroviral agent is retained as this is still considered clinically relevant."*

Summary of significant changes in the RMP: A summary of significant changes is provided in RMP Annex 8.

Administrative Information on the RMP

Part Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
Part 1: Product(s) Overview	November 2025	8.2
Part II: Safety Specification		
SI – Epidemiology of the Indication(s) and Target Population(s)	November 2025	8.2
SII – Non-Clinical Part of the Safety Specification	February 2021	7.1
SIII – Clinical Trial Exposure	February 2021	7.1
SIV – Populations Not Studied in Clinical Trials	January 2025	8.0
SV – Post-Authorization Experience	January 2025	8.0
SVI – Additional European Union (EU) Requirements for the Safety Specification	January 2025	8.0
SVII – Identified and Potential Risks	January 2025	8.0
SVIII – Summary of the Safety Concerns	June 2021	7.2
Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)	June 2021	7.2
Part IV: Plan for Post-Authorization Efficacy Studies	Not applicable	Not applicable
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	January 2025	8.0
Part VI: Summary of the Risk Management Plan	January 2025	8.0
Part VII: Annexes		
Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	Not applicable	Not applicable
Annex 3 – Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	Not applicable	Not applicable
Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms	Not applicable	Not applicable
Annex 5 – Protocols for Proposed and Ongoing Studies in RMP Part IV	Not applicable	Not applicable
Annex 6 – Details of Proposed Additional Risk Minimization Activities (If Applicable)	Not applicable	Not applicable

Part	Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
	Annex 7 – Other Supporting Data (Including Referenced Material)	November 2025	8.2
	Annex 8 – Summary of Changes to the Risk Management Plan Over Time	November 2025	8.2

Other RMP versions under evaluation: None

RMP Version Number: Not Applicable

Submitted on: Not Applicable

Procedure number: Not Applicable

Details of the currently approved RMP:

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QPPV representative: Sina Schader

Qualified person responsible for pharmacovigilance (QPPV) oversight declaration:
The content of the RMP has been reviewed and approved by the marketing authorization holder QPPV through an electronic document system per company standard operating procedure.

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List of Abbreviations

AbbVie	AbbVie Inc.
ADD	average daily dose
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
ATV	atazanavir
AV	atrioventricular
BID	twice daily
cART	combination antiretroviral therapy
CHER	Children with HIV Early Antiretroviral Therapy
CI	confidence interval
CYP	cytochrome P450
CYP3A	cytochrome P450 3A isoform subfamily
D:A:D	Data Collection on Adverse Events of Anti-HIV Drugs
DDI	drug-drug interaction
EACS	European AIDS Clinical Society
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiography
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESRD	end-stage renal disease
EU	European Union
FI	fusion inhibitors
GGT	gamma-glutamyl transferase
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCP	health care professional

HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
IBD	international birth date
INN	international nonproprietary name
IRIS	immune reconstitution inflammatory syndrome
IVDU	intravenous drug user(s)
LPV	lopinavir
LPV/r	lopinavir/ritonavir
LRx	IMS® LRx Germany (database)
MAH	marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MM	million
MSM	men who have sex with men
MTCT	mother-to-child transmission
NIH	National Institutes of Health
NNTA	*N*-nitroso-2,4-thiazole amine
NRTI	nucleos(t)ide reverse transcriptase inhibitor
PACTG	Paediatric AIDS Clinical Trials Group
PENTA	Paediatric European Network for Treatment of AIDS
PI	protease inhibitor
PK	pharmacokinetic(s)
PL	package leaflet
PSUR	periodic safety update report
PTD	patient treatment day
PTY	patient treatment years
PV	pharmacovigilance
PY	person year(s)
QD	once daily
QPPV	qualified person responsible for pharmacovigilance
QTc	QT interval corrected for heart rate
RMP	risk management plan
RNA	ribonucleic acid
SmPC	Summary of Product Characteristics

SQV	saquinavir
TSH	thyroid-stimulating hormone
UK	United Kingdom
US	United States

Part I: Product(s) Overview

Table 1. Product Overview

Active substance(s) (INN or common name)	Ritonavir
Pharmacotherapeutic group(s) (ATC Code)	Protease inhibitor (PI) (J05AE03)
Marketing Authorization	AbbVie Deutschland GmbH & Co. KG
Medicinal products to which this RMP refers	1 (2 pharmaceutical forms); Powder for oral suspension Film-coated tablet
Invented name(s) in the European Economic Area (EEA)	Norvir
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Protease inhibitor (PI) Ritonavir is a peptidomimetic inhibitor of human immunodeficiency virus (HIV), type 1 (HIV-1) and type 2 (HIV-2) proteases and has been approved for use in numerous countries globally.
	Summary of mode of action: Inhibition of HIV protease prevents cleavage of the *gag-pol* polyprotein, resulting in the production of immature, noninfectious virus.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	SmPC
Indication(s) in the EEA	Current (if applicable): Ritonavir is indicated as a pharmacokinetic enhancer of co-administered protease inhibitors as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected patients (adults and children of 2 years of age and older).
	Proposed (if applicable): N/A

Dosage in the EEA	Current (if applicable): *Ritonavir dosed as a pharmacokinetic enhancer* When ritonavir is used as a pharmacokinetic enhancer with other protease inhibitors, the Summary of Product Characteristics (SmPC) for the particular protease inhibitor should be consulted. The following HIV-1 protease inhibitors have been approved for use with ritonavir as a pharmacokinetic enhancer at the noted doses. *Adults* 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. 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. Refer to the darunavir SmPC for further information on once daily dosing in ART experienced patients. Darunavir 800 mg once daily with ritonavir 100 mg once daily in ART-naïve patients. *Children and adolescents* Ritonavir is recommended for children 2 years of age and older. For further dosage recommendations, refer to the SmPC of other protease inhibitors approved for co-administration with ritonavir.

	Proposed (if applicable): <u>Posology</u> Ritonavir should be prescribed by physicians who are experienced in the treatment of HIV infection. When ritonavir is used as a pharmacokinetic enhancer with other protease inhibitors, the Summary of Product Characteristics (SmPC) for the particular protease inhibitor should be consulted. The following HIV-1 protease inhibitors have been approved for use with ritonavir as a pharmacokinetic enhancer at the noted doses. *Adults* 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. Tipranavir 500 mg BID with ritonavir 200 mg BID. Tipranavir with ritonavir should not be used in treatment naïve 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. Refer to the darunavir SmPC for further information on once daily dosing in ART experienced patients. Darunavir 800 mg once daily with ritonavir 100 mg once daily in ART-naïve patients. *Children and adolescents* Ritonavir is recommended for children 2 years of age and older. For further dosage recommendations, refer to the SmPC of other protease inhibitors approved for co-administration with ritonavir.
Pharmaceutical form(s) and strengths	Current (if applicable): Each tablet contains 100 mg of ritonavir. Each sachet of the commercial container closure configuration for powder for oral suspension contains a single unit dose of 100 mg of ritonavir.
	Proposed (if applicable): Not applicable

Is/will the product be subject to additional monitoring in the EU?	No

ART = antiretroviral therapy; ARV = Antiretroviral; ATC = anatomical therapeutic chemical; BID = twice daily; EEA = European Economic Area; EU = European Union; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; HIV-2 = human immunodeficiency virus type 2; INN = International Nonproprietary Name; PI = protease inhibitor; QD = once daily; RMP = risk management plan; SmPC = Summary of Product Characteristics

Part II: Safety Specification

Module SI Epidemiology of the Indication(s) and Target Population(s)

Indication:

Ritonavir is indicated as a pharmacokinetic (PK) enhancer of co-administered protease inhibitors as part of antiretroviral combination therapy in human immunodeficiency virus type 1 (HIV-1) infected adults and children older than 2 years of age (United States [US] > 1 month).

The incidence of human immunodeficiency virus (HIV) infections is decreasing globally due to HIV prevention and treatment programs, with an estimated 1.3 million (MM) (95% confidence interval [CI]: 1.0 MM – 1.7 MM) new cases globally in 2023, of which 56,000 were among adults and children across Western and Central Europe and North America (UNAIDS 2024). Across the European Union and European Economic Area (EU/EEA), 24,731 new HIV diagnoses were reported across 30 countries in 2023, a rate of 5.3 per 100,000 (no CI reported). Rates range from a high of 21.0 per 100,000 in Malta to 2.1 per 100,000 in Slovenia and Austria (ECDC 2024).

In 2023, the number of people globally who were living with HIV was estimated as 39.9 MM (95% CI: 36.1 MM – 44.6MM), of whom 38.6 MM (95% CI: 34.9 MM – 43.1 MM) were 15 years of age and older and 1.4 MM (1.1 MM – 1.7 MM) were children younger than 15 years, and 53% of all people living with HIV were women and girls (UNAIDS 2024). Across Western and Central Europe and North America 2.3 MM were living with HIV and acquired immune deficiency syndrome (AIDS) in 2023 (UNAIDS 2024). Specifically, across the EU/EEA, 0.2%, or 810,000 adults and children ≥ 15 years of age were living with HIV in 2015, with an estimated up to 15% of which, based on modeling, were unaware of their HIV infection (Pharris 2016).

Globally, an estimated 630,000 (95% CI: 500,000 – 820,000) AIDS-related deaths occurred in 2023 of which 13,000 were adults and children across Western and Central Europe and North America (UNAIDS 2024).

Within the EU/EEA, more males (17,793) than women (6,688) were diagnosed with new HIV infections in 2023, a male:female ratio of 2.7:1, and the higher incidence of infection among

men was observed across age strata, except among persons younger than 15 years of age (primarily due to mother-to-child transmission [MTCT]). Among transmission groups, men who have sex with men (MSM) constituted 46.7% of new cases, followed by heterosexual contact – 24.8% for women and 21.2% for men, intravenous drug users (IVDU) – 4.1%, and MTCT – 0.9%. By age, the highest rate of new infection occurred in the 25 to 29 year age group for men (19.6 per 100,000 population) and in 30 to 39 year age group for women (7.2 per 100,0000 population). The number of MTCT HIV cases in 2015 was 217 (ECDC 2024).

Risk Factors:

Populations at highest risk of HIV infection (WHO, UNAIDS, and UNICEF [2011])

- Sex workers
- Clients of sex workers
- People who inject drugs
- MSM
- Infants born to HIV-infected mothers

The main treatment options:

The goals of HIV antiretroviral therapy (ART) are to maximally and durably suppress plasma HIV-1 ribonucleic acid (RNA) in order to allow immune system recovery in an overall attempt to prolong the duration and quality of life for persons infected with HIV. Treatment goals in pediatric patients include normal growth and physical, pubertal, neurological, and psychological development and immune reconstitution, while minimizing long-term drug toxicity and viral drug resistance, thus optimizing general health for a full and productive adult life (Paediatric European Network for Treatment of AIDS [PENTA] 2015, European AIDS Clinical Society [EACS] 2016). Combination antiretroviral therapy (cART), consisting of ARV drugs from at least 2 different classes, is typically required to achieve these therapeutic goals. To date, a multitude of anti-HIV medicines have been centrally authorized in the EU representing 6 different mechanisms of action including nucleoside or nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), PIs with or without ritonavir as a PK enhancer, fusion inhibitors (FI), chemokine receptor (CCR5) antagonists, and integrase strand transfer inhibitors.

Important co-morbidities: Liver disease including hepatitis B and C, cardiovascular disease, kidney disease, diabetes, osteoporosis, malignancies, and use of potentially interacting drugs, especially those medicinal products that are highly dependent on cytochrome P450 3A isoform subfamily (CYP3A) for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.

Module SII Non-Clinical Part of the Safety Specification

Key Safety Findings (from Non-Clinical Studies)	**Relevance to Human Usage**
Toxicity	
<u>Single and repeat dose toxicity:</u> • Not acutely toxic. Primary target organs in animals are liver, kidney, eye (retina), stomach (pyloric necrosis and gastritis), thyroid gland, and blood (erythrocytes). Findings observed only in rats: • Hepatic changes involved hepatocellular, biliary, and phagocytic elements and were accompanied by increases in hepatic enzymes (below). • Hyperplasia of the retinal pigment epithelium (RPE) and retinal degeneration observed in rodents but not in dogs. Ultrastructural evidence suggests retinal changes may be secondary to phospholipidosis. Renal changes including tubular degeneration, chronic inflammation, and proteinuria were noted in rats and considered species-specific spontaneous disease. Changes in the thyroid gland included hypertrophy of follicular cells, decreased serum thyroxine (T4), and/or increased serum thyroid-stimulating hormone (TSH) levels. All thyroid changes were reversible upon discontinuation of ritonavir. Stomach findings include pyloric necrosis and gastritis. Blood findings include decreases in erythrocyte number with increased variability in size (anisocytosis) and shape (poikilocytosis).	Retinal changes (hypertrophy of RPE) secondary to phospholipidosis are considered to have low probability for translation to humans; clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. Stomach findings were not consistently observed across all oral routes of administration, were observed in a limited number of studies, and are considered not relevant for humans. Decreases in erythrocyte number associated with increased variability in size (anisocytosis) and shape (poikilocytosis) are considered not relevant to humans due to presence in single species (rat but not mouse or dog); observations in clinical trials have not identified similar changes in humans. No clinically significant renal abnormalities were noted in clinical trials. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests.

Key Safety Findings (from Non-Clinical Studies)	**Relevance to Human Usage**
Reproductive toxicity: No evidence for impairment of male or female fertility.	No issues for humans.
Developmental toxicity: Fetal abnormalities observed in rats include embryolethality, reduced weight, delayed skeletal ossification, and visceral changes (including delayed testicular descent) in association with maternal toxicity. Developmental toxicity in rabbits (embryolethality, decreased litter size, and decreased foetal weights) in association with maternal toxicity. No malformations observed.	Not relevant to humans as findings associated with a degree of maternal toxicity that is unlikely to occur in humans. Antiretroviral Pregnancy Registry (APR) has not identified an association of ritonavir with birth defects. In the SmPC section 4.6, pregnancy statement noted "Norvir can be used during pregnancy if clinically needed."
Nephrotoxicity: Renal tubular degeneration observed in rats and considered an exacerbation of rat specific chronic progressive nephropathy.	No relevance to human, as renal clearance of ritonavir is negligible. Per SmPC information, Norvir is used with caution in patients with renal insufficiency depending on the type of the coadministered protease inhibitor.
Hepatotoxicity: Elevated liver enzyme activities ALT, AST, GGT, and histopathologic lesions on hepatocytes, bile duct, and Kupffer cells. Rats more sensitive than dogs with some differences in presentation. Hepatocellular phospholipidosis is potential underlying mechanism.	Findings of this nature have similar manifestations in humans and are amenable to monitoring through evaluation of liver enzymes. Human studies with ritonavir have indicated a reduced sensitivity versus animals.
Genotoxicity: No mutagenicity or clastogenicity observed in in vitro assays: 1) bacterial reverse mutation (Ames) using *S. typhimurium* and *E. coli*, 2) mouse lymphoma, and 3) chromosomal aberration in human lymphocytes or in vivo (mouse micronucleus test).	No issues for humans.
Carcinogenicity: Increased incidence of liver neoplasms in male mice. No increased tumor response in rats.	Hepatocellular adenomas in mice were likely related to mitogenic stimulation in conjunction with hepatocellular toxicity. A tumor response of this nature is associated with nongenotoxic compounds and is considered to have little relevance for humans.

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Usage
General Safety Pharmacology	
Cardiovascular: No meaningful changes in CV assays.	No issues for humans.
Nervous system: Minimal potential for stimulant or depressant activity, effects on muscle, sedative-hypnotic potentiation, or body temperature.	No issues for humans.
Mechanisms for drug interactions: Ritonavir is a potent inhibitor of CYP3A- and CYP2D6-mediated biotransformation.	SmPC section 4.3 Contraindications provides a list of medicines that are contraindicated with ritonavir due to drug-drug interactions (DDI).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; SmPC = Summary of Product Characteristics; TSH = thyroid-stimulating hormone

Non-Clinical Safety Findings that are Included as Safety Concerns

The nonclinical safety considerations for ritonavir tablets are characterized and are found to be consistent with the currently approved ritonavir formulations.

Safety Concerns	
Important identified risks	Not applicable
Important potential risks	Not applicable
Missing information	Not applicable

Module SIII Clinical Trial Exposure

Patient exposure during AbbVie ritonavir clinical trials as of 31 August 2019 is provided in Table 2 through Table 6. Phase 2 to 4 trials conducted in adults were to include persons ≥ 18 years of age; trials conducted in pediatric patients were to include persons < 18 years of age.

In addition to the exposure data from AbbVie-conducted clinical trials, 2 Paediatric AIDS Clinical Trials Group (PACTG) studies (Studies PACTG 345 and PACTG 366) were also included in the following exposure tables because the data from these 2 studies were submitted in support of the paediatric indication.

Table 2. Duration of Exposure

Adults Exposed in Phase 1 Studies

	Persons (n)		
Population	**Female**	**Male**	**Total**
Healthy Volunteers	484	1024	1508
HIV-1 Infected	5	137	142
Overall	**489**	**1161**	**1650**

HIV = human immunodeficiency virus

Duration of Exposure in Adult Phase 2 to 4 Studies

Duration of Exposure (months)	Persons (n)[a]	Person Time (years)
≤ 1	253	--
> 1 to ≤ 3	280	--
> 3 to ≤ 6	344	--
> 6 to ≤ 12	383	--
> 12 to ≤ 24	537	--
> 24	312	--
Overall	**2109**	**2197.53**

Duration of Exposure in Paediatric Phase 2 to 4 Studies

Duration of Exposure (months)	Persons (n)[b]	Person Time (years)
≤ 1	25	--
> 1 to ≤ 3	10	--
> 3 to ≤ 6	23	--
> 6 to ≤ 12	56	--
> 12 to ≤ 24	125	--
> 24	18	--
Overall	**257**	**325.05**

a. Excludes 20 persons with missing start or end dates for ritonavir. Includes a Phase 4 study (Study M99-047) that only collected serious adverse events (SAEs).

b. Excludes 8 persons with missing start or end dates for ritonavir. Includes persons from non-AbbVie conducted studies (Studies PACTG 345 and PACTG 366).

Table 3. Exposure by Age Group and Gender

Exposure in Adult Phase 2 to 4 Studies by Age Group and Gender

Age Group (years)	Persons (n)[a]			Person Time (years)		
	Female	Male	Total[b]	Female	Male	Total
18 to < 25	1	24	25	--	--	--
25 to < 35	75	536	611	--	--	--
35 to < 45	73	887	960	--	--	--
45 to < 55	17	402	419	--	--	--
55 to < 65	7	72	79	--	--	--
65 to < 75	5	9	14	--	--	--
Overall[c]	**178**	**1930**	**2109**	**204.41**	**1993.03**	**2197.53**

Exposure in Paediatric Phase 2 to 4 Studies by Age Group and Gender

	Persons (n)[d]			Person Time (years)		
Age Group	Female	Male	Total	Female	Male	Total
< 28 days	0	0	0	--	--	--
28 days to < 24 months	32	30	62	--	--	--
24 months to < 12 years	71	84	155	--	--	--
12 to < 18 years	13	26	39	--	--	--
≥ 18 years[e]	1	0	1	--	--	--
Overall	**117**	**140**	**257**	**147.17**	**177.88**	**325.05**

a. Excludes 20 persons with missing start or end dates for ritonavir. Includes a Phase 4 study (Study M99-047) that only collected serious adverse events (SAEs). Age and gender data not reported for 1 person.

b. Total includes those with missing gender data.

c. Overall includes those with missing age data.

d. Excludes 8 persons with missing start or end dates for ritonavir. Includes persons from non–AbbVie-conducted studies (Studies PACTG 345 and PACTG 366).

e. Maximum age reported was 21 years.

Table 4. Exposure by Study Type and Protease Inhibitor Usage

	Persons (n)		Person Time (years)	
Study Type	**Mono**	**Dual/ PK enhancer**	**Mono**	**Dual/ PK enhancer**
Adult Phase 2 to 4 Studies[a]	1548	561	1562.64	634.89
Paediatric Phase 2 to 4 Studies[b]	184	73	227.54	97.50

Mono = ritonavir used as a single PI; Dual/PK enhancer = ritonavir used in combination with another PI (indinavir, SQV); PI = protease inhibitor; PK = pharmacokinetic

a. Excludes 20 persons with missing start or end dates for ritonavir. Includes a Phase 4 study (Study M99-047) that only collected SAEs.

b. Excludes 8 persons with missing start or end dates for ritonavir. Includes persons from non-AbbVie conducted studies (Studies PACTG 345 and PACTG 366).

Table 5. Exposure by Ethnic Origin

Exposure by Study Type and Race

	Persons (n)			Person Time (years)		
Study Type	**White**	**Black**	**Other**	**White**	**Black**	**Other**
Adult Phase 2 to 4 Studies[a]	1738	169	202	1869.31	152.12	176.09
Paediatric Phase 2 to 4 Studies[b]	44	152	61	57.69	198.34	69.01

Exposure by Study Type and Ethnicity

	Persons (n)		Person Time (years)	
Study Type	**Hispanic**	**Not Hispanic**	**Hispanic**	**Not Hispanic**
Adult Phase 2 to 4 Studies[a]	161	1948	137.72	2059.81
Paediatric Phase 2 to 4 Studies[b]	56	201	62.55	262.50

a. Excludes 20 persons with missing start or end dates for ritonavir. Includes a Phase 4 study (Study M99-047) that only collected serious adverse events (SAEs).

b. Excludes 8 persons with missing start or end dates for ritonavir. Includes persons from non–AbbVie-conducted studies (Studies PACTG 345 and PACTG 366).

Table 6. Exposure for Special Populations

Special Population	Persons (n)
Mild or Moderate Hepatic Impairment[a]	28
Pregnant Women	88[b]

a. Mild or moderate hepatic impairment defined as Child-Pugh Class A or B. Studies were Phase 1 studies conducted in adults (Studies M01-328 and M96-604).

b. Study W96-221 was a non-AbbVie study (and is not included in the previous exposure tables above) that evaluated the safety, tolerability, and efficacy of a 4-week course of ritonavir (300 mg up to 600 mg BID) from Week 36 of pregnancy through delivery.

Module SIV Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Clinical Development Program

Criterion 1: Significant hepatic impairment
Reason for exclusion: Significant hepatic impairment identified by abnormal values of ALT, AST, or ALP > 3.0 × upper limit of normal (ULN) laboratory range or bilirubin above ULN laboratory range.
Is it considered to be included as missing information?: No
Rationale: Current product labeling indicates that ritonavir should not be given as a PK enhancer to subjects with severe hepatic impairment and should not be given to those with decompensated liver disease either as a PK enhancer or an ARV agent.

Criterion 2: Co-administration of medications metabolised by CYP3A
Reason for exclusion: Clinically important drug-drug interactions through CYP3A can result in serious and important adverse outcomes.
Is it considered to be included as missing information?: No
Rationale: Current product labeling indicates that ritonavir should not be coadministered/is contraindicated with certain medicinal products that are highly dependent on CYP3A and/or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Specific recommendations for individual drugs are provided in the SmPC in section 4.3, section 4.4, and section 4.5.

Criterion 3: Significant renal impairment
Reason for exclusion: Significant renal impairment identified by abnormal value of serum creatinine > 1.5 × ULN laboratory range. Limited experience and ritonavir not studied in patients with renal impairment and consideration of potential toxicity from other ARV drugs used concomitantly with ritonavir.
Is it considered to be included as missing information?: No
Rationale: As stated in product labeling, renal clearance is negligible; therefore, a decrease in the total body clearance is not expected in patients with renal impairment.

Criterion 4: Pregnant or lactating women
Reason for exclusion: Limited data in this population and reproductive toxicity from animal data.
Is it considered to be included as missing information?: No
Rationale: APR results through 31 July 2018 demonstrate no increase in the rate of birth defects compared to rates observed in population-based birth defect surveillance systems. Sufficient numbers of first trimester exposures to ritonavir have been monitored to detect at least a 1.5-fold increase in risk of birth defects overall or a 2-fold increase in risk of birth defects in the more common classes, CV and genitourinary systems; no such increases have been detected to date. In summary, the APR results demonstrated that the prevalence of birth defects in ritonavir exposed pregnancies is not significantly different than the prevalence of birth defects in the general population. In conclusion, no signal of teratogenicity is identified from the use of ritonavir during pregnancy (Antiretroviral Pregnancy Registry [APR] Steering Committee 2018). Product labeling contains language regarding limited data, hence consideration for use only when the benefits outweigh the risk to the fetus.

Criterion 5: Paediatric population
Reason for exclusion: Ritonavir not initially studied in this population.
Is it considered to be included as missing information?: No
Rationale: Clinical studies conducted in pediatric population post-initial authorization; however, the data is limited for children less than 2 years of age, and in EU, the drug is not to be used for children less than 2 years of age. For ritonavir used as a pharmacokinetic enhancer, the SmPC also refers the prescriber to the SmPC of the co-administered protease inhibitor for additional clinical trial information.

SIV.2 Limitations to Detect Adverse Reactions in the Clinical Development Program

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged use.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Development Program

Table 7. Exposure of Special Populations Included or Not in the Clinical Development Program

Type of special population	Exposure	Implications
Children	For ritonavir used as a pharmacokinetic enhancer, the SmPC refers the prescriber to the SmPC of the co-administered protease inhibitor for additional clinical trial information. Limited data are available from clinical trials on the use of ritonavir in pediatric subjects less than 2 years of age. Ritonavir is not indicated for subjects < 2 years of age in the EU. However, in the US, the use of ritonavir as an ARV treatment agent is approved for children > 1 month of age based on Studies PACTG 345 and PACTG 366, which were used as supporting information for US Supplement 34. AbbVie Study M98-940 evaluated 100 HIV-1–infected children from 6 months to 12 years of age at 2 lopinavir/ritonavir (LPV/r) dose levels (230/57.5 mg/m^2 and 300/75 mg/m^2). The Children with HIV Early Antiretroviral Therapy (CHER) study was a Phase 3, randomized clinical trial in 411 HIV-1–infected infants 6 to 12 weeks of age to evaluate whether early ARV therapy given over a limited period of time in children infected with HIV-1 would delay disease	In AbbVie Study M98-940, the treatment-naïve subjects were coadministered lamivudine and stavudine, whereas treatment-experienced subjects were coadministered nevirapine and 1 or 2 NRTIs chosen at the investigator's discretion. The most commonly reported adverse events were related to infections and to the digestive system. The majority of adverse events were reported as mild and probably not related to study drug. PACTG Study P1030 was a prospective, Phase 1/2, open-label, multicenter trial of LPV/r-based combination ARV therapy that included 31 subjects younger than 6 months of age infected with HIV-1 to evaluate LPV/r dose requirements in this age group. The AUC_{0-12} in older infants was higher compared to younger infants (by 72%). Infants younger than 6 months of age generally had lower lopinavir AUC_{0-12} than older children between 6 months to 12 years of age (in Study M98-940). Seven subjects in Study P1030 had adverse events that were considered possibly related to study treatment, while no adverse events were considered definitely related to study treatment. The Children with HIV Early Antiretroviral Therapy (CHER) study was conducted by the National Institute of Allergy and Infectious Diseases, part of the US National Institutes of Health (NIH). The safety results reported in the HIV-infected population of 14 days to less than 6 months of age treated with LPV/r in the P1030 and CHER studies are consistent with results observed in the older pediatric population (≤ 12 years of age) as reported in the pediatric registration trial,

Type of special population	Exposure	Implications
	progression compared to those treated when the immune system begins to decline. In the CHER study, LPV/r was used at 2 dosage levels: 300/75 mg/m^2 and 230/57.5 mg/m^2 BID.	Study M98-940. There were no new safety signals identified specific to children in the study population. Ritonavir is not indicated for subjects < 2 years of age in the EU. However, in the US, the use of ritonavir as an ARV treatment agent is approved for children > 1 month of age based on Studies PACTG 345 and PACTG 366, which were used as supporting information for US Supplement 34. This RMP includes information on the potential for underdosing with the powder for oral suspension formulation in children.
Elderly	Of 2,109 adult subjects with age reported in Phase 2 to 4 studies, 14 (0.66%) were ≥ 65 years of age at initiation of ritonavir treatment.	Limited data are available from clinical trials on the use of ritonavir in the elderly population (adult subjects older than 65 years of age). Product labeling does state that ritonavir plasma exposures (100 mg dose) were not different among subjects 50 to 70 years of age compared with younger subjects. SmPC section 4.2 states no dose adjustment is necessary for the elderly. As agreed by the CHMP/PRAC, "Geriatric Population" has been removed as a Missing Information safety concern because no specific safety concerns in the elderly population have emerged in over 2 decades of use.
Pregnant or breastfeeding women	A total of 86 pregnant women were enrolled in Study W96-221, that evaluated the safety, tolerability, and efficacy of a 4-week course of ritonavir (from 300 mg up to 600 mg BID), from Week 36 of pregnancy through delivery. According to the APR (APR Steering Committee 2018), prospective exposure data for ritonavir are as follows: • First trimester: 3,209 • Second/third trimester: 3,433	Although limited data for ritonavir in pregnancy are available from clinical trials, ritonavir is part of the Antiviral Pregnancy Registry (APR). The APR is a prospective, international, voluntary, exposure-driven pregnancy registry designed to monitor for potential increased birth defects following fetal exposure to ARVs. Pregnant women are registered by their caregivers before pregnancy outcome is known. In June 2025, the APR Steering Committee issued an interim cumulative report for the period of 01 January 1989 through 31 January 2025 (APR Steering Committee 2025).

Type of special population	Exposure	Implications
		Analysis of the APR data will be provided with the ritonavir Periodic Safety Update Report (PSUR; letter from EMA dated 20 January 2015 ref: EMA/44374/2015). AbbVie continues to comply with this request with each PSUR for the EU. No signal for birth defects for Norvir has been identified through the registry since inception. Since the initial approval of Norvir, there have been a number of published studies using ritonavir both as an ARV agent and as a PK enhancer (Watts 2006, Giaquinto 2008, Clumeck 2008). Some of these studies have included populations with limited data in the ritonavir clinical development program, such as pregnant women and paediatrics (Watts 2006, Zorrilla 2007).

Type of special population	Exposure	Implications
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment	**Patients with Hepatic Impairment** The use of ritonavir in patients with severe hepatic impairment (Child-Pugh Class C) has not been studied. Ritonavir was studied in 28 patients with mild or moderate hepatic impairment defined as Child-Pugh Class A or B (see Table 6). These studies were Phase 1 studies conducted in adults (Study M01-328 and Study M96-604). **Patients with Renal Impairment** The use of ritonavir in patients with renal impairment has not been formally studied.	**Patients with Hepatic Impairment** The product label indicates that ritonavir should not be used in subjects with severe hepatic impairment. In patients with mild or moderate hepatic impairment, dose-normalized steady-state ritonavir concentrations in subjects with mild hepatic insufficiency (400 mg BID, n = 6) were similar to those in control subjects dosed with 500 mg BID. Dose-normalized steady-state ritonavir exposures in subjects with moderate hepatic impairment (400 mg BID, n = 6) were about 40% lower than those in subjects with normal hepatic function (500 mg BID, n = 6). **Patients with Renal Impairment** Renal impairment is not expected to impact the PK of ritonavir because of its negligible renal clearance. Product labeling indicates no dose adjustment is needed in subjects with renal impairment.

AbbVie = AbbVie Inc.; APR = Antiretroviral Pregnancy Registry; ART = antiretroviral therapy; ARV = Antiretroviral; AUC_{0-12} = area under the concentration-time curve from time 0 to 12 hours; BID = twice daily; CHER = Children with HIV Early Antiretroviral Therapy; CI = confidence interval; EMA = European Medicines Agency; EU = European Union; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; LPV/r = lopinavir/ritonavir; MAH = marketing authorisation holder; NIH = National Institutes of Health; NRTI = Nucleos(t)ide reverse transcriptase inhibitor; PACTG = Paediatric AIDS Clinical Trials Group; PI = protease inhibitor; PK = pharmacokinetic(s); PSUR = periodic safety update report; RMP = risk management plan; SmPC = Summary of Product Characteristics; US = United States

Module SV Post-Authorization Experience

SV.1 Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

Two separate exposure analyses were conducted to estimate usage characteristics and distribution of ritonavir. Methods for the respective exposure estimates are presented below before the data presentation.

SV.1.2 Exposure

Patient Exposure to Norvir (ritonavir) from Marketing Experience – Germany

In response to a request from the European regulators to provide utilization demographics for ritonavir, AbbVie and IQVIA conducted an analysis using real-world data from Germany.

Method

A cross-sectional study was performed using the IQVIA® LRx Germany (LRx) database to identify a sample of patients in Germany with exposure to ritonavir.

Database

The LRx database is composed of redeemed prescriptions from the public health insured patients in Germany. The database covers 60% of all billed statutory health insurance prescriptions, and data are collected from the prescription data processing centers in Germany. These dispensed prescriptions are processed at the individual patient level and across doctors; making it possible to track patients across pharmacies via their health insurance number even if they change practices. Practices covered include outpatient centers and authorized physicians in hospitals; providing access to drugs administered in various settings. Available patient level information include drug prescribed, prescription date, dosage form, strength, package size, number of packages dispensed, physician specialty code, regional code, health insurance number, date of birth, and gender. Data from more than 50 million patients per annum are currently available; per month, data pertaining to 30 million prescriptions are available. Data are updated monthly.

The LRx database has limitations consistent with prescription databases. The database does not contain any diagnosis information; therefore, it is not possible to determine the indication for which a drug was prescribed. This does not affect drugs with a single indication; but, any off-label use is not captured. While demographic characteristics are available in the data, this information is missing for some patients.

Cohort

The study included patients with exposure to ritonavir as identified by the presence of the Anatomic Therapeutic Classification (ATC) code J05AE03 between 01 September 2013 and 31 July 2016 in the LRx Germany database. All patients with a record of any exposure to ritonavir were included in the study sample. Since this is a cross-sectional analysis, no minimum observation period was required for patients before or after exposure.

Analysis

Analysis was performed on the resulting sample cumulatively over the analysis period (01 September 2013 to 31 July 2016) and also by 3 discrete intervals: 01 September 2013 to 31 August 2014, 01 September 2014 to 31 August 2015, and 01 September 2015 to 31 July 2016. Patients with at least 1 prescription for ritonavir in any one 12-month interval were counted in both that 12-month interval and the cumulative period.

Demographic characteristics reported included age and gender and are presented in the following tables. For patients with exposures across multiple 12-month intervals, age was reported as of the last data year within which data for the subject was observed.

Table 8. Estimated Number of Unique Patients Exposed from 01 September 2013 Through 31 July 2016 from LRx

	Cumulative (01 September 2013 to 31 July 2016)	01 September 2013 to 31 August 2014	01 September 2014 to 31 August 2015	01 September 2015 to 31 July 2016
Total	13,069	9,261	8,128	7,109

LRx = IQVIA® LRx Germany (database)

Table 9. Ritonavir Cumulative and Interval Exposure by Patient Age from LRx

	Cumulative (01 September 2013 to 31 July 2016) (N = 13,069)	01 September 2013 to 31 August 2014 (N = 9,261)	01 September 2014 to 31 August 2015 (N = 8,128)	01 September 2015 to 31 July 2016 (N = 7,109)
Age, n (%)				
0 – 1	16 (0.1)	12 (0.1)	3 (0.0)	2 (0.0)
2 – 11	82 (0.6)	50 (0.5)	38 (0.5)	25 (0.4)
12 – 18	75 (0.6)	55 (0.6)	36 (0.4)	22 (0.3)
19 – 64	11,966 (91.6)	8,446 (91.2)	7,530 (92.6)	6,634 (93.3)
65 – 74	651 (5.0)	501 (5.4)	409 (5.0)	341 (4.8)
75 – 84	181 (1.4)	132 (1.4)	78 (1.0)	65 (0.9)
85 +	30 (0.2)	24 (0.3)	12 (0.1)	8 (0.1)
Unknown	68 (0.5)	41 (0.4)	22 (0.3)	12 (0.2)

LRx = IQVIA® LRx Germany (database)

Table 10. Ritonavir Cumulative and Interval Exposure by Patient Gender from LRx

	Cumulative (01 September 2013 to 31 July 2016) (N = 13,069)	01 September 2013 to 31 August 2014 (N = 9,261)	01 September 2014 to 31 August 2015 (N = 8,128)	01 September 2015 to 31 July 2016 (N = 7,109)
Gender, n (%)				
Male	5,135 (39.3)	3,774 (40.8)	3,255 (40.0)	2,833 (39.9)
Female	2,297 (17.60)	1,626 (17.6)	1,454 (17.9)	1,248 (17.6)
Unknown	5,637 (43.1)	3,861 (41.7)	3,419 (42.1)	3,028 (42.6)

LRx = IQVIA® LRx Germany (database)

Summary

This report presents the results of a cross-sectional analysis of demographic and exposure characteristics of patients treated with ritonavir in Germany. Overall, the majority of patients (91.6%) were between 18 and 64 years old. Gender was reported for approximately half of the patients, and the majority of those among whom it was reported (nearly 69%) were males.

The results of the analysis should be viewed in light of some limitations associated with the analysis. Gender was not available for about 43% of the study sample. Due to the high proportion of patients with unknown gender, the actual gender distribution in the real-world might differ from the reported information.

Exposure Worldwide and by EU Country

An estimate of the patients treated with ritonavir was calculated from AbbVie sales. Available data span the interval 01 March 1996 through 30 November 2024.

The exposure estimate is approximate because the product has had variable dosage regimens in the past. Two separate calculations are made, one using a total daily dose of 1200 mg and one using a total daily dose of 200 mg. These are potential exposures based on 2 different methods of dosing. These numbers should not be added together but, rather, considered as a range.

The total number of capsules, tablets, sachets, and liters distributed was divided by the average daily dose (ADD) determined from the drug label and clinical usage supported by the literature to estimate the number of patient treatment days (PTD). PTD were further divided by 365.25 to estimate the number of patient treatment years (PTYs) (Table 11).

An estimated 5,177,967 of ritonavir have been distributed worldwide for the period from 01 March 1996 through 30 November 2024, assuming a 200 mg ADD, or 862,994 PTY, assuming a 1200 mg ADD. Breakdown of PTY distribution by AbbVie commercial region and EU countries are provided in Table 12.

Table 11. Estimated Ritonavir Patient Exposure from AbbVie Sales

Estimated Cumulative Patient Exposure from 01 March 1996 through 30 November 2024 from AbbVie Sales – 1,200 mg ADD/200 mg ADD						
		Average Daily Dose (mg) – 1,200 mg ADD/200 mg ADD	Patient Treatment Days		Patient Treatment Years	
Formulation	**Amount Distributed**		**1,200 mg ADD**	**200 mg ADD**	**1,200 mg ADD**	**200 mg ADD**
Capsules	1,969,895,677	12 capsules/ 2 capsules	164,157,973	984,947,838	449,440	2,696,640
Sachets	3,703,417	12 sachets	308,618	1,851,708	845	5,070
Tablets	1,475,150,643	12 tablets/ 2 tablets	122,929,220	737,575,322	336,562	2,019,371
Oral Solution	915,574	15 mL	27,812,924	166,877,545	76,148	456,886
Total	**3,449,665,311**		**315,208,736**	**1,891,252,413**	**862,994**	**5,177,967**

ADD = average daily dose

Table 12. Estimated Ritonavir Patient Exposure from AbbVie Sales by EU Country from 01 March 1996 through 30 November 2024

EU Country	1200 mg ADD PTY	200 mg ADD PTY
Austria	[redacted]	[redacted]
Belgium		
Bulgaria		
Croatia		
Cyprus		
Czechia		
Denmark		
Estonia		
Finland		
France		
Germany		
Greece		
Hungary		
Ireland		
Italy		
Latvia		
Lithuania		
Malta		
Netherlands		
Poland		
Portugal		
Romania		
Slovakia		
Slovenia		
Spain		
Sweden		
United Kingdom		
Total	**271,767**	**1,630,602**

ADD = average daily dose; EU = European Union; PTY = patient treatment years

Module SVI Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Ritonavir is a PI ARV medicinal product whose chemical structure and mode of action are not known to pose a potential for illegal use.

Module SVII Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Nitrosamine

A nitrosamine, *N*-nitroso-2,4-thiazoleamine (NNTA), was detected in Norvir tablets and Norvir powder for oral suspension above the FDA and EMA Carcinogenic Potency Categorization Approach (CPCA) acceptable intake limits (EMA 2024). Some nitrosamines are probable or possible human carcinogens.

Based on over 28 years of postmarketing data, both routine surveillance and aggregate reviews of adverse event data have not identified any safety concerns related to either de novo cancer development or worsening of pre-existing cancers with Norvir use. In summary, no discernible clinical impact from the presence of the nitrosamine impurity was detected.

Clinical practice and global guidelines have evolved whereby protease inhibitors (including Norvir) are no longer used as HIV monotherapy but as pharmacokinetic (PK) enhancers of co-administered protease inhibitors in HIV-1 therapy (HIV.gov 2024). Norvir is currently used almost exclusively as a PK enhancer at doses less than 400 mg/day, with the 100 mg to 200 mg/day doses most frequently used.

Considering the evolving role of ritonavir in the HIV treatment paradigm, AbbVie is undertaking measures to address the formation of NNTA in Norvir including updating the SmPC to remove use as an antiretroviral at the no longer used 1200 mg/day maximum daily dose and to retain information on use as a PK enhancer at much lower doses, which shall also reduce nitrosamine exposure.

In conclusion, given the lack of demonstrable clinical impact on the well-established safety profile of Norvir, nitrosamine impurities can be classified as a risk not considered important for

inclusion in the list of safety specifications/concerns. The overall benefit/risk profile of Norvir in the context of nitrosamine impurities remains positive.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

New Important Identified Risks

Not applicable.

New Important Potential Risks

Not applicable.

New Missing Information

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2 Presentation of the Missing Information

Not applicable.

Module SVIII Summary of the Safety Concerns

Table 13. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance (PV) activities beyond adverse reaction reporting and signal detection include:

The MAH commits to monitor the safety topic "Potential Underdosing for the Norvir Powder for Oral Suspension" in future PSURs of ritonavir, per the request in CHMP/PRAC Rapporteur's assessment report, Procedure No. EMEA/H/C/000127/II/0161 (ref: EMA/PRAC/158475/2021).

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional Pharmacovigilance Activities

None.

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

Part IV: Plans for Post-Authorization Efficacy Studies

Not applicable.

Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

This section is not applicable.

V.2 Additional Risk Minimization Measures

This section is not applicable.

V.3 Summary of Risk Minimization Measures and Pharmacovigilance Activities

This section is not applicable.

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Norvir (ritonavir)

This is a summary of the risk management plan (RMP) for Norvir. The RMP details important risks of Norvir, how these risks can be minimized, and how more information will be obtained about Norvir's risks and uncertainties (missing information).

Norvir's summary of product characteristics (SmPCs) and its package leaflets (PLs) give essential information to health care professional (HCP) and patients on how Norvir should be used.

This summary of the RMP for Norvir should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Norvir's RMP.

I The Medicine and What it Is Used For

Norvir is indicated as a pharmacokinetic enhancer of co-administered protease inhibitors as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected patients (adults and children of 2 years of age and older).

Further information about the evaluation of Norvir benefits can be found in Norvir's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/norvir).

II Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Norvir, together with measures to minimize such risks and the proposed studies for learning more about Norvir's risks, are outlined below.

Norvir does not currently have risks designated as "important identified risks" or "important potential risks."

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and health care professionals;
- Important advice on the medicine's packaging;
- The authorized pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessments so that immediate action can be taken as necessary. These measures constitute routine PV activities.

II.A List of Important Risks and Missing Information

Important risks of Norvir are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a correlation with the use of Norvir. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

II.B Summary of Important Risks

This section is not applicable.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Norvir.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Norvir.

Part VII: Annexes

Annex 1	EudraVigilance Interface
Annex 2	Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program
Annex 3	Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan
Annex 4	Specific Adverse Drug Reaction Follow-Up Forms
Annex 5	Protocols for Proposed and Ongoing Studies in RMP Part IV
Annex 6	Details of Proposed Additional Risk Minimization Activities (If Applicable)
Annex 7	Other Supporting Data (Including Referenced Material)
Annex 8	Summary of Changes to the Risk Management Plan Over Time

Annex 4. Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

Annex 6. Details of Proposed Additional Risk Minimization Activities (If Applicable)

Not applicable.

Annex 7. Other Supporting Data (Including Referenced Material)

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