EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 September 2025
EMADOC-1700519818-2433345
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Norvir

International non-proprietary name: Ritonavir

Procedure No. EMA/VR/0000249795

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

95% CI	95% confidence interval
AI	acceptable intake
AIDS	acquired immunodeficiency syndrome
AR	assessment report
ART	antiretroviral therapy
ARV	antiretroviral
ASMF	Active Substance Master File
BID	bis in die (twice daily dosage)
CAPA	corrective and preventative action
CD	cluster of differentiation
CHMP	Committee for Medicinal Products for Human Use
CPCA	carcinogenic potency categorization approach
DLP	data lock point
eCTD	electronic common technical document
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
MAH	Marketing Authorisation Holder
MDD	maximum daily dose
NNTA	N-nitroso-2,4-thiazole amine
NUI	non-urgent request for information
OECD	Organisation for Economic Co-operation and Development
PBT	persistent, bio-accumulative and toxic
PEC	predicted environmental concentration
PI	protease inhibitor
PI	product information
PIL	patient information leaflet
PK	pharmacokinetic
PSUR	Periodic Safety Update Report
QR	quick response
RH	relative humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TAMC	total aerobic microbial count
TYMC	total yeast and mold count
vPvB	very persistent and very bio-accumulative
WHO	World Health Organisation

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, AbbVie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 06 February 2025 an application for group of variations.

The following variations were requested in the group:

Variations requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II
B.II.f.1.a.1	B.II.f.1.a.1 As packaged for sale	Variation type IB
B.II.f.1.e	B.II.f.1.e Change to an approved stability protocol	Variation type IB

A grouped application consisting of: Type II (C.I.6.a): To modify the approved therapeutic indication to reflect current clinical use as a pharmacokinetic enhancer of other antiretroviral products only. Consequently, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the SmPC and the Package Leaflet are updated accordingly. The updated Risk Management Plan (RMP) version 8.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the PI. Type IB (B.II.f.1.a.1): To reduce the shelf life of Norvir 100 mg powder for oral suspension as packaged for sale, from 36 months to 18 months.Type IB (B.II.f.1.e): To change the stability protocol of Norvir 100 mg powder for oral suspension to reflect updated long term testing intervals as a consequence of the reduction in shelf life.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the RMP.

Information relating to orphan designation

Not applicable

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

Not applicable

MAH request for additional data exclusivity

Not applicable

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Patrick Vrijlandt

Timetable	Actual dates
Submission date	06 February 2025
Start of procedure:	25 February 2025
CHMP Rapporteur's preliminary assessment report circulated on:	24 March 2025
Joint Rapporteur's updated assessment report circulated on:	17 April 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2025
MAH responses submitted to the CHMP on:	17 July 2025
CHMP Rapporteur's preliminary assessment report on the MAH responses circulated on:	19 August 2025
PRAC RMP advice and assessment overview adopted by PRAC	04 September 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	09 September 2025
CHMP opinion:	18 September 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Following findings of the nitrosamine impurity, N-nitroso-2,4-thiazole amine (NNTA), in Norvir 100 mg film coated tablets by a third party, confirmatory testing by AbbVie has shown that the levels of NNTA in Norvir tablets and powder for oral suspension are above the carcinogenic potency categorisation approach (CPCA)-established acceptable intake (AI) limit of 18ng/day. The level of NNTA exposure increases with dosage and storage of the product.

In order to minimise the impact of the NNTA exposure the MAH proposed the following changes:

- To modify the approved therapeutic indication to reflect current clinical use as a pharmacokinetic enhancer of other antiretroviral products only. This will impact the maximal daily dose (MDD).

- To reduce the shelf life of Norvir 100 mg powder for oral suspension as packaged for sale, from 36 months to 18 months.
- To change the stability protocol of Norvir 100 mg powder for oral suspension to reflect updated long term testing intervals as a consequence of the reduction in shelf life.

During the procedure, the following changes were recommended:

- To reduce the shelf life of Norvir 100 mg film-coated tablet as packaged for sale, from 2 years to 18 months.
- To change the stability protocol of Norvir 100 mg film-coated tablets to reflect updated long term testing intervals as a consequence of the reduction in shelf life.

Disease or condition

HIV-1 infection and, if not appropriately treated, the subsequent development of a state of acquired immunodeficiency (AIDS), remains an incurable disease. The goal of antiretroviral (ARV) therapy for HIV-1 infection is to delay disease progression and prolong survival by achieving maximal and durable suppression of HIV-1 replication, leading to life-long treatment.

2.1.2. About the product

With the current type II variation, the MAH is proposing a modification of the indication.

The current indication approved by the EMA for Norvir is: "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)."

The sought after indication for Norvir is: "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)."

2.2. Quality aspects

The current application includes two quality variations:

- Type IB (B.II.f.1.a.1): To reduce the shelf life of Norvir 100 mg powder for oral suspension as packaged for sale, from 36 months to 18 months and to reduce the shelf life of Norvir 100 mg film-coated tablet as packaged for sale, from 2 years to 18 months.
- Type IB (B.II.f.1.e): To change the stability protocol of Norvir 100 mg powder for oral suspension and Norvir 100 mg film-coated tablets to reflect updated long term testing intervals as a consequence of the reduction in shelf life.

2.2.1. Introduction

Following findings of the nitrosamine impurity, NNTA, in Norvir 100 mg film coated tablets by a third party, confirmatory testing by AbbVie has shown that the levels of NNTA in Norvir tablets and powder for oral suspension are above CPCA-established AI limit of 18ng/day. The level of NNTA exposure increases with dosage and storage of the product.

The MAH is proposing to reduce the shelf life of Norvir powder for oral suspension and Norvir tablets since the initial testing data for NNTA indicate that a reduced product shelf life of 18 months may be appropriate to achieve an AI limit of 120.6 ng/day for NNTA, based on 200 mg/day MDD.

Norvir Tablets:

For Norvir tablets, the MAH proposed an MDD of 200 mg with a reduction in the shelf life to 18 months with no changes in the storage conditions based on data for Norvir tablets that has been generated to date. For logistic and commercial reasons, a shelf-life less than 18 months was deemed not feasible by the MAH.

Additional stability data are available from 3 commercial batches of Norvir tablets generated at climatic Zone II and Zone IVb storage conditions in accordance with ICH and WHO guidelines. Stability samples were tested for NNTA and the data are appended to the initial confirmatory nitrosamine testing.

Norvir Powder for Oral Suspension:

For Norvir powder for oral suspension, the MAH proposed an MDD of 200 mg with a reduction in the shelf life to 18-months and no changes in storage conditions based on data for Norvir powder for oral suspension that has been generated to date. An additional data analysis was completed for Norvir powder for oral suspension using the available NNTA data from the 30°C/75% RH storage condition confirmatory testing to estimate expiration dating.

2.2.2. Discussion on the quality aspects

The MAH proposed to reduce the shelf life of Norvir 100 mg powder for oral suspension to 18 months based on an MDD of 200 mg Ritonavir/day. According to the stability data provided by the MAH, all test results for NNTA in Norvir Powder for oral suspension stay within the interim AI limit of 120.6 ng/day under all conditions tested up to at least 18 months. Thus, based on the accepted MDD of 200 mg/day, the proposed shelf life of 18 months is acceptable for both the tablets and the powder for oral suspension. The MAH has provided sufficient information to support this shelf life for the interim period in which corrective and preventative actions (CAPAs) are introduced to further lower the amount of NNTA in Norvir products.

For the film-coated tablets, no storage conditions are required as the stability data under intermediate conditions indicate that the product will comply with the specification for all parameters, including NTTA, up to the proposed shelf life of 18 months.

For the powder for oral solution the already approved storage condition of store below 30°C can be maintained based on the provided stability data.

In addition, the MAH proposed to change the stability protocol of Norvir 100 mg powder for oral suspension and Norvir 100 mg film-coated tablets. The time points of 48 & 60 months are deleted from the stability protocol, and the time points 24 & 36 months are optional. Furthermore, to ensure the microbiological quality over the proposed shelf life of 18 months, the tests for Total Aerobic Microbial Count (TAMC) and Total Yeast and Mold Count (TYMC) will also be performed at the 18 months timepoint. The changes in the stability protocol are acceptable.

2.2.3. Conclusion on the quality aspects

Based on the provided stability data and a maximum daily dose of 200 mg, a shelf life of 18 months for Norvir powder for oral suspension is acceptable with the storage conditions of storage

below 30ºC. For Norvir 100 mg film-coated tablets, a shelf life of 18 months is acceptable with no requirement for special storage conditions. Moreover, the proposed changes to the stability protocol of Norvir powder for oral suspension and Norvir tablets are accepted to reflect updated long term testing intervals as a consequence of the reduction in shelf life.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

The ERA has been restructured to comply with the 2024 Committee for Medicinal Products for Human Use Environmental Risk Assessment guidelines. Based on a recalculation of the Predicted Environmental Concentration (PEC) to ensure compliance with the 2024 Guidelines, it has been determined that both Phase I and Phase II assessments are required. To this end, AbbVie is working towards obtaining study reports for Phase II studies on ritonavir from another MAH. If the study reports cannot be obtained by AbbVie, or for studies that were not completed, AbbVie will complete the required physicochemical properties and environmental fate and affect studies in accordance with the 2024 Guideline. Additionally, the results of an Organisation for Economic Co-operation and Development (OECD) octanol/water partition coefficient study (OECD 107) will be used to determine if additional secondary poisoning and/or Persistent, Bio-accumulative and Toxic (PBT) or very Persistent and very Bio-accumulative (vPvB) assessments are required.

2.3.2. Discussion on non-clinical aspects

According to the revised guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*), for type II variations, the ERA dossier should be updated if there is an anticipated increase in the environmental exposure. For the current procedure that is not the case, since the maximum dose is reduced, and therefore no increase in use is anticipated. However, the MAH committed to updating the ERA by obtaining the study reports from another MAH, and/or performing the necessary studies themselves. This is supported.

2.3.3. Conclusion on the non-clinical aspects

For the current procedure, no increase in use is anticipated that will impact environmental exposure. The updated ERA and underlying study reports will be assessed when they become available.

2.4. Clinical aspects

2.4.1. Introduction

Clinical use

Norvir was originally developed as a protease inhibitor (PI) to treat HIV-1 infection in treatment-naïve or treatment-experienced adults and children with doses of up to 1200 mg/day, supported by both clinical and surrogate endpoints (i.e., changes in plasma viral load and CD4+ counts) as primary efficacy variables.

Over the past 3 decades, many new HIV therapies were developed and the use of ritonavir shifted from a PI to a PK enhancer of other concomitant antiviral therapies, which required only doses of 100 to 400 mg/day. This development and use as a PK enhancer was also supported by changes in HIV treatment guidelines. Current global guidelines (including for Europe, the United States, China, Australia, and South Africa) recommend use of Norvir as a PK enhancer of other PIs at lower daily doses of up to 400 mg/day, and it is most commonly used at doses of 100 to 200 mg/day.

Nitrosamine Impurities

Elevated levels of NNTA, a nitrosamine, were found in Norvir 100 mg tablets during testing by a third party. Some nitrosamines are known to be mutagenic carcinogens. The lifetime AI for NNTA has been determined by major health authorities, such as EMA to be 18 ng/day and the United States Food and Drug Administration (FDA) to be 26.5 ng/day based on the recommended CPCA. The EMA established an NNTA interim limit for a period of 3 years of 120.6 ng/day for ritonavir products at shelf life.

Pursuant to third party notification of elevated NNTA levels, the MAH tested batches of Norvir 100 mg tablets and Norvir powder for oral suspension that were expired and within shelf life, which confirmed NNTA levels above EMA CPCA acceptable intake limits.

The exposure to NNTA with the currently used 100 mg/day to maximum 400 mg/day ritonavir dosing is approximately 65% lower than that for the no longer used 1200 mg/day dose compared to doses $\leq$ 200 mg/day. Therefore, this lowers exposure to NNTA even more (~83% lower). In order to ensure product quality and minimise NNTA impurity levels while maintaining a viable product shelf-life, the MAH proposed to lower the MDD to 200 mg/day and to remove the 400 mg/day dose to comply with the EMA established interim 120.6 ng/day AI limit for NNTA. This is critical to preserving the availability of Norvir, an effective HIV treatment, to patients. By reducing the MDD, exposure to NNTA is decreased. In addition, reducing product shelf life of Norvir powder for oral suspension will decrease exposure to NNTA further, since NNTA forms during storage of the product. The proposed MDD of 200 mg will ensure that the vast majority of patients requiring Norvir as a booster for their HIV therapy will be assured of treatment and product availability with a reasonable shelf life. Tipranavir is the only medicinal product used in combination with ritonavir at a 400 mg/day dose, with limited use as a last-line therapy in patients with no other therapeutic options. Based on data from IQVIA, tipranavir was prescribed to only approximately 63 patients in Europe in 2024. Tipranavir is not approved in all countries in which Norvir is approved.

Review of literature did not provide evidence of a causal relationship of NNTA found in Norvir to cancer. Furthermore, the association of nitrosamine as a human carcinogen appears stronger with dietary intake than with medicinal products, perhaps underscoring the relative importance of the quantity of nitrosamine consumed over time.

The reporting rate for all malignancies reported in Norvir-using HIV-infected patients in the AbbVie Safety Database (12.10/100,000) is less than the background rate for malignancies globally (237.7/100,000), North America (553.2/100,000), and in Europe (554.0/100,000).

A medical review of the individual case reports of malignancies was conducted. Overall, the cases were confounded by risk factors for cancer including smoking, hepatitis B/C, and pre-existing conditions/medical history, or presented with unknown/uncertain latency including time to diagnosis to treatment initiation with Norvir.

2.4.2. Discussion on clinical aspects

Since registration of ritonavir in 1996 a paradigm shift has occurred with respect to clinical practice of prescription of HIV treatment. Norvir has been approved both as a PK booster as well as a 'stand-alone' ARV to be used in combination with other ARVs. As stand-alone treatment the total recommended daily dose was 1200 mg/day. However, this is no longer a used treatment option and currently Norvir is exclusively used as a PK booster, with a recommended dose of 100-400 mg/day. Considering the fact that guidelines and prescribers currently only recommend/prescribe Norvir as a PK booster modification of the indication to an only PK booster indication is appreciated. This would reduce the MDD from 1200 mg to 400 mg.

However, to determine exposure to NNTA an MMD of 200 mg/day can be used, as 200 mg/day and 100 mg/day are the most widely used dosages in the current clinical practice. This would imply a higher exposure to NNTA in patients also receiving tipranavir, however, this can be accepted during the period in which the CAPAs to reduce NNTA impurities are being implemented to ensure availability of the product during this time.

Although it is agreed that the use of the 400 mg/ day dose is limited - only recommended when in combination with Tipranavir - this dosing regimen is currently used in the EU and simply dismissing this use is not acceptable. As HIV is an incurable disease with a high rate of resistance development, the palette of ART should be as wide as possible, especially for people with multi-resistant HIV. It is considered premature to remove the tipranavir posology prior to all efforts to substantially reduce nitrosamine impurities are thoroughly investigated and implemented. It is therefore suggested to keep the tipranavir posology regardless of the increased exposure to nitrosamines. The risk to patients in these 3 years that the interim limit for NNTA exposure is granted is considered higher when changing ART (and potentially changing it back in about 3 years time), due to adverse events and increases in viral load (commonly referred to as breakthrough infections), compared to a potential increased risk of development of cancer due to exposure of nitrosamines. The MAH agreed upon the dosing regimen including tipranavir to be reinstated.

Of note, the modification of the approved therapeutic indication of Norvir to reflect current clinical use as a pharmacokinetic enhancer of other antiretroviral products has consequences for several sections of the SmPC. Apart from updates of sections 4.1 and 4.2, sections 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 also needed to reflect relevant information specific to use of Norvir as pharmacokinetic enhancer. Therefore, wording specific to the (no longer recommended) use of Norvir as 'stand-alone' ARV was removed.

Section 4.5 was updated as a consequence of the modification of the approved therapeutic indication to reflect current clinical use of Norvir as a pharmacokinetic enhancer of other antiretroviral products only. When Norvir was used in combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children of 2 years of age and older, the now deleted indication), the posology was much higher than when Norvir is used as a pharmacokinetic enhancer, which was reflected in section 4.5. This section has been updated to only reflect relevant interactions based on the use of Norvir as pharmacokinetic enhancer.

Norvir has been shown to enhance PK exposure of co-administered protease inhibitors such as indinavir and saquinavir. The PK interaction between Norvir and indinavir was evaluated in 5 groups of healthy adult volunteers in a randomized, multiple-dose, open-label study. At steady state, Norvir increased plasma indinavir concentrations with area under the curve (AUC) increased up to 475% and maximum concentration (Cmax) increased up to 110%. In a study to evaluate the PK interaction between Norvir and saquinavir in healthy volunteers in 6 groups of a single-dose crossover study, coadministration of Norvir and saquinavir resulted in a > 50-fold increase in the

AUC and a 22-fold increase in the Cmax of saquinavir. Section 5.2 of the Norvir SmPC was updated to describe these studies.

2.4.3. Conclusion on the clinical aspects

The modification of the approved therapeutic indication of Norvir to reflect current clinical use as a pharmacokinetic enhancer of other antiretroviral products only is accepted. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been amended. The Package Leaflet is updated accordingly. These changes are accepted.

2.4.4. PSUR cycle

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

2.5. Risk management plan

The MAH submitted an updated RMP version 8.0, dated January 2025 and DLP 30 November 2024 with this application. The RMP was revised to update the therapeutic indication and dosing of ritonavir to the current clinical use as a pharmacokinetic enhancer only, at a maximum daily dose of 200 mg, as supported by current EU and global guidelines. The antiretroviral indication at doses of 600 mg BID (1200 mg/day) has been removed, since ritonavir is no longer used for this purpose. The dose reduction provides a further benefit of reducing exposure to a nitrosamine impurity, NNTA. Consequently relevant sections throughout the RMP were revised with the updated indication and MMD. There were no revisions in the main parts (Part SVIII Summary of safety concern, Part II Pharmacovigilance Plan, Part V Risk Minimization Measures) of the RMP.

The CHMP received the following PRAC Advice on the submitted RMP:

The PRAC considered that the risk management plan version 8.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 8.0 with the following content:

Safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Routine pharmacovigilance activities are sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.6. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

2.6.1. User consultation

Not applicable

2.6.2. Additional monitoring

Not applicable

2.6.3. Quick Response (QR) code

Not applicable

3. Benefit-Risk Balance

3.1. Benefit-risk assessment and discussion

Following findings of the nitrosamine impurity, NNTA, in Norvir 100 mg film coated tablets by a third party, confirmatory testing by AbbVie has shown that the levels of NNTA in Norvir tablets and powder for oral suspension are above the CPCA established AI limit of 18ng/day. The level of NNTA exposure increases with dosage and storage of the product.

In order to minimise the impact of the NNTA exposure the Applicant proposed the following changes:

- To modify the approved therapeutic indication to reflect current clinical use as a pharmacokinetic enhancer of other antiretroviral products only. This will impact the maximal daily dose.
- To reduce the shelf life of Norvir 100 mg powder for oral suspension as packaged for sale, from 36 months to 18 months.
- To reduce the shelf life of Norvir 100 mg film-coated tablet as packaged for sale, from 2 years to 18 months.
- To change the stability protocol of Norvir 100 mg powder for oral suspension and Norvir 100 mg film-coated tablets to reflect updated long term testing intervals as a consequence of the reduction in shelf life.

As Norvir is currently exclusively used as a PK booster, adjustment of the indication to reflect the current use as a PK booster is acceptable. As 'stand-alone' ARV to be used in combination with other ARV, the total daily dose was 1200 mg/day (which is no longer reflected in the indication), while as a PK booster the dose is 100-400 mg/day. Although it is agreed that the use of the 400 mg/day dose is limited, based on a NUI this dosing regimen is currently used in the EU. The MAH did not sufficiently substantiate the removal of this dosing regimen from the SmPC. As HIV is an incurable disease with a high rate of resistance development, the palette of ART should be as wide as possible, especially for people with multiresistant HIV. It would be preferred to keep the option of dosing 400 mg/day as this is the recommended Norvir dose when combined with Tipranavir.

However, to calculate the interim limit of NNTA exposure (120 ng/day) a maximal daily dose of 200 mg/day of ritonavir could be used, as 200 mg/day and 100 mg/day are the most widely used dosages in the current clinical practice. This would imply a higher exposure to NNTA in patients also receiving tipranavir, however, this can be accepted during the period in which the CAPAs to reduce NNTA impurities are being implemented (September 2027). The risk of the increased exposure is weighed against the risks of adverse events and increases in viral load, commonly referred to as breakthrough infections, when patients should switch ART in case their current regiment including tipranavir is no longer available (and potential switch back in 2/3 years).

Based on the provided stability data and a maximum daily dose of 200 mg a shelf-life of 18 months for Norvir Powder for oral suspension is acceptable with the storage conditions of storage below 30ºC and for Norvir 100 mg film-coated tablets, a shelf-life of 18 months is acceptable with no requirement for special storage conditions.

3.2. Conclusions

The overall benefit-risk balance of Norvir remains positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends by consensus the variations to the terms of the marketing authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB
B.II.f.1.a.1	B.II.f.1.a.1 As packaged for sale	Variation type IB	I
B.II.f.1.e	B.II.f.1.e Change to an approved stability protocol	Variation type IB	

A grouped application consisting of: Type II (C.I.6.a): To modify the approved therapeutic indication to reflect current clinical use as a pharmacokinetic enhancer of other antiretroviral products only. Consequently, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC and the Package Leaflet are updated accordingly. The updated RMP version 8.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the PI. Type IB (B.II.f.1.a.1): To reduce the shelf life of Norvir 100 mg powder for oral suspension as packaged for sale, from 36 months to 18 months and to reduce the shelf life of Norvir 100 mg film-coated tablet from 2 years to 18 months. Type IB (B.II.f.1.e): To change the stability protocol of Norvir 100 mg powder for oral suspension and Norvir 100 mg film-coated tablets to reflect updated long term testing intervals as a consequence of the reduction in shelf life.

The group of variations leads to amendments to the annexes I and IIIB, and to the RMP.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular, the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Norvir-H-C-000127-II-EMA/VR/0000249795