14 September 2017
EMA/CHMP/749789/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ritonavir Mylan

International non-proprietary name: ritonavir

Procedure No. EMEA/H/C/004549/0000

Note

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

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Table of contents

List of abbreviations

AP	Applicant's Part (or Open Part) of a DMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AUC	Area under curve
AUC0-T	Cumulative area under the plasma concentration time curve calculated from 0- TLQC using the linear trapezoidal method
AUC 0-∞	Area under the curve from time zero to infinity
BP	British Pharmacopoeia
CEP	Certificate of Suitability of the Ph.Eur.
Cmax	Peak Plasma Concentration
MS	Member State
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DMF	Drug Master File = Active Substance Master File
DP	Decentralised (Application) Procedure
DSC	Differential Scanning Calorimetry
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography
IH	In house
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control test
IR	Infrared
KF	Karl Fischer titration
HPLC/MS	High performance liquid chromatography mass spectrometry
LDPE	Low density polyethylene
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantification / Quantitation
LoQ	List of Questions
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MS	Mass Spectrometry
ND	Not detected
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PP	Polypropylene
PVC	Poly vinyl chloride
PXRD	Powder X-Ray Diffraction
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RMP	Risk Management Plan
RP	Restricted Part (or Closed Part) of a DMF
RRT	Relative retention time
RSD	Relative standard deviation
SPC/SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count

TGA	Thermo-Gravimetric Analysis
Thalf	Terminal elimination half-life, calculated as ln(2)/λz
TLIN	Time point where log-linear elimination phase begin
TLC	Thin layer chromatography
TLQC	Time of last observed quantifiable plasma concentration
Tmax	Time of maximum observed plasma concentration: it is occurs at more than one time
point,	Tmax is defined as the first time point with this value
TYMC	Total Combined Yeasts/Moulds Count
UV	Ultraviolet
XRD	X-Ray Diffraction
λz	Apparent elimination rate constant, estimated by linear regression of the terminal linear
portion	of the log concentration versus time curve

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Jenson R+ Limited submitted on 5 December 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Ritonavir Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2016.

On 19 May 2017, the applicant was changed from Jenson R+ Limited to MYLAN S.A.S.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3).

The applicant applied for the following indication:

"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 legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC)

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Norvir instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Norvir, 100 mg, film-coated tablet
- Marketing authorisation holder: Abbvie Ltd
- Date of authorisation: 26-08-1996
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: EU/1/96/016/005-007

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Norvir, 100 mg, film-coated tablet
- Marketing authorisation holder: Abbvie Ltd
- Date of authorisation: 26-08-1996
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: EU/1/96/016/005-007

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Norvir, 100 mg, film-coated tablet
- Marketing authorisation holder: Abbvie Ltd
- Date of authorisation: 26-08-1996
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: EU/1/96/016/005-007
- Bioavailability study number: 10-VIN-327

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

- The application was received by the EMA on 5 December 2016.
- The procedure started on 23 December 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 27 March 2017.
- During the meeting on 21 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 May 2017.
- The CHMP and PRAC Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 June 2017.
- During the PRAC meeting on 6 July 2017, the PRAC agreed on a PRAC Assessment Overview and

Advice to CHMP.

- During the CHMP meeting on 20 July 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 17 August 2017.
- The CHMP and PRAC Rapporteur circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 30 August 2017.
- During the meeting on 14 September 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Ritonavir Mylan.

2. Scientific discussion

2.1. Introduction

Current treatment for HIV infection consists of highly active antiretroviral therapy, or HAART. This has been highly beneficial to many HIV-infected individuals since its introduction in 1996 when the protease inhibitor-based HAART initially became available. Current optimal HAART options consist of combinations of at least three drugs belonging to at least two types, or "classes," of antiretroviral agents.

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 are unable to initiate new rounds of infection. Ritonavir has selective affinity for the HIV protease and has little inhibitory activity against human aspartyl proteases.

Ritonavir was the first protease inhibitor (approved in 1996) for which efficacy was proven in a study with clinical endpoints. However, due to ritonavir's metabolic inhibitory properties its use as a pharmacokinetic enhancer of other protease inhibitors is the prevalent use of ritonavir in clinical practice

Coadministration of low dose ritonavir can increase the total area under the concentration-versus time curve (AUC) of most other PIs, as well as the minimum concentration (Cmin). Boosting with ritonavir also increases the maximum drug concentration (Cmax), although to a lesser extent than the AUC or Cmin. P-glycoprotein is expressed in epithelial cells of the gastrointestinal tract, liver, and blood–brain barrier, as well as in CD4+ lymphocytes. Its inhibition by ritonavir may thus not only help retain PI levels intracellularly but also increase the oral bioavailability, systemic exposure, and central-nervous-system penetration of the primary PI and decrease the secretion of circulating drug into the intestinal lumen.

This application is for a generic form of Ritonavir film-coated tablets in the strength of 100 mg. The active ingredient and the route of administration are the same for both products.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 100 mg of ritonavir as active substance.

Other ingredients are:

Tablet core: copovidone, sorbitan laurate, colloidal anhydrous silica, sodium chloride, sodium stearyl fumarate.

Film-coating: hypromellose, titanium dioxide (E171), macrogols, hydroxypropylcellulose, talc, iron oxide yellow (E172), colloidal anhydrous silica, polysorbate 80.

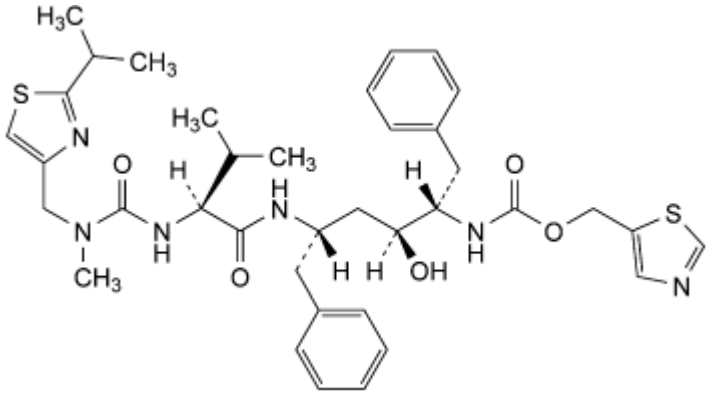
The product is available in pack sizes of 30, 90 and 100 film-coated tablets in HDPE bottle with polypropylene screw cap with inbuilt desiccant, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of ritonavir is thiazol-5-ylmethyl [(1S,2S,4S)-1-benzyl-2-hydroxy-4-[[(2S)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoyl]amino]-5-phenylpentyl]carbamate corresponding to the molecular formula $C_{37}H_{48}N_6O_5S_2$. It has a relative molecular mass of 721 g/mol and the following structure:

Figure 1. Active substance structure



Ritonavir is a white or almost white powder, non-hygroscopic, practically insoluble in water, freely soluble in methanol and in methylene chloride, very slightly soluble in acetonitrile.

Ritonavir exhibits stereoisomerism due to the presence of four chiral centres. The active substance manufacturer consistently produces the S-isomer of ritonavir.

Polymorphism has been observed for ritonavir. Two forms are observed, designated Form-I and Form-II. The polymorphic form of three consecutive batches of ritonavir active substance has been tested by XRD. It has been confirmed that the process consistently produces Form-II.

As there is a monograph of Ritonavir in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for Ritonavir which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification includes tests for appearance, solubility (Ph. Eur.), identification (IR), assay (HPLC), related substances (HPLC), water content (KF) and sulfated ash (Ph. Eur.) in line with the Ph. Eur. monograph of ritonavir and identification of polymorph (PXRD), residual solvents (GC) and phenol impurity (LC-MS/MS) in line with the Certificate of Suitability.

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. Monograph and Certificate of Suitability. All additional methods have been adequately validated and described according to ICH Q2. Satisfactory information regarding the reference standards used for assay and related substance testing has been presented.

Batch analysis data on 3 production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

The relevant supporting information has been assessed by the EDQM before issuing the Certificate of Suitability. The re-test period of the active substance as stated in the Certificate of Suitability is 60 months if stored in double polyethylene bags (outer black) placed in a polyethylene container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Ritonavir 100mg film-coated tablets are immediate release, yellow coloured, film-coated, capsule shape tablets debossed with “M163” on one side and plain on other side with dimensions approximately 19.10 mm x 10.20 mm (Length x Width).

The purpose of the pharmaceutical development was to develop a generic version of ritonavir 100 mg film-coated tablets which can be demonstrated to be bioequivalent to the EU reference product, Norvir 100 mg film-coated tablets

The early formulation development was performed with reference to the US reference product, Norvir 100 mg soft gelatin capsules however, the comparative in-vivo (bioequivalence studies) and in-vitro (comparative dissolution and impurity profile studies) studies presented to support this application have been performed between the test product and the EU reference product, i.e. Norvir 100 mg film-coated tablets

Since the ritonavir active substance is insoluble in water, tablets prepared in a conventional way resulted in incomplete bioavailability. In order to enhance its bioavailability from the tablet dosage form, it was concluded that ritonavir must be present in the form of solid dispersion in the tablet. A solid dispersion can be prepared by using any of the following techniques; melt granulation, melt

extrusion, solvent evaporation or spray drying. Based on past experience, the applicant decided to explore solvent evaporation techniques for making the solid dispersion during development trials.

The applicant selected the excipients for product development studies taking into consideration the requirement of disintegration time in the range of 35 to 45 minutes, past experience, literature search and pre-formulation studies.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. Compatibility studies between the active substance and chosen excipients have been performed to support the choice of excipients.

A number of pilot scale formulation studies were performed to evaluate the effect of different concentrations of excipients on tablet characteristics. The resulting tablets were compared by physical evaluation and in vitro dissolution testing to Norvir 100 mg soft capsules, and the formulation was optimised taking account of these test results.

The final proposed formulation of ritonavir 100 mg film-coated tablets is qualitatively similar to that of the reference product, Norvir 100 mg film-coated tablets, with the exception the proposed formulation contains sodium chloride and does not contain calcium hydrogen phosphate, anhydrous.

Table 1. Qualitative composition of ritonavir 100 mg film-coated tablets versus the EU reference product, Norvir 100 mg film-coated tablets

Active substance: Ritonavir	*Active substance:* Ritonavir
Tablet core: Copovidone Sorbitan laurate - Silica, colloidal anhydrous Sodium stearyl fumarate Sodium chloride	*Tablet core:* Copovidone Sorbitan laurate Calcium hydrogen phosphate, anhydrous Silica, colloidal anhydrous Sodium stearyl fumarate -
Film-coating: Hypromellose Titanium dioxide (E171) Macrogols Hydroxypropyl cellulose Talc Silica, colloidal anhydrous Polysorbate 80	*Film-coating:* Hypromellose Titanium dioxide (E171) Macrogols Hydroxypropyl cellulose Talc Silica, colloidal anhydrous Polysorbate 80

The optimisation and scale-up of the manufacturing process has been adequately performed and was supported by relevant physicochemical and stability testing.

The polymorphic form of ritonavir has been monitored and tested in the active substance, ritonavir premix and finished product by XRD testing. The active substance manufacturer consistently produces the same polymorphic form ritonavir. The applicant has characterised the polymorphic form throughout the various manufacturing steps and has demonstrated that the form of ritonavir is maintained in the finished product at release and throughout the shelf life.

The applicant performed a comparative bio-equivalence study between ritonavir 100 mg film-coated tablets {Manufactured by Mylan Laboratories Limited, Nashik, India} and Norvir 100 mg film-coated

tablets (Abbott Laboratories Limited, UK) in order to demonstrate bioequivalence of the test and reference products. The composition and manufacturing process of the test batch used in the bio-equivalence study are identical to that proposed for commercial supply.

In addition, the applicant presented the results of comparative dissolution studies and comparative impurity profiles as supportive data.

Due to the poor solubility of ritonavir in three standard dissolution media, i.e. 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer, the applicant proposed to use a surfactant in the dissolution medium to be used for routine quality control. The selection of dissolution medium, choice of surfactant, agitation speed and volume were supported by relevant development studies.

The discriminatory power of the dissolution method has been demonstrated by testing finished product with quantitative changes in excipients and significant manufacturing process changes. The specifications for release and shelf-life have been derived from the dissolution profile of the test product batch that was found to be bioequivalent to the reference product and considering the principles of the CHMP/CVMP Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017).

Bulk tablets can be packaged and stored in Low Density Polyethylene (LDPE) bags placed in an outer triple laminated bag along with desiccant (silica gel) bags in between the LDPE bag and outer triple laminated bag and sealed. The triple laminated bags are then placed in a suitable tertiary pack (HDPE drum).

The primary packaging for placing on the market is HDPE bottle with polypropylene screw cap with inbuilt desiccant. The materials comply with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: preparation of ritonavir-excipient premix (mixing, distillation, drying, milling), blending with remaining excipients, compression and film-coating. The process is considered to be a standard manufacturing process.

An appropriate specification for ritonavir excipient premix including tests for description, identification (HPLC), methylene chloride (GC), water content (KF), assay (HPLC) and X-ray diffraction is applied by the manufacturer.

The critical steps in the manufacturing process are the preparation of powder blend and compression of tablets (before coating). The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. These steps have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC, TLC), colour identification (visual), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), related substances (HPLC), assay (HPLC), water (Ph. Eur.) and microbiological purity (Ph. Eur.).

The finished product is released on the market based on the release specifications, through traditional final product release testing. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and related substances testing has been presented.

Batch analysis results are provided for three pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three pilot scale batches of finished product stored for up to 24 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. These batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing (HDPE bottle). Stability data from studies of finished product packed in simulated bulk pack (LDPE bag) for 12 months at long term conditions (30°C / 75% RH) have also been provided.

Samples were tested for description, assay, related substances, dissolution, water content and microbiological purity. The analytical procedures used are stability indicating. All results were within specification limits and no trends were observed (apart from a single out of specification result for an impurity in one batch on accelerated conditions). The applicant presented additional data demonstrating that polymorphic form and enantiomeric purity of ritonavir does not change on storage of the tablets.

One batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The study results indicated that there was no significant change in assay, related substances and dissolution. Thus, it can be concluded that ritonavir 100 mg film-coated tablets are not photosensitive.

An in-use stability study was performed up to 100 days at long term storage conditions (25 ºC / 60% RH) with simulated opening and removing of one tablet each day.

Forced degradation / stress studies were performed by exposing ritonavir to acidic, basic, oxidative, high temperature, UV light and high humidity conditions. The main impurity formed was impurity F (a heat-dependant degradant).

The applicant also commits to perform stability studies on the first three larger production scale batches at accelerated stability conditions (i.e. 40 ± 2°C / 75 ± 5% RH) for 6 months and at long-term stability conditions (i.e. 25 ± 2°C / 60 ± 5% RH), till the end of the proposed shelf life.

Based on available stability data, the proposed shelf-life of 24 months when stored below 30°C, with an in-use shelf life after opening of 100 days when stored below 30°C in the original bottle in order to protect from moisture, as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Pharmacodynamic, pharmacokinetic and toxicological properties of ritonavir are well known. As ritonavir is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required.

The CHMP considered that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Ritonavir Mylan is considered unlikely to result in any significant increase in the combined sales volumes for all ritonavir containing products and the exposure of the environment to the active substance. Thus, the environmental exposure is expected to be similar and not increased

2.3.3. Discussion on non-clinical aspects

The non-clinical documentation submitted in support of this application is adequate for the purpose of a generic product authorisation. The active substance pharmacological and toxicological properties are well known. Impurities associated with this product do not pose any untoward risk to health and therefore no additional studies will be requested.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Ritonavir Mylan including a description of impurities expected and their acceptability thresholds which is acceptable. The non-clinical data are reflected in the appropriate sections of the SmPC and in line with the requirements for generic

products.

The CHMP considered that there are no objections to approval of Ritonavir Mylan from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing ritonavir. To support the marketing authorisation application the applicant conducted one bioequivalence study with an open label, two-treatment, two- period, two-sequence, single centre, balanced, single dose, crossover design under fed] conditions. This study was the pivotal study for the assessment.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

This is a generic application for only one strength; hence a biowaiver is not applicable.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

Table 2. Tabular overview of clinical studies

Type of study	Study number	Objective of the study	Study design	Test products; dosage regimen; route of administration	No of subjects	Healthy subjects or patients	Duration of treatment
BE	10-VIN-327	To compare the rate and extent of absorption of Ritonavir 100mg tablets of Matrix Laboratories Limited, India and Norvir (Ritonavir) Tablets 100 mg of Abbott GmbH and Co in healthy, adult, human subjects under fed condition. To evaluate the safety and tolerability of Ritonavir 100mg tablets in healthy human subjects.	Open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover under fed conditions	One tablet formulation, single dose, oral administration	54 enrolled, 47 randomised	Healthy adult human subjects	Single dose

2.4.2. Pharmacokinetics

Study 10-VIN-327

Study Title: *"An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover bioequivalence study of Ritonavir 100mg tablets of Matrix Laboratories Limited, India and Norvir® (Ritonavir) Tablets 100 mg of Abbott GmbH and Co, KG Knollstrasse, 67061, Ludwigshafen,*
Germany in healthy, adult, human subjects under fed condition."

Methods

Study design

This was a randomised, open label, two-treatment, two- period, two-sequence, single centre, balanced, single dose, crossover comparative oral bioavailability study to establish comparative bioequivalence of Ritonavir 100mg film coated tablets (Applicant: Mylan S.A.S. previously Matrix) and

Norvir (Ritonavir) 100mg film coated tablets (MAH: Abbott GmbH and Co. Germany) in 54 healthy, adult human subjects under fed conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety of the subjects.

Based on the randomised schedule and following an overnight fast of at least 10 hours subjects received a high-fat, high-calorie breakfast 30 minutes prior to drug administration.

Thirty minutes after the start of the breakfast, a single dose of the assigned formulation was administered with approximately 240 ml of water at ambient temperature, starting at 08:30, to one subject per minute. Water was allowed ad libitum until 1 hour pre-dose and beginning 1 hour after drug administration.

Subjects received a standard meal at about 4, 8 and 12 hours after dosing in each period. During housing, all meal plans were identical for all periods.

Subjects were confined to the clinical facility from at least 10 hours prior to dosing of the investigational product until after the 24-hour blood sample collection in each study period. Subjects were to report to the clinical facility again for the 36 and 48 hour ambulatory blood sample. The two periods were separated by a wash-out phase of at least 7 days.

Blood samples were taken at the following time points: pre-dose and at 0.00, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours post dose.

Test and reference products

Product Characteristics	Test Product	Reference Product
Name	Ritonavir	Norvir® (Ritonavir)
Strength	100 mg	100 mg
Dosage Form	Tablets	Tablets
Manufactured by	Matrix Laboratories Limited (Now known as Mylan Laboratories Inc.), F-4 & F-12, MIDC, Malegaon, Sinnar, Nashik-422113, INDIA.	Manufactured by: Abbott GmbH and Co. KG Knollstrasse, 67061, Ludwigshafen, Germany. Manufactured for: Abbott Laboratories Limited Abbott House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire SL6 4XE, United Kingdom
Batch/Lot number	1033015	911418D
Batch Size (Bio batch)	110,000	--
Measured Content(s) (% of Label Claim)	98.8%	100.1%
Commercial Batch Size	----	----
Expiry Date (Retest Date)	Mar.2012	Feb.2012
Location of Certificate of Analysis	Module-05, Appendix-16.1.6	Module-05, Appendix-16.1.6
Member State where the reference product is purchased from:	-	UK
This product was used in the following trials:	Study no.: 10-VIN-327	Study no.: 10-VIN-327

Population studied

54 healthy adult human subjects were enrolled as per the protocol whilst 47 subjects completed both study periods.

Main inclusion criteria:

- Subjects aged between 18 and 55 years (both inclusive).
- Subjects' weight within normal range according to normal values for Body Mass Index (18.5 to 24.9 kg/m2) with minimum of 50 kg weight.
- Subjects with normal health as determined by personal medical and medication history, clinical examination and laboratory examinations within the clinically acceptable reference range.
- Subjects having normal12-lead electrocardiogram (ECG).
- Only non-smokers (no history of smoking) were eligible to participate in the study.
- Subjects having normal chest X-Ray (PIA view) whose X-Ray was taken within 6 months prior to the dosing of Period 01.
- Subjects having negative urine screen for drugs of abuse (including amphetamines, barbiturates, benzodiazepines, marijuana, cocaine, and morphine).
- Subjects having negative alcohol breath test.
- Subjects willing to adhere to the protocol requirements and to provide written informed consent.

Analytical methods

Analysis of ritonavir was performed using HPLC/MS/MS.

This method involved the extraction of ritonavir and abacavir together with the respective internal standards from human plasma.

Storage period of study samples

Samples were stored at the clinical facility in a deep freezer under frozen conditions at a set temperature of below -20°C till the completion of the periods and then at -78°±8°C till their shipment to the analytical site. During transit the temperature was maintained below -79°C. Upon receipt the samples were then stored in a deep freezer at -70°±15°C at the bioanalytical lab from the date of their receipt until they were analysed.

Dosing started on the 11 January 2011 and the bioanalysis was performed between 18 February 2011 to 14 March 2011 (63 days of storage).

The long-term stability of Ritonavir in human plasma covers 116 days at -70°C and -20°C nominal.

2268 samples were expected according to the protocol however 2088 blood samples were received (180 missing samples). The missing samples are accounted for in the dossier (samples of persons who had not completed the study).1985 samples were deemed valid and analysed. 8 samples were re-assayed and the reason for their repeats was documented and presented.

Bioanalytical report

The bioanalytical report was submitted with 20% of the subject chromatograms presented as well as the method SOPs. Certificates of analysis for the reference and internal standards have been provided and were acceptable.

Incurred Sample Reanalysis

200 samples of Ritonavir were identified for incurred sample reanalysis. 94.50% is the percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for the ligand binding assays.

Validation of the test method

The method has been validated and the limits of the assessed parameters were justified.

Pharmacokinetic variables

Primary parameters: Cmax, AUC0-T,

Secondary parameters: AUC0-∞, Tmax, AUC0-T/ AUC0-∞, Kel and T1/2.

Bioequivalence criteria: The 90% confidence intervals of the relative mean AUC 0-t and Cmax of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data.

Statistical methods

The mean, standard deviation (S.D.) and coefficient of variation (C.V.) were calculated for plasma concentrations at each individual time point as well as for the pharmacokinetic parameters. ANOVA was performed on the ln-transformed data of Cmax, AUC0-t and AUC0-∞. ANOVA was performed with the PROC GLM of SAS® Version 9.2 (SAS Institute Inc., USA). ANOVA model include sequence, subject nested into sequence, period and formulation effects. Subject nested into sequence was used as error term for checking the significance of Sequence.

The sequence effect was tested at the 0.10 level of significance and all other main effects were tested at the 0.05 level of significance.

Criteria for Bioequivalence

Statistical inference of ritonavir was based on a bioequivalence approach using the following standards:

The ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters Cmax and AUC0-T were all to be within the 80.00 to 125.00% bioequivalence range.

Results

Table 3. Pharmacokinetic parameters for ritonavir (non-transformed values)

	Mean ± SD [N=47]	
	Treatment T (Test) [N= 47]	**Treatment R (Reference) [N= 47]**
$AUC_{(0-t)}$	4436.407 ± 2338.6863	4279.134 ± 2375.6891
$AUC_{(0-\infty)}$	5171.607 ± 2428.7245	4949.134 ± 2492.7397
C_{max}	604.699 ± 301.8686	618.503 ± 351.1751
T_{max}*	4.543 ± 0.6241	4.681 ± 0.6714
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours		
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity		
C_{max} maximum plasma concentration		
T_{max} time for maximum concentration		

Table 4. Statistical analysis for ritonavir (ln-transformed values)

Pharmacokinetic Parameter	**Geometric Mean Ratio Test/Reference (%)**	**Confidence Intervals Lower % - Upper %**	**CV%***
$AUC_{(0-t)}$	104.69%	96.28% -113.84%	24.54
C_{max}	100.91%	92.51% - 110.06%	25.46
$AUC_{0-\infty}$	105.64%	98.50% - 113.30%	20.41
* estimated from the Residual Mean Squares			

Safety data

Blood pressure and radial pulse rate were measured before dosing of investigational products (in the morning of the day of dosing) and at 1, 3, 6 and 13 hours after dosing in each period. Post-dose blood pressure and radial pulse rate were measured within 45 minutes of the scheduled time.

Clinical examination (vital signs (sitting blood pressure, oral temperature, radial pulse rate and respiratory rate), physical examination and systemic examination) was done at the time of admission and before discharge in each period and at the end of study. Subjects were questioned for well-being at the time of recording sitting blood pressure, radial pulse rate and during clinical examination and at the time of ambulatory blood sample collection.

Post study safety assessment (Haematology and Biochemical parameters - SGOT, SGPT, Bilirubin, Creatinine and Urea) was done at the end of study (after collecting last blood sample).

Two adverse events were reported in two subjects during the entire duration of the study. AE were mild in Intensity.

- One adverse event in period-I
- One adverse event in period-II.

There were no significant adverse events were reported during the conduct of the study. No deaths were reported during the entire duration of the study.

The adverse event vomiting observed in two subjects was considered as possible to the drug product and common with the reference product.

Conclusions

Based on the presented bioequivalence study the test formulation Ritonavir 100mg film coated tablet (MAH: Mylan Laboratories) is considered bioequivalent with the reference product Norvir 100mg film coated tablet ((ritonavir) manufactured by Abbott Germany, MAH: Abbott UK).

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The 90% confidence intervals calculated for the primary parameters Cmax and AUC0-t for Ritonavir fall within the 80.00 – 125.00% acceptance range after single dose administration under fed conditions. This is in line with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **.

The two treatments were well tolerated by the subjects (in both periods) enrolled in the study. The adverse events mentioned above are all included in the SmPC and there are no new concerns arising from this study. The two products had similar safety profiles.

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of ritonavir was provided which was considered acceptable by the CHMP. In addition, in the pivotal bioequivalence study the test formulation Ritonavir 100mg film coated tablet (Applicant: Mylan S.A.S) was considered bioequivalent with the reference product Norvir 100mg film coated tablet ((ritonavir) manufactured by Abbott Germany, MAH: Abbott UK). This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	• PR prolongation • Immune reconstitution & inflammatory syndrome (IRIS) Manifesting as Autoimmune Disorders (such as Grave's Disease)
Important potential risks	• Drug-Drug Interaction (DDI) with HCV Products
Missing information	• Limited experience with 100mg tablets in HIV-1-infected patients, including children

Summary of safety concerns	
	• Geriatric population

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed to address the risks.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
PR prolongation	Sections 4.4 and 5.1 of the SPC contain adequate information on this risk. Section 2 of PIL describes this safety concern to patients in adequate detail. Product is POM	None
IRIS Manifesting as Autoimmune Disorders (such as Grave's Disease)	Sections 4.4 and 4.8 of the SPC contain adequate information on this risk. Section 2 of PIL describes this safety concern to patients in adequate detail. Product is POM	None
Drug-Drug Interaction (DDI) with HCV Products	Section 4.5 of the SPC contains adequate information on this risk. Section 2 of PIL describes this safety concern to patients in adequate detail. Product is POM	None
Limited experience with 100mg tablets in HIV-1-infected patients, including children	Sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SPC contain adequate information on this risk. Sections 1 and 2 of PIL describe this safety concern to patients in adequate detail. Product is POM	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Geriatric population	Section 4.2 of the SPC contains adequate information on this risk. Product is POM	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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.

2.7. Product information

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of ritonavir film-coated tablets. The reference product Norvir is indicated for the treatment of HIV infection. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with an open label, two-treatment, two- period, two-sequence, single centre, balanced, single dose, crossover design under fed conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in

line with the respective European requirements. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Ritonavir Mylan met the protocol-defined criteria for bioequivalence when compared with the reference product Norvir. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ritonavir Mylan is favourable in the following indication:

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 CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.