CBG MEB

Public Assessment Report

Scientific discussion

Ritonavir Sandoz 100 mg film-coated tablets

(ritonavir)

NL/H/3150/001/DC

Date: 3 November 2016

This module reflects the scientific discussion for the approval of Ritonavir Sandoz 100 mg film-coated tablets. The procedure was finalised on 8 October 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ritonavir Sandoz 100 mg film-coated tablets, from Sandoz B.V.

The product is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infected adults and children of 2 years of age and older.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Norvir 100 mg, film-coated tablet. Norvir has been registered in Europe by AbbVie Ltd since 1996 via a centralised procedure (EU/1/96/016/005-006).

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Germany, Spain, Finland, France, Italy, Luxembourg, Poland, Romania and Slovenia.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Ritonavir is a white to off white, capsule shaped, film-coated tablet debossed with ‘H’ on one side and ‘R9’ on the other side. Each film-coated tablet contains as active substance 100 mg of ritonavir.

The film-coated tablets are packed in white high density polyethylene (HDPE) bottles closed with white child resistant (screw cap) polypropylene caps.

The excipients are:
Tablet – copovidone, sorbitan laureate (E493), colloidal anhydrous silica (E551), anhydrous calcium hydrogen phosphate and sodium stearyl fumarate.
Film-coating – hypromellose (E464), titanium dioxide (E171), macrogol/PEG MW 400 (E1521), macrogol/PEG MW3350 (E1521), hydroxypropyl cellulose (E463), talc (E553b), colloidal anhydrous silica (E551) and polysorbate 80 (E433).

II.2 Drug Substance

The active substance is ritonavir, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The substance is a white or almost white powder which is practically insoluble in water, freely soluble in methanol and sparingly soluble in acetonitrile Ritonavir exhibits polymorphism and has four chiral centres. The manufacturer produces crystalline form-I.The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The active substance consists of several reaction steps followed by purification. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for several parameters. Batch analytical data demonstrating compliance with this specification have been provided for three production scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three production scaled batches of drug substance that were stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) in accordance with applicable ICH guidelines. The results remained within the specification limits and no changes or trends were observed. Based on the data submitted, a retest period could be granted of 48 months without any special storage conditions.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of the excipients is justified and their functions explained. The qualitative composition of the proposed product is identical to the reference product Norvir 100 mg, film-coated tablets. Dissolution profiles have been provided between the test and the reference batch used in the bioequivalence studies, demonstrating comparable dissolution of test and reference product. The test batch used in the bioequivalence studies was manufactured according to the finalised manufacturing process and composition. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of the preparation of a ritonavir premix in the first step. The process includes steps such as sifting, dry mixing, hot melt extrusion, milling, sifting, final mixing/lubrication, compression and coating. The hot melt extrusion is considered a non-standard procedure. The manufacturing process has been validated according to relevant guidelines. Process validation data on the product have been presented for three production scaled batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur., with exception of the Opadry film-coating material. All specifications, including the in-house specification set for the Opadry, are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, average weight, water content, hardness, dissolution, uniformity of dosage units, related compounds, assay and microbial quality. Except for the tests for water content and related substances, the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production scaled batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for 3 batches on production scale stored at 25°C/60% RH (36 months) and at 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. From the results can be seen that the product remains relatively stable throughout the tested period. The results of photostability studies showed that the product is not sensitive to light. Based on the updated results of the stability studies, the claimed shelf-life of 36 months without any storage restrictions is justified.
In use stability data has been provided demonstrating that the product remains stable for 120 days following first opening of the container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ritonavir Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ritonavir Sandoz is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Norvir which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ritonavir is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH initially submitted one bioequivalence study under fasting conditions. However, according to the SmPC of Ritonavir Sandoz, the dose should be administered with food to optimise the absorption of ritonavir. As stated in the EMA guideline on the investigation of Bioequivalence, for products where the SmPC recommends intake of the reference medicinal product only in fed state, the bioequivalence study should generally be conducted under fed conditions. Therefore, the MAH submitted one additional bioequivalence study, under fed conditions. The two studies are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Ritonavir 100 mg tablets (Hetero Europe S.L., Spain) is compared with the pharmacokinetic profile of the reference product Norvir 100 mg, film-coated tablet (AbbVie Ltd, UK).

The choice of the reference product in the bioequivalence studies is accepted, as Norvir has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Study I – Fasted conditions
Design
An open label, balanced single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 19-43 years. Each subject received a single dose (100 mg) of one of the 2 ritonavir formulations.

The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16 and 24 hours after administration of the products.

Except for the fasting conditions, the design of the study is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Two subjects were withdrawn due to adverse events and two subjects did not return for the second period. One subject was withdrawn from the study due to protocol violations. Therefore, a total of 49 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ritonavir under fasted conditions.

Treatment N=49	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	3893 ± 1689	4208 ± 1839	441 ± 196	1.75 (0.75 – 4.50)	5.7 ± 1.1
Reference	3866 ± 1824	4151 ± 1981	467 ± 227	2.0 (0.50 – 4.50)	5.6 ± 0.9
***Ratio (90% CI)**	1.02 (0.94 – 1.10)	--	0.95 (0.87 – 1.05)	--	--
CV (%)	22.8	--	27.6	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Study II – Fed conditions
Design
An open label, balanced single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 64 healthy male subjects, aged 20-41 years. Each subject received a single dose (100 mg) of one of the 2 ritonavir formulations. The tablet was orally administered with 240 ml water 30 minutes after the start of intake of a high fat high caloric breakfast (fried chicken, Bombay toast, French fries and milk). There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 16, 20, 24 and 36 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Two subjects dropped out on their own Sandoz. One subject was withdrawn due to adverse events (vomiting) and four subjects did not return for the second period. Therefore, a total of 57 were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ritonavir under fed conditions.

Treatment N=57	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	5726 ± 2382	6130 ± 2687	706 ± 388	4.5 (2.00 – 12.00)	8.7 ± 2.8
Reference	6018 ± 2627	6387 ± 2850	771 ± 386	4.5 (1.50 – 5.50)	8.3 ± 2.3
***Ratio (90% CI)**	1.02 (0.94 – 1.10)	--	0.95 (0.87 – 1.05)	--	--
CV (%)	22.8	--	27.6	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Ritonavir Sandoz 100 mg film-coated tablets is considered bioequivalent with Norvir 100 mg, film-coated tablets. Bioequivalence was demonstrated under both fasted and fed conditions.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ritonavir Sandoz 100 mg film-coated tablets.

- Summary table of safety concerns as approved in RMP

Important identified risks	• PR prolongation • Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease)
Important potential risks	• Drug-drug interactions with HCV products • Risk of bleeding • Osteonecrosis
Missing information	• Severe hepatic impairment • Severe renal impairment • Use during pregnancy and lactation • Limited experience with the 100 mg tablet in HIV-1-infected children less than 2 years of age

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Norvir. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Ritonavir Mylan 100 mg film-coated tablets (FR/H/0509/001). The PLs are predominantly identical in content. A comparative overview of the consistency between the two PLs was included in the bridging report. Other differences due to a different company house style have been subject to a successful user test for another product (Levetiracetam Hetero 750 mg film-coated tablets). The test confirms that the MAH's house style does not affect the readability of the tablet. Therefore, the bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ritonavir Sandoz 100 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Norvir 100 mg, film-coated tablets. Norvir is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ritonavir Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 October 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached