CBG MEB

Public Assessment Report

Scientific discussion

Lopinavir/Ritonavir Accord 200 mg/50 mg film-coated tablets

(lopinavir/ritonavir)

NL/H/3142/001/DC

Date: 22 December 2015

This module reflects the scientific discussion for the approval of Lopinavir/Ritonavir Accord 200 mg/50 mg film-coated tablets. The procedure was finalised on 14 April 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 Lopinavir/Ritonavir Accord 200 mg/50 mg film-coated tablets from Accord Healthcare Ltd.

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

The choice of this medicine to treat protease inhibitor experienced HIV-1 infected patients should be based on individual viral resistance testing and treatment history of patients (see sections 4.4 and 5.1 of the approved SmPC).

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 Kaletra 200 mg/50 mg film-coated tablets. Kaletra has been registered in Europe by AbbVie Ltd since 2001 via a centralized procedure EU/1/01/172/001-006.

The concerned member states (CMS) involved in this procedure were Germany and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Lopinavir/Ritonavir Accord 200 mg/50 mg is a yellow, oval, biconvex, film-coated tablet, debossed with “H” on one side and “L3” on other side.

The film-coated tablets are packed in white high density polyethylene (HDPE) bottles containing 2 grams silica gel as desiccant and closed with white propylene caps, or PVC/PVDC-Al blisters.

The excipients are:
Tablet core – copovidone, sorbitanlaurate, colloidal anhydrous silica, sodium stearyl fumarate
Film-coating - hypromellose (E464), titanium dioxide (E171), macrogol (Polyethylene glycol 400) hydroxypropyl cellulose (E463), talc (E553b), colloidal anhydrous silica (E551), macrogol (Polyethylene glycol 3350), yellow ferric oxide (E172), polysorbate 80 (E433)

II.2 Drug Substances

Lopinavir
The active substance lopinavir is an established active substance, described in the European Pharmacopoeia (Ph.Eur). Lopinavir is practically insoluble in water. It exhibits polymorphism and is manufactured in the amorphous form.

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 manufacturing process consists of two chemical reaction steps followed by a purification and drying step. No class 1 organic solvents are used in the process. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The specification for the drug substance is in accordance with the Ph.Eur. monograph and the specification by the drug substance supplier. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches.

Stability of drug substance
Stability data have been presented on three full-scaled batches of drug substance that were stored at 2-8°C (36 months), 25°C/60% RH (36 months) and 40°C/75% RH (6 months).
Except for a slight increase in water content, no trends or changes were observed for any of the tested parameters. All parameters remained within the specified limits. The retest period of 36 months is justified. Although the drug substance complies with the drug substance specification throughout storage at long-term conditions, the applied storage condition is restricted to 'Preserve in tight, light resistant containers, store at temperature between 2°C and 8°C', which is acceptable.

Ritonavir
The active substance ritonavir is an established active substance, described in the Ph.Eur. The drug substance is practically insoluble in water. Ritonavir exhibits polymorphism and is manufactured as polymorphic Form-I. The ASMF procedure is used.

Manufacturing process
The manufacturing process is described in four chemical reaction steps followed by a purification and drying step. No class 1 organic solvents are used in the process. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The MAH has set the specification in line with the Ph.Eur. monograph and the specification by the active sutance manufacturer, with additional requirements for microbial quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches.

Stability of drug substance
Stability data have been presented on at least three production scale batches of drug substance stored at 25°C/60% RH (48 months), 30°C/65% RH (12 months), 30°C/75% RH (48 months) and 40°C/75%RH (6 months). No changes or trends were observed at any of the storage conditions. The claimed retest period of 48 months without any special storage requirements is justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The qualitative composition of the proposed product is identical to the reference product Kaletra. Dissolution profiles have been provided between the test and reference batch used in the bioequivalence study, demonstrating comparable dissolution of test and reference product. The test batch used in the bioequivalence study was manufactured according to the finalized composition and manufacturing process. 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 following steps include processes 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 adequately validated with 2 production-scale batches.

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 appearance, identification, average mass, water content, uniformity of dosage units, dissolution, related substances, 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 two full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for 2 batches on production scale stored at 25°C/60% RH (24 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.
Except for an increase in water content observed at both storage conditions, the drug product remains relatively stable. Results of a photostability study have been presented in the dossier, showing that the drug product is not sensitive to light. Based on the updated results of the stability studies, the claimed shelf-life of 24 months with storage precaution 'This medicinal product does not require any special storage conditions' is justified.

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 Lopinavir/Ritonavir Accord 200 mg/50 mg film-coated tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Lopinavir/Ritonavir Accord 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 Kaletra 200 mg/50 mg, 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

Lopinavir and ritonavir are well-known active substances 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 has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Lopinavir/Ritonavir Accord 200 mg/50 mg (Accord Healthcare Ltd, UK) is compared with the pharmacokinetic profile of the reference product Kaletra 200 mg/50 mg film-coated tablets (AbbVie, UK).

The choice of the reference product in the bioequivalence study is justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male subjects, aged 18 - 43 years. Each subject received a single dose (200 mg/50 mg) of one of the 2 lopinavir and ritonavir formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

A single dose, crossover study to assess bioequivalence is considered adequate. Fasting conditions has been applied, which is acceptable, as the tablet can be taken with or without food.

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
Three subjects did not report at the facility for Period II. Forty-one subjects completed the study and were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of lopinavir under fasted conditions.

Treatment N=41	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	39.3 ± 20.7	42.8 ± 23.9	3.88 ± 1.66	3.3 ± 1.1	5.2 ± 1.7
Reference	37.9 ± 16.7	41.4 ± 19.4	3.68 ± 1.35	4.3 ± 0.9	4.3 ± 0.9
***Ratio (90% CI)**	0.98 (0.86 - 1.11)	--	1.01 (0.92 - 1.12)	--	--

CV (%)	35.7	--	26.7	--	--

$AUC_{0-\infty}$ 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*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of ritonavir under fasted conditions.

Treatment N=41	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1552 ± 962	1703 ± 1085	196 ± 117	4.0 ± 1.2	5.9 ± 1.2
Reference	1474 ± 757	1647 ± 876	173 ± 82	4.3 ± 0.9	6.3 ± 1.6
***Ratio (90% CI)**	0.97 (0.86 - 1.10)	--	1.05 (0.93 - 1.18)	--	--
CV (%)	34.1	--	32.8	--	--

$AUC_{0-\infty}$ 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 study
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 study Lopinavir/Ritonavir Accord 200 mg/50 mg is considered bioequivalent with Kaletra 200 mg/50 mg film-coated tablets.

The MEB has been assured that the bioequivalence study has 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 Lopinavir/Ritonavir Accord.

- Summary table of safety concerns as approved in RMP

Important identified risk (s)	• Lipid elevations • Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorder (such as Graves disease)
Important potential risk (s)	• Drug interaction with HCV protease inhibitors (telaprevir and boceprevir) • QT prolongation with supratherapeutic doses • PR prolongation at therapeutic dosing
Missing information	• Unknown risk of premature birth in women using a lopinavir/ritonavir-based anti-retroviral regimen during pregnancy • Use in elderly patients

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 Kaletra. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study 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

The package leaflet has not been evaluated via a user consultation study. The package leaflet (PL) for Lopinavir/Ritonavir Accord 200 mg/50 mg, film-coated tablets is predominantly identical in content to the currently approved and successfully user tested package leaflet for the originator product Kaletra 200 mg/50 mg film-coated tablets. A comparative overview on the consistency between the two leaflets has been provided in the bridging report.
The company's house style has been subject to a successful user tests for other products. These tests confirm that the house style of the MAH does not affect readability of the leaflet. The member states agree that the package leaflet for Lopinavir/Ritonavir Accord does not need additional testing and that bridging is sufficient.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lopinavir/Ritonavir Accord 200 mg/50 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Kaletra 200 mg/50 mg film-coated tablets. Kaletra 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 Lopinavir/Ritonavir Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 April 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