19 November 2015
EMA/828552/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lopinavir/Ritonavir Mylan

International non-proprietary name: lopinavir / ritonavir

Procedure No. EMEA/H/C/004025/0000

Note

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

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List of abbreviations

API	Active Pharmaceutical Ingredient
AUC	Area under curve
$AUC_{0-\infty}$	Area under the curve from time zero to infinity
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
CEP	Certificate of Suitability of the Ph.Eur.
CI	Confidence Interval
Cmax	Peak Plasma Concentration
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DMF	Drug Master File = Active Substance Master File
DSC	Differential Scanning Calorimetry
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
GC	Gas Chromatography
GC-MS	Gas chromatography mass spectrometry
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HIV	Human Immuno Deficiency Virus
HPLC	High Pressure Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP OES	Inductively Coupled Plasma Optical Emission Spectrometry
IPC	In-process control test
IR	Infrared
Kel	Elimination Rate Constant
KF	Karl Fischer titration
LOA	Letter of Access
LOD	Limit of Detection
LOQ	(1) Limit of Quantification/Quantitation, (2) List of Questions
MA	Marketing Authorisation
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
PIL	Patient Information Leaflet
PP	Polypropylene
PVC	Poly vinyl chloride
QOS	Quality Overall Summary
RH	Relative Humidity
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan S.A.S. submitted on 19 December 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Lopinavir/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 22 May 2014.

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 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) of Directive 2001/83/EC.

The applicant applied for the following indication:

Lopinavir/ritonavir 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 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 Kaletra 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 accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Kaletra 100 mg/25 mg & 200 mg/50 mg, film-coated tablets
- Marketing authorisation holder: AbbVie Ltd
- Date of authorisation: (20 March 2001)
- Marketing authorisation granted by:
  - Community

  Community Marketing authorisation numbers:
  EU/1/01/172/004, EU/1/01/172/005, EU/1/01/172/006, EU/1/01/172/007, EU/1/01/172/008.

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

- Product name, strength, pharmaceutical form: Kaletra 100 mg/25 mg & 200 mg/50 mg, film-coated tablets
- Marketing authorisation holder: AbbVie Ltd
- Date of authorisation: (20 March 2001)
- Marketing authorisation granted by:

- Community

Community Marketing authorisation numbers:
EU/1/01/172/004, EU/1/01/172/005, EU/1/01/172/006, EU/1/01/172/007, EU/1/01/172/008.

■ 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: Kaletra 200 mg/50 mg Filmtabletten
- Marketing authorisation holder: AbbVie Ltd
- Date of authorisation: (20 March 2001)
- Marketing authorisation granted by:
  - Community
  - Member State (EEA): Germany
  - (Community) Marketing authorisation number(s): EU/1/01/172/004
- Bioavailability study number(s): 14-VIN-321

Information on paediatric requirements

Not applicable

Licensing status

The product was not licensed in any country at the time of submission of the application.

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 19 December 2014.
- The procedure started on 22 January 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 April 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 7 May 2015.
- During the meeting on 21 May 2015, the CHMP agreed on the List of Questions to be sent to the applicant..
- The applicant submitted the responses to the CHMP List of Questions on 21 August 2015.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 28 September 2015.
- During the CHMP meeting on 22 October 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 26 October 2015.
- During the meeting on 19 November 2015, 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 Lopinavir/Ritonavir Mylan.

2. Scientific discussion

2.1. Introduction

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 35 million people living with HIV worldwide in 2012. This figure showed an increase from previous years as more people are receiving the life-saving antiretroviral therapy (UNAIDS, 2013). There's no cure for HIV/AIDS, but antiretroviral therapy can dramatically slow the progression of the disease and have reduced AIDS deaths in many developed nations. The world is within reach of providing antiretroviral therapy to 15 million people by 2015. Standard of care for the treatment of HIV-1 infection uses combination antiretroviral therapy (ART) to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablet containing 100 mg of lopinavir and 25 mg of ritonavir or 200 mg of lopinavir and 50 mg of ritonavir as active substances.

Other ingredients are: sorbitan laurate, silica, colloidal anhydrous, copovidone, sodium stearyl fumarate and for the film coating: hypromellose, titanium dioxide (E171), macrogol, hydroxypropyl cellulose, talc, silica, colloidal anhydrous, polysorbate 80.

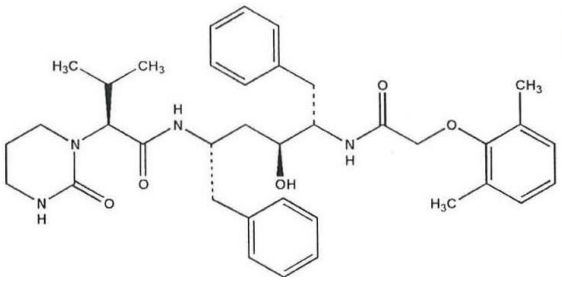
The product is available in HDPE bottle with white opaque polypropylene screw cap with aluminium induction sealing liner wad and desiccant and also in OPA/Al/PVC-aluminium blister as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

Lopinavir

The chemical name of lopinavir is (2S)-N-[(1S,3S,4S)-1-Benzyl-4-[[2-(2,6-dimethylphenoxy)acetyl]-amino]-3-hydroxy-5-phenylpentyl]-3-methyl-2-[2-oxotetrahydropyrimidin-1(2H)-yl]butanamide and it has the following structure:



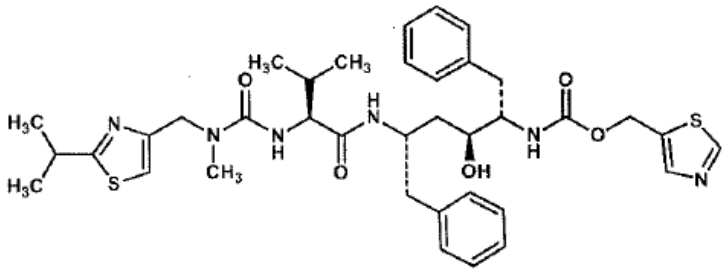
The active substance is a white or yellowish-white, slightly hygroscopic powder, practically insoluble in water.

Lopinavir exhibits stereoisomerism due to the presence of four chiral centres. Enantiomeric purity is controlled routinely by chiral HPLC and specific optical rotation.

Polymorphism has been observed for active substance. Polymorphic form is controlled by the active substance manufacturing process. The manufacturing process of lopinavir involves crystallisation in ethanol and water. Based on the literature, other polymorphs require crystallisation from solvents in absence of water. Batch analysis data provided confirmed that the active substance manufacturer consistently produces the same form (Type-I higher hydrate form).

Ritonavir

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 and it has the following structure:



The active substance is a white or almost white powder, practically insoluble in water.

Ritonavir exhibits stereoisomerism due to the presence of four chiral centres. Enantiomeric purity is controlled routinely by chiral HPLC.

Polymorphism has been observed for active substance and is controlled by a XRD identification test in the active substance specifications. Batch analysis data provided confirmed that the active substance manufacturer consistently produces the same form (Form-I).

As there are monographs of active substances in the European Pharmacopoeia, the manufacturers of the lopinavir and ritonavir active substances have been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for 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 relevant information for both substances has been assessed by the EDQM before issuing the respective Certificates of Suitability.

Lopinavir

The release specifications comply with the Ph. Eur. monograph and the CEP. Additional specifications mentioned in the CEP are for: residual solvents (GC), residual catalysts (ICP-OES), residual compound 2,6-Dimethyl phenoxy acetyl chloride (HPLC).

Ritonavir

The release specifications comply with the Ph. Eur. monograph and the CEP. Additional specifications mentioned in the CEP are for: residual solvents (GC) and polymorphic form identification (XRD).

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented for both active substances.

Batch analysis data of three batches of each active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Lopinavir

Stability data were provided for three production scale batches of the active substance from the proposed supplier stored in a container closure system representative of that intended for the market for 24 months under long term conditions at 30°C/65% RH and 6 months stability at 40°C/75%RH.

The parameters tested are the same as for release except for residual solvents, residual catalysts, residual compound 2,6-Dimethyl phenoxy acetyl chloride.

All tested parameters were within the specifications. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The retest period of 36 months when "stored in an air-tight container" proposed by the API supplier is considered acceptable. The retest period followed by the finished product manufacturer is 12 months and is considered satisfactory as well.

Ritonavir

The CEP mentions a re-test period of 36 months for the active substance stored under nitrogen in a double polyethylene bag (outer black) in a triple laminated aluminium bag placed in polyethylene drum. The retest period followed by the finished product manufacturer is 12 months, even though more than 12 months is proposed by the drug substance manufacturer.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The composition of the finished product is provided.

The aim of the development was to produce a finished product equivalent to Kaletra film coated tablets.

The excipients used are the same as for the reference medicinal product except for the colorant of the film coating. They are well known pharmaceutical ingredients whose quality is compliant with Ph. Eur. standards. The colorants used in Opadry coating material comply with EU regulation 231/2012. 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. Results of active substance/excipients compatibility studies were provided and demonstrated that all the excipients chosen were compatible with the two active substances. Studies results were also provided to justify excipients quantities and grades used.

Lopinavir and ritonavir are water insoluble active substances. When administered as tablet prepared by conventional techniques, the oral bioavailability of these drugs is negligible. In order to have clinically significant concentrations of these drugs, the reference product Kaletra film coated tablets has been made using melt extrusion technique in which both the drugs are present in the form of solid dispersion. Therefore to make a generic bioequivalent product, it was decided to prepare a solid dispersion by melt extrusion where both the substances are present in amorphous form.

The formulation used during bioequivalence studies is the same that the used for marketing.

Bioequivalence study was performed showing bioequivalence between the 200/50 mg strength tablets of the test and reference product.

A request for a biowaiver for the other strength 100 mg/25 mg was proposed on the basis that: both strengths are manufactured by the same manufacturer using the same manufacturing process, the qualitative composition of the different strengths is the same, the composition of the strengths are quantitatively proportional, lopinavir and ritonavir exhibits linear pharmacokinetics in the proposed dose range, and the similarity of the dissolution profiles of the different strengths. The biowaiver request was considered acceptable.

The discriminatory power of the dissolution method has been demonstrated.

The proposed 100 mg/25 mg tablet is similar and comparable to the reference product tablets as far as shape and size is concerned. Therefore acceptability of the 100 mg/25 mg tablet formulation by paediatric patient population should be similar to the reference product acceptability. Before prescribing Lopinavir/ Ritonavir 100 mg/25 mg tablets, infants and young children should be assessed for the ability to swallow intact tablets. The following statement is mentioned in section 4.2 of the SmPC "Before prescribing lopinavir/ritonavir 100/25 mg tablets, infants and young children should be assessed for the ability to swallow intact tablets. For infants and young children unable to swallow tablets, more suitable formulations containing lopinavir/ritonavir should be checked for their availability".

The primary packaging is OPA/Al/PVC-aluminium blister pack or HDPE bottle with white opaque polypropylene screw cap with aluminium induction sealing liner wad and desiccant. The material complies 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 nine main steps: sifting, mixing, hot melt extrusion, milling and sifting, blending, compression, film coating, inspection, packaging. The process is considered to be a standard manufacturing process based on applicant and manufacturing site experience with hot melt extrusion (HME) technique. This was considered acceptable.

Major steps of the manufacturing process have been validated on three pilot batches of each strength. Holding times were validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. The applicant has committed to perform process validation studies on the first three production-scale batches of lopinavir and ritonavir 100 mg/25 mg and 200 mg/50 mg film coated tablets according to the process validation protocol provided.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (HPLC, thin-layer chromatography), colour identification for titanium dioxide , dissolution (HPLC, Ph. Eur.), uniformity of dosage units (Ph. Eur.), related substances (HPLC), assay (HPLC), water (By KF), microbiological test (Ph. Eur.).

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 impurities testing has been presented.

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

Stability of the product

Stability data were provided for 3 pilot scale batches of each strength of finished product stored under long term conditions for 12 months at 25°C/60% RH and for 6 months under accelerated conditions at 40°C/75% RH according to the ICH guidelines. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested according to shelf life specifications described in the section above. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results demonstrated that lopinavir and ritonavir film coated tablets are not photosensitive.

Stability of bulk tablets in the packaging simulating the packaging proposed for transfer of the finished product to the approved Europe repackaging site is also studied for 12 months under long term conditions 25°C/60% RH and 6 months under accelerated conditions 40°C/75% RH. Results demonstrate stability of bulk tablets for 12 months without any special storage precaution.

In-use stability studies are also performed on two batches of the 200 mg/50 mg strength packaged in HDPE bottle. Every pack was opened every day for about 2 min and the condition of the patient withdrawing one

tablet shall be simulated by tilting the bottle. Then the bottles are tightly closed. The procedure continued until 120th day was reached. Results demonstrate stability for 120 days after opening. The need for an in-use shelf-life of 120 days was considered justified. The justification for choosing only the higher strength for performing the in-use stability study was considered acceptable.

The results demonstrate compliance to shelf-life specification. Based on available stability data, the proposed shelf-life of 24 months without any storage conditions as stated in the SmPC (section 6.3) is acceptable as well as the 120 days shelf-life after opening (section 6.3).

Adventitious agents

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

The finished product is presented as film-coated tablet containing 100 mg of lopinavir and 25 mg of ritonavir or 200 mg of lopinavir and 50 mg of ritonavir as active substances. 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

None.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Both lopinavir and ritonavir are peptidomimetic inhibitors of the HIV-1 and HIV-2 proteases (Kaletra SmPC 2014, Norvir SmPC 2014). Protease inhibitors (PIs) prevent the formation of mature virions by blocking the processing of viral Gag-Pol proteins in infected cells (Safrin 2012). Gag and Gag-Pol gene products are translated into precursor proteins as HIV virions mature. These proteins are post-translationally processed by HIV protease to become structural elements of the core of future viral particles (Menéndez-Arias 2002). Protease inhibitors prevent the cleavage of the Gag-Pol polyprotein resulting in the production of immature, noninfectious viral particles. This action effectively terminates the propagation of infection.

Lopinavir has about 10-fold greater potency than ritonavir as a PI (Sham 1998, SBOA 2000), however it has

poor oral bioavailability. Ritonavir, in addition to its PI activity, is a potent inhibitor of CYP3A-mediated lopinavir metabolism and is thus co-administered with lopinavir as a pharmacokinetic enhancer. Given together these compounds produce sustained suppression of HIV replication.

2.3.2. Pharmacokinetics

The pharmacokinetics of ritonavir, lopinavir and the combined administration of these compounds have been extensively evaluated in a variety of animal models. As the current submission is for a fixed dose combination of lopinavir/ritonavir, the non-clinical pharmacokinetics of concomitant lopinavir/ritonavir dosing is the primary focus of this section of the summary. Due to the extent of data available, these sections are presented in summary form, highlighting the principle findings from the development of these compounds as reviewed in US FDA regulatory documents (Summary Basis of Approval documents; SBOA 1995, SBOA 2000). Data from other sources were noted.

2.3.3. Toxicology

The systemic toxicity of lopinavir and/or ritonavir has been evaluated in a variety of species, principally subsequent to oral administration (intravenous acute toxicity also evaluated for ritonavir and lopinavir/ritonavir). In acute toxicity studies, both compounds (and their combination) demonstrated a low potential for acute oral toxicity. In repeat dose toxicity studies, the liver appeared to be the primary organ of toxicity with effects being noted across species (mouse, rat and dog). The mutagenic and clastogenic potential of both compounds (individually and combined) has been evaluated in vitro and in vivo with negative results being obtained in all assays. Carcinogenicity studies with ritonavir and lopinavir/ritonavir were performed in mice and rats and occurrences of hepatic carcinomas/adenomas were noted, though these were considered to be of non-genotoxic origin and not relevant to human exposure. In developmental and reproductive studies, foetal effects were associated with maternally toxic doses of ritonavir or the lopinavir/ritonavir combination.

2.3.4. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Lopinavir and Ritonavir - 100 mg/25 mg and 200 mg/50 mg - film-coated tablets manufactured by Mylan SAS is considered unlikely to result in any significant increase in the combined sales volumes for all lopinavir/ritonavir containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.5. Discussion on non-clinical aspects

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Lopinavir and Ritonavir -100 mg/25 mg and 200 mg/50 mg - film-coated tablets manufactured by Mylan SAS is considered unlikely to result in any significant increase in the combined sales volumes for all Lopinavir/Ritonavir containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.6. Conclusion on the non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. The pharmacology, pharmacokinetics and toxicology data as well known for lopinavir and ritonavir and thus new non-clinical data are not required. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

2.4. Clinical aspects

Exemption

Mylan is applying for a marketing authorisation for 2 different strengths of Lopinavir/Ritonavir film coated tablets (200 mg/50 mg and 100 mg/25 mg).

The bio-equivalence study was performed on Lopinavir and Ritonavir 200 mg/50 mg film coated tablets and the applicant states that the results can be extended to the lower strengths based on the following facts:

- Both the strengths of Lopinavir and ritonavir 100 mg/25 mg and 200 mg/50 mg film coated tablets are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process.
- The excipients included in the composition of the formulation are well established and no interaction with the pharmacokinetics of the active substance is expected.
- The qualitative composition of both the strengths is the same. Lopinavir and ritonavir 100 mg/25 mg and 200 mg/50 mg film-coated tablets are direct scale up/scale down formulations.
- Pharmacokinetics of both drugs i.e. Lopinavir and Ritonavir is linear over the dosage range.
- Both the strengths exhibit similar in-vitro performance. So the dissolution profiles can be considered similar.

In order to accept the biowaiver request, the applicant had to discuss dose linearity over the dose range applied for (100/25 - 200/50 mg), and clarify the issues raised regarding the evaluation of comparative dissolution studies based on similarity factor.

Linear pharmacokinetics of Lopinavir and Ritonavir:
The administration of 200 mg/50 mg of Lopinavir and Ritonavir film-coated tablets twice daily showed a Lopinavir AUC0–12 that was 55% lower than that achieved by the standard 400/100 mg twice daily dose (90% CI 0.40–0.51). The Lopinavir C_{max} and C_{trough} were also significantly lower (46% and 70%, respectively).

Ritonavir pharmacokinetic parameters were lower for the 200 mg/50 mg Lopinavir and Ritonavir film-coated tablets twice daily dose versus the other two doses (400/100 mg and 200/150 mg; twice daily) evaluated.

Further as per the guideline , for the drugs which meet the above clauses and display linear pharmacokinetics, the bioequivalence study should in general be conducted at the highest strength.

Thus study is conducted on 200 mg/50 mg strength Lopinavir and Ritonavir film-coated tablets available in market of submission and the remaining strength (100 mg/25 mg Lopinavir and Ritonavir film-coated tablets) was applied for Biowaiver.

2.4.1. Pharmacokinetics

The applicant has submitted one bioequivalence study in support of this application.

Methods

This was a randomised, open-label, balanced, two-period, two-sequence, two treatment, single dose, crossover comparative oral bioavailability study to establish comparative bioequivalence of Lopinavir/Ritonavir 200 mg/50 mg film coated tablets (Mylan Laboratories Limited Nashik India) and Kaletra 200 mg/50 mg film coated tablets (MAH: Abbvie Ltd) in 72 healthy, adult, human subjects under fasting 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 and tolerability of a single dose of Lopinavir/Ritonavir 200 mg/50 mg.

Study design

Based on the randomised schedule and following an overnight fast of at least 10 hours in both periods each volunteer received a single oral dose of Lopinavir/Ritonavir 200/50 mg film coated tablet (either one tablet of the reference or test product) with 240 ml of water during period I and period II.

Subjects were dosed while in sitting posture and were instructed to remain seated in an upright position for the first 4 hours following drug administration. Drinking water was not permitted one hour before dosing and until one hour post dose. Subjects were confined to the clinical facility from a time adequate to ensure 10 hours fasting until after the 24 hours post dose blood sample collection in each study period.

The two periods were separated by a wash-out phase of at least 8 days.

Blood samples were taken at the following time points: The pre-dose blood sample of 6.0 mL was collected within one hour prior to the dosing. The post-dose blood samples of 6.0 mL each was drawn at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00 and 36.00 hours following drug administration in each period. Adverse events and vital signs have been monitored at the specified time-points during the study. Blood sampling time adjustments are presented in the dossier.

Table 1. Test and reference products

Product Characteristics	Reference product	Test Product
Name	Kaletra® (Lopinavir/Ritonavir)	Lopinavir and Ritonavir
Strength	200 mg/50 mg	200 mg/50 mg
Dosage form	Filmtabletten (Film-coated tablets)	Film-coated tablets
Manufacturer	Abbvie Ltd, Maiden Head SL6 4XE,Vereinigtes Konigreich	Mylan Laboratories Limited, F-4 & F-12, MIDC, Malegaon, Sinnar, Nashik-422 113, Maharashtra, India
Batch number /Lot number	346608D	2006494
Batch size (Biobatch)	--	115,000
Measured content (s) (% of label claim)	Lopinavir: 101.6 % Ritonavir: 96.8 %	Lopinavir: 103.1 % Ritonavir: 98.3 %
Expiry date (Retest date)	May-2016	April 2016
Location of Certificate of Analysis	5312-compar-ba-be-stud-rep, Appendix-16.1.6	5312-compar-ba-be-stud-rep, Appendix-16.1.6
Member State where the reference product is purchased from:	Germany	-
This product was used in the following trials:	Study no.: 14-VIN-321	Study no.: 14-VIN-321

Population(s) studied

72 healthy adult human subjects were enrolled as per the protocol. The study started with 72 subjects and 71 completed the study.

Main inclusion criteria

Healthy, willing, volunteers of age between 18 and 45 years (both inclusive) were selected on the basis of laboratory evaluations during screening, medical history, clinical examination (including physical examination and systemic examination), Chest X-ray (PA view), ECG recordings. Urine screen for drugs of abuse and alcohol breath test were performed on the day of admission in each period.

Protocol deviations

Subject 43 withdrew prior to dosing in period 1 however he was replaced with another subject (no: 1043). Subject 31 reported an adverse event in period 1 hence he was withdrawn from the study.

Population studied

Table 2. Patient disposition

Study population	N
Total no. of subjects completed	71
Total subjects analyzed in Bioanalytical phase	72
Total subjects to be analyzed for safety reasons but not included for pharmacokinetic and statistical analysis	1
Total subjects considered for pharmacokinetic and statistical analysis	71

Analytical methods

Analysis of Lopinavir/Ritonavir was performed using test method AMP-137-01.

This HPLC/MS/MS method involved the estimation of Lopinavir, Ritonavir from human plasma using internal standards Lopinavir D8, Ritonavir D6. 3168 blood samples were to be collected for the 72 subjects however 3132 samples were received since one subject dropped out (36 missing samples were all accounted for the study). 40 samples were re-assayed for Lopinavir and 19 samples were re-assayed for Ritonavir. The reasons for their reanalysis were documented and presented.

Validation of the test method

The method has been validated (MV-07-001-LPVRTV-00) and partially revalidated 2 times. The following parameters were addressed; selectivity of Lopinavir/Ritonavir and the internal standard (IS), calibration curve (linearity), specificity, recovery of both the analyte and the internal standard, precision, accuracy, dilution integrity accuracy and precision, stability of the stock solution (short and long term stability in the biological matrix, bench top, dry extract, coolant, freeze-thaw, in-injector stability), and matrix effect. Each parameter has been assessed and the limits are justified. This is deemed acceptable.

Partial validation was carried out twice, first due to a change in the internal standard for Lopinavir and ritonavir; second to prove instrument ruggedness after change of internal standard for Lopinavir and ritonavir.

Calibration curve range for the partial validation:

1st partial validation: Lopinavir 99.942 ng/ml to 7995.382 ng/ml, Ritonavir: 10.149-811.899 ng/ml

2nd partial validation: Lopinavir 100.007 ng/ml to 8000.520 ng/ml, Ritonavir: 10.001-800.051 ng/ml

The effect of interfering drugs was also studied using the following used medicines in the study due to the adverse effects: Dicyclomine hydrochloride and paracetamol. No effect on the determination of the analyte and the internal standard was observed.

Bioanalytical report

The bioanalytical report was submitted with 20% of the subject chromatograms presented as well as the method SOP. Lopinavir D8 and Ritonavir D6 were used as internal standards (IS) and were sourced from

Clearsynth. A certificate of analysis for the reference standards of Lopinavir, Ritonavir, Lopinavir D8 and Ritonavir D6 has been provided and are deemed acceptable.

For the actual study the calibration curve range was Lopinavir 100.016 ng/ml to 8001.286 ng/ml, Ritonavir: 10.001 – 500.032 ng/ml

Lopinavir: Inter batch accuracy 93.35-103.72%, precision: 2.43-2.87%

Ritonavir: Inter batch accuracy 96.40-99.99%, precision 4.64-5.01%

Incurred Sample Reanalysis

208 samples were identified for incurred sample reanalysis. 99.04% (Lopinavir) and 93.75% (Ritonavir) 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.

Pharmacokinetic variables

Primary parameters: AUC_{0-t} and C_{max}

Secondary parameters: K_{el}, $t_{1/2}$, AUC_%Extrap_obs, $AUC_{0-\infty}$, T_{max}.

Bioequivalence criteria:

Based on the statistical results of 90% confidence interval of the geometric least square mean ratio for the pharmacokinetic parameters C_{max} and AUC_0-t of Lopinavir and Ritonavir then conclusions were drawn whether test formulation is bioequivalent to reference formulation under fasting condition. Acceptance range for bioequivalence is 80.00%-125.00% for 90% confidence intervals of the geometric least square means ratio for C_{max} and AUC_0-t of Lopinavir and Ritonavir.

Statistical methods

Statistical tests like ANOVA, least square means for test and reference formulations, difference between test and reference formulations, intra-subject variability and power were calculated for ln-transformed pharmacokinetic parameters C_{max}, AUC_0-t and $AUC_{0-\infty}$. Geometric least square means of test and reference formulations, its ratio, 90% confidence interval for geometric least square mean ratio and Two One-Sided Tests for 90% confidence interval limits were calculated for pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Lopinavir and Ritonavir.

Results

Table 3. Pharmacokinetic parameters for Lopinavir 200 mg (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	Confidence Intervals		CV %
		Lower%	Upper%	
C_{max} (ng/mL)	93.05	85.55%	101.21%	30.74
AUC_{0-t} (hr*ng/mL)	93.32	84.71%	102.80%	35.62
AUC_{0-inf} (hr*ng/mL)	94.77	86.27%	104.10%	34.54

Table 4. Pharmacokinetic parameters for Ritonavir 50 mg (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	Confidence Intervals		CV %
		Lower%	Upper%	
C_{max} (ng/mL)	91.03	82.76%	100.14%	35.07
AUC_{0-t} (hr*ng/mL)	93.39	85.48%	102.03%	32.42
AUC_{0-inf} (hr*ng/mL)	95.13	87.72%	103.15%	29.57

Safety data

Two subjects (subject number 40 and 59) reported adverse event after administration of test product and three subjects (subject number 53, 31 and 32) reported adverse event after administration of reference product. These were not serious adverse events, the adverse events related to subjects 53, 40, 31 and 32 were possibility related to the product and the adverse event related to subjects 59 was judged as Unlikely to the product. The volunteers that encountered the adverse events completely recovered before the end of the study. No statistical significant differences between the test and reference treatments were observed. No difference in the incidence was observed.

2.4.2. Pharmacokinetic conclusion

Based on the presented bioequivalence study the test product Lopinavir/Ritonavir 200 mg/50 mg film-coated tablets (manufactured by Mylan Laboratories Limited, Nashik, India) is bioequivalent to the Innovator's Kaletra (Lopinavir/Ritonavir) Filmtabletten (Filmcoated Tablets) 200 mg /50 mg of Abbvie Ltd, Maiden Head SL6 4XE.

The results of study 14-VIN-321 with the 200 mg/50 mg film coated tablet formulation can now be extrapolated to Lopinavir/Ritonavir 100 mg/25 mg film coated tablets since the two pending conditions of the biowaiver as stated in the Guideline on the Investigation Bioequivalence CPMP/EWP/QWP/1401/98 Rev 1 are considered resolved.

2.4.3. Pharmacodynamics

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

2.4.4. Additional data

Dissolution studies were provided.

2.4.5. Post marketing experience

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

2.4.6. Discussion on clinical aspects

The applicant has presented one bioequivalence study using the 200 mg/50 mg combination. The results concluded that the test product is bioequivalent to the chosen reference product. There are no major issues in the bioequivalence studies.

2.4.7. Conclusion on clinical aspects

Based on the submitted bioequivalence study results the test product Lopinavir/Ritonavir 200 mg/50 mg film coated tablets of Mylan Laboratories Limited Nashik India and the reference Kaletra 200 mg/50 mg film coated tablets (MAH: Abbvie Ltd) are considered bioequivalent in healthy, adult, human subjects under fasting conditions.

The results of study 14-VIN-321 with the 200 mg/50 mg film coated tablet formulation can be extrapolated to Lopinavir/Ritonavir 100 mg/25 mg film coated tablets according to the conditions set in the guideline on the Investigation Bioequivalence CPMP/EWP/QWP/1401/98 Rev 1.

2.5. Risk management plan

The CHMP received the following PRAC opinion on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3 is acceptable.

The CHMP endorsed this opinion without changes.

The CHMP endorsed the Risk Management Plan version 3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Use in patients with hepatic impairment Increased risk of bleeding in patient with haemophilia Hypertriglyceridaemia and hypercholesterolemia Pancreatitis Hyperglycaemia Immune reactivation Syndrome Osteonecrosis Interaction with CYP3A metabolized drugs Interaction with St John's wort
Important potential risks	Lipodystrophy QT prolongation with supratherapeutic doses and PR prolongation at therapeutic dosing
Missing information	Safety in elderly patients Unknown risk of premature birth in women using lopinavir/ritonavir based antiretroviral regimen during pregnancy

Pharmacovigilance plan

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks: Use in patients with hepatic impairment	Section 4.2, 4.3, 4.4, 4.5 and 4.8 of the SPC contain adequate information on the complications associated with exposure to lopinavir/ritonavir in patients with hepatic impairment. Section 2 and 4 of the PL contain adequate information on the complications associated with exposure	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	to lopinavir/ritonavir in patients with hepatic impairment. Product is POM only.	
Important identified risks: Increased risk of bleeding in patient with haemophilia	Section 4.4, 4.5 and 4.8 of the SPC contain adequate information on the risk of increased bleeding in patients with haemophilia. Section 2 of the PL contain adequate information on the risk of increased bleeding in patients with haemophilia. Product is POM only.	None
Important identified risks: Hypertriglyceridaemia and hypercholesterolemia	Section 4.4 and 4.8 of the SPC contain adequate information on hypertriglyceridaemia and hypercholesterolemia. Section 4 of the PL contains adequate information on hypertriglyceridaemia and hypercholesterolemia. Product is POM only.	None
Important identified risks: Pancreatitis	Section 4.4 and 4.8 of the SPC contain adequate information on pancreatitis. Section 2 and 4 of the PL contain adequate information on pancreatitis. Product is POM only.	None
Important identified risks: Hyperglycaemia	Section 4.4 and 4.8 of the SPC contain adequate information on hyperglycaemia. Section 2 and 4 of the PL contain adequate information on hyperglycaemia. Product is POM only.	None
Important identified risks: Immune reactivation Syndrome	Section 4.4 and 4.8 of the SPC contain adequate information on immune reactivation Syndrome. Section 2 and 4 of the PL contain adequate information on immune	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	reactivation Syndrome. Product is POM only.	
Important identified risks: Osteonecrosis	Section 4.4 and 4.8 of the SPC contain adequate information on osteonecrosis. Section 2 and 4 of the PL contain adequate information on osteonecrosis. Product is POM only	None
Important identified risks: Interaction with CYP3A metabolized drugs	Section 4.3, 4.4, 4.5 and 4.8 contain adequate information on interaction with CYP3A metabolized drugs. Section 2 of the PL contains adequate information on interaction with CYP3A metabolized drugs. Product is POM only.	None
Important identified risks: Interaction with St John's wort	Section 4.3 and 4.5 contain adequate information on interaction with St John's wort. Section 2 of the PL contains adequate information on interaction with St John's wort. Product is POM only.	None
Important potential risks: Lipodystrophy	Section 4.4 and 4.8 contain adequate information on lipodystrophy. Section 2 and 4 of the PL contain adequate information on lipodystrophy. Product is POM only.	None
Important potential risks: QT prolongation with supratherapeutic doses and PR prolongation at therapeutic dosing	Section 4.4, 4.5, 4.8 and 5.1 contain adequate information on cardiac conduction abnormalities. Section 2 and 4 of the PL contain adequate information on cardiac conduction abnormalities. Product is POM only.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information: Safety in elderly patients	None	None
Missing information: Unknown risk of premature birth in women using lopinavir/ritonavir based antiretroviral regimen during pregnancy	Section 4.2, 4.5, 4.6 and 5.3 contain adequate information on complications associated with exposure to lopinavir/ritonavir during pregnancy. Section 2 of the PL contains adequate information on complications associated with exposure to lopinavir/ritonavir during pregnancy. Product is POM only.	None

2.6. Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.7. PSUR submission

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.

3. Benefit-risk balance

This application contains adequate quality, non-clinical and clinical data and bioequivalence has been shown. From a quality, clinical and non-clinical perspective a favourable benefit/risk ratio that is comparable to the reference product can therefore be concluded. One minor issue remains outstanding.

The CHMP, having considered the data submitted in the application 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 Lopinavir/Ritonavir Mylan 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 is favourable and therefore <recommends the granting of the marketing authorisation.

Conditions or restrictions regarding supply and use

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

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.