October, 2021

Public assessment summary report

Name of the Finished Pharmaceutical Product	ALLTERA 50
Manufacturer	Mylan Laboratories Limited, F4 & F12, MIDC, Malegaon, Sinnar, Nashik – 422 113, Maharashtra, India
Active Pharmaceutical Ingredients	Lopinavir and Ritonavir

1. Introduction

Alltera 50 is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in infants and children patients14 days and older, weighing over 3 kg.

The active pharmaceutical ingredients of Alltera 50 are lopinavir and ritonavir. The combination of these APIs is well-established and documented for the treatment of HIV/AIDS. The efficacy and safety of lopinavir and ritonavir are well established based on extensive clinical experience in the treatment of HIV infection.

Comprehensive information on the use of this product and for side effects and warnings,is described in the summary of product characteristics (SmPC).

2. Assessment of quality

Active pharmaceutical Ingredient (API)

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. Batch analysis data provided confirmed that the active substance manufacturer consistently produces the same form.

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

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture:

The development of the final composition of the granules for oral suspension has been described. The aim was to develop a stable product; bioequivalent to Kaletra oral solution (lopinavir/ritonavir

80 mg/20 mg per mL). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. 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 used.

Manufacture of the product

Lopinavir and ritonavir are practically insoluble in water. To improve upon the solubility of the two APIs, hot melt extrusion technology was used to prepare the lopinavir premix blend and ritonavir premix blend as two separate parts, which were then compacted, milled and blended together. The blend was finally filled in sachets. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. This was considered acceptable. Major steps of the manufacturing process have been validated on three batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Specifications:

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), water content (KF), PXRD and microbial limits.

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.

Satisfactory batch analysis results are provided confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Other ingredients:

Other ingredients used in the granules for oral suspension include copovidone, sorbitanmonolaurate, colloidal silicon dioxide, ethyl cellulose, mannitol, acesulfame potassium, sodium stearylfumarate and vanilla flavour. BSE/TSE compliance declarations were provided for all excipients.

Stabilitytesting:

Stability studies have been performed for 24 months at30°C/75%RH as long-term storage condition and for six months at 40°C/75%RH as accelerated condition. The product proved to be quite stable at these conditions. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

3. Assessment of bioequivalence

A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Lopinavir/Ritonavir granules (2 sachets X 40/10 mg) 40 mg/10 mg of Mylan Laboratories Limited, India with Kaletra® (lopinavir/ritonavir) oral solution 80mg/20mg per ml of AbbVie Inc., North Chicago, IL 60064 USA, in normal healthy adult human subjects under fed conditions .

The objective of the study was to compare the bioavailability of the stated Lopinavir/Ritonavir 40mg/10mg granules manufactured byMylan Laboratories Limited, India (test drug) with the reference formulation Kaletra® (AbbVie Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fed conditions.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for lopinavir and ritonavir were analyzed using a validated LC-MS/MS method. The study was performed with 72 participants; data generated from a total of 68 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

4. Conclusion

Based onassessment of data on quality and bioequivalence the assessors considered that the benefit–risk profile ofAlltera 50 was acceptable for the treatment of human immunodeficiency virus (HIV-1) infection in combination with other antiretroviral agents in infants and children patients14 days and older, weighing over 3 kg'.