This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product	[CV001trade name][*]
Manufacturer of Prequalified Product	Hetero Labs Limited Sy.No.321, Biotech Park, Phase - III C/o M/s. Aspiro Pharma Limited Karkapatla (V) Markook (M), Siddipet (D) Telangana State, India
Active Pharmaceutical Ingredient(s) (API)	Remdesivir
Pharmaco-therapeutic group (ATC Code)	Nucleosides and nucleotides excl. reverse transcriptase inhibitors (J05AB16)
Therapeutic indication	[CV001 trade name] is indicated for the treatment of non-severe COVID-19 (oxygen saturation over 90% and no signs of pneumonia or severe respiratory distress) in patients weighing at least 40 kg, who are at high risk of progressing to severe COVID-19. [CV001 trade name] may also be used for the treatment of severe COVID-19 in adults and children (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen.

1. Introduction

[CV001 trade name] is indicated for the treatment of non-severe COVID-19 in patients weighing at least 40 kg, who are at high risk of progressing to severe COVID-19.

[CV001 trade name] may also be used for the treatment of severe COVID-19 in adults and children (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen.

2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

Active pharmaceutical Ingredient (API)

Remdesivir is a white to off-white powder or a yellow non hygroscopic solid. It is soluble in ethanol

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

and only slightly soluble in water. Remdesivir contains six chiral centres and exhibits isomerism.

The manufacture of the API entails several steps and is well described.

The API specifications include tests for description, solubility, identification (IR and UPLC), water content (KF), specific optical rotation, related substances (UPLC), assay (UPLC), pentafluorophenol impurity content (HPLC≤ 0.019%), residual solvents (GC), bacterial endotoxins and microbial limits.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packing material.

Other ingredients

Other ingredients used in the formulation include betadex sulfobutyl ether sodium.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white to yellow lyophilized cake or powder, presented in a 30mL clear tubular glass vial (USP Type I). The filled vial is closed with grey bromobutyl rubber stopper with a flip off aluminium seal.

The objective of the formulation development was to obtain a stable and robust formulation, pharmaceutically equivalent to the WHO recommended comparator product Veklury 100 mg powder for concentrate for solution for infusion (manufactured by Gilead Sciences, Inc). The excipients were selected based on their use in the comparator product. The qualitative and quantitative composition of the multisource and comparator products are the same. A manufacturing process using aseptic filtration was used for the multisource product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.
According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include appropriate tests for description, identification of the API (UV and UPLC), reconstitution time, uniformity of dosage units (by weight variation), pH, water content (KF), assay (UPLC), colour absorbance (UV), related substances (UPLC), visible and sub visible particles, bacterial endotoxins and sterility. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated storage condition in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

According to the WHO guidelines on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products, no bioequivalence study is necessary, when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the

comparator product.
These conditions are fulfilled for [CV001 trade name].

4. Summary of product safety and efficacy

[CV001 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality [CV001 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Veklury® (Gilead Sciences) for which benefits have been proven in terms of clinical efficacy.
The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. Reference is made to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [CV001 trade name] is used in accordance with the SmPC.

Bioequivalence

Not applicable.

Efficacy and Safety

Regarding clinical efficacy and safety, [CV001 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [CV001 trade name] was acceptable for the following indication: ‘treatment of non-severe COVID-19 (oxygen saturation over 90% and no signs of pneumonia or severe respiratory distress) in patients weighing at least 40 kg, who are at high risk of progressing to severe COVID-19 and treatment of severe COVID-19 in adults and children (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen’ and would allow inclusion of [CV001 trade name], manufactured at Hetero Labs Limited, Sy.No.321, Biotech Park, Phase – III, C/o M/s. Aspiro Pharma Limited, Karkapatla (V), Markook (M), Siddipet (D), Telangana State, India in the list of prequalified medicinal products.