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:	[TB328 trade name][1]
Manufacturer of Prequalified Product:	Livzon (Group) Pharmaceutical Factory No.38, Chuangye Road North, Jinwan District, Zhuhai, Guangdong, 519045, P. R. China
Active Pharmaceutical Ingredient (API):	Kanamycin (as sulfate)
Pharmaco-therapeutic group (ATC Code):	Antimycobacterial antibiotics for treatment of tuberculosis. ATC Code J01GB04
Therapeutic indication:	[TB328 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by kanamycin-sensitive strains of *Mycobacterium tuberculosis* in adults and children. Kanamycin is only indicated as a second-line antimycobacterial drug when first-line drugs cannot be used because of resistance or intolerance.

1. Introduction

[TB328 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by kanamycin-sensitive strains of *Mycobacterium tuberculosis* in adults and children. (see Part 4 for full indications).

[TB328 trade name] should be initiated by a health care provider experienced in the management of tuberculosis infection.

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)

Kanamycin sulfate has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [TB328 trade name] is of good quality and manufactured in

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

accordance with WHO Good Manufacturing Practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the solution for injection include sodium bisulfite, sodium citrate, sulfuric acid and water for injection. The excipient specifications are pharmacopoeial based.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is available as a clear colourless to slightly yellow or yellow-green solution, filled in 3 ml type I neutral borosilicate colourless glass ampoule.

Each vial contains the equivalent of 500 mg kanamycin activity. Two strengths were developed: 500 mg and 1000 mg. The two strengths are distinguished by means of the volume of the glass vial.

The solution for injection contains sodium bisulfite, sodium citrate, sulfuric acid and water for injection as excipients. The choice and concentration of excipients used for the finished pharmaceutical product are the same as the WHO recommended comparator product Kanamycin Injection 1g/3ml (Bristol-Myers Squibb). Formulation screening was conducted to evaluate the impact of the composition, pH and sterilization process on the critical quality attributes and to develop a process for manufacturing the finished pharmaceutical product.

Specifications

The specifications for the solution for injection include tests for description, identification of the API (TLC and HPLC) and sulfate, colour of solution, pH, bacterial endotoxins, sterility, visible particulates, particulate matter, filling volume, related substances (HPLC) and assay (HPLC).

Stability testing

Stability studies have been performed on samples at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. Photostability results revealed that a special precautionary statement for protection from light is not necessary.

Chemical and physical stability have been studied for the injection after dilution with the infusion fluids specified in the SmPC. Chemical and physical in-use stability has been demonstrated for 8 hours at 25°C.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The applicant requests a biowaiver as per WHO Technical Report Series, No. 992 which indicates that 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.

The appropriate comparator product is Kantrex (250 mg/ml, Bristol-Myers Squibb) solution for injection. The proposed product is also a solution for injection, i.e. Kanamycin 250 mg/ml (as mono-sulfate). The formulations contain comparable excipients.

As the proposed product meets the biowaiver requirements described above, a biowaiver can be granted.

4. Summary of Product Safety and Efficacy

[TB328 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, [TB328 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Kantrex (250 mg/ml, Bristol-Myers Squibb) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered 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 [TB328 trade name] is used in accordance with the SmPC.

Bioequivalence

N/A

Efficacy and Safety

Regarding clinical efficacy and safety, [TB328 trade.name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [TB328 trade.name] was acceptable for the following indication: '**in combination with other antituberculosis agents for the treatment of tuberculosis caused by kanamycin-sensitive strains of *Mycobacterium tuberculosis* when first-line drugs cannot be used because of resistance or intolerance**' and has advised that the quality, efficacy and safety of [TB328 trade.name] allow inclusion of [TB328 trade.name], manufactured at Livzon (Group) Pharmaceutical Factory, No.38, Chuangye Road North, Jinwan District, Zhuhai, Guangdong, 519045, People's Republic of China, in the list of prequalified medicinal products.