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	[TB319 trade name][*]
Manufacturer of Prequalified Product	Qilu Pharmaceutical Co., Ltd.
Active Pharmaceutical Ingredient(s) (API)	Amikacin (as sulfate)
Pharmaco-therapeutic group (ATC Code)	Aminoglycoside antibacterials (ATC Code J01GB06)
Therapeutic indication	[TB319 trade name] is indicated in combination with other antituberculosis agents for the treatment of multi-drug resistant tuberculosis (MDR-TB) caused by amikacin-sensitive strains of *Mycobacterium tuberculosis*.

1. Introduction

{DotWP-ProductName} is indicated in combination with other antituberculosis agents for the treatment of multi-drug resistant tuberculosis (MDR-TB) caused by amikacin-sensitive strains of *Mycobacterium tuberculosis*.

Amikacin is only indicated as a second-line antimycobacterial agent when first-line medicines cannot be used because of resistance or intolerance.

Consideration should be given to current official treatment guidelines for tuberculosis (e.g., those of the WHO).

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)

A CEP (Certificate of Suitability) issued by the EDQM was submitted, ensuring good manufacturing control and applicability of the Ph. Eur monograph to control the quality of the API.

Other ingredients

Other ingredients include sodium metabisulfite, sodium citrate dihydrate, sulfuric acid (for pH adjustment) and water for injection. No excipient with the risk of transmitting TSE/BSE is used.

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

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource solution for injection is a clear, colourless to slightly yellow liquid filled into colourless 2 ml type I glass ampoules. The injection can be further diluted for intravenous infusion with the infusion solutions specified in the SmPC.

The composition of the multisource injection is qualitatively and quantitatively the same as stated in the label of the comparator product. Sodium metabisulfite acts as antioxidant, the API being susceptible to oxidation. The injection is buffered at a pH of 3.5 to 5.5 (the range specified in the USP and BP monographs for this injection) with sodium citrate and sulfuric acid as pH adjusting agent.

The manufacturing process includes the steps of compounding, filtration, filling and sealing of the ampoules, followed by moist-heat sterilization. To protect amikacin from oxidation during compounding, the antioxidant is dissolved in the buffered water for injections before the API is added. Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture. Process validation have been conducted on three consecutive batches.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC, TLC) and counter ion, pH, colour and clarity, kanamycin A limit (TLC), sodium metabisulfite content, visible particulates, particulate matter, uniformity of dosage units (by weight variation), volume of injection, related substances (HPLC), assay (HPLC), sterility and bacterial endotoxins.

Stability testing

Stability studies have been performed at 30°C/75%RH as long-term storage condition and at 40°C/75%RH as accelerated condition for six months. The data showed an increase of related substances at both storage conditions, marginally significant at accelerated storage. Therefore excursions above 30°C should be avoided. The data support the proposed shelf life and storage conditions as defined in the SmPC. 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 24 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 Amakin or Amikin (250 mg/ml, Bristol-Myers Squibb or Apothecon) or Amikacin sulphate (250 mg/ml, Bedford, US) solution for injection. The proposed product is also a solution for i.m. or i.v. injection, i.e. Amakacin 250 mg/ml solution for injection. The formulations do not contain excipients which may affect availability of amakacin.

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

4. Summary of product safety and efficacy

[TB319 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator products. According to the submitted data on quality and bioavailability, [TB319 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products Amakin or Amikin (250 mg/ml, Bristol-Myers Squibb or Apothecon) or Amikacin sulphate (250 mg/ml, Bedford, US) solution for injection, for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB319 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer 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 [TB319 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB319 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB319 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, safety and efficacy the team of assessors considered that the benefit–risk profile of [TB319 trade name] was acceptable for the following indication: 'treatment of multi-drug resistant tuberculosis (MDR-TB) caused by amikacin-sensitive strains of *Mycobacterium tuberculosis*', and would allow inclusion of [TB319 trade name], manufactured at Qilu Pharmaceutical Co., Ltd., No. 317 Xinluo Road, High-Tech Zone, Jinan, Shandong, P.R. China, in the list of prequalified medicinal products.