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	[TB383 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Unit 2, Plot No. 25-27 Survey No 366 Premier Industrial Estate Kachigam Daman, 396 210 India
Active Pharmaceutical Ingredient(s) (API)	Pyridoxine hydrochloride
Pharmaco-therapeutic group (ATC Code)	Pyridoxine: other plain vitamin preparations (A11HA02)
Therapeutic indication	[TB383 trade name] is for the treatment and prevention of isoniazid-induced peripheral neuropathy in patients at risk of the condition

1. Introduction

[TB383 trade name] is for the treatment and prevention of isoniazid-induced peripheral neuropathy in patients at risk of the condition.

In children, to prevent isoniazid toxicity:

- pyridoxine is indicated for all children treated for drug-resistant tuberculosis with high-dose isoniazid regimens;
- pyridoxine can be given to children treated with isoniazid regimens for severe forms of tuberculosis such as tuberculous meningitis and osteoarticular tuberculosis.

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 for pyridoxine hydrochloride ensuring good manufacturing control and applicability of the Ph.Eur. monograph to control the quality of the API. Test for particle size has been included as an additional parameter in the API specifications of the FPP manufacturer.

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

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 tablet formulation include microcrystalline cellulose, colloidal anhydrous silica, sodium starch glycolate, anhydrous citric acid and magnesium stearate, all being pharmacopoeial controlled. None of the excipients are derived from human or animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white, circular, flat face, bevelled edged, uncoated tablet having a scoreline on one side and plain surface on the other side. The scoreline is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility data. The tablets are packaged in Alu/Alu strips and HDPE bottles.

The objective of the product development was to obtain a stable and robust formulation of pyridoxine hydrochloride 50mg tablets. The quality target product profile was defined and critical quality attributes were identified. The selection of excipients in the formulation of pyridoxine hydrochloride tablets was based on compatibility studies with the API and suitability to achieve the defined quality target product profile. Based on the physicochemical characterisation of the API and the manufacturer's prior experience with higher strengths of the FPP the composition was finalized. Dry mixing and compression process was used to manufacture the finished product. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

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 are pharmacopoeial based and include tests for description, identification of API (UV and HPLC), average weight, hardness, friability, disintegration time, dissolution (UV detection), uniformity of dosage units (by weight variation), related substances (HPLC), assay (HPLC), loss on drying, subdivision of tablets (by weight variation) and microbial limits.

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 condition in the packaging proposed for marketing of the product. The data provided indicates that the product is stable at both 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

No bioequivalence study has been performed. A complete BCS based biowaiver is considered not needed for pyridoxine, but dissolution data should be submitted showing very rapid or rapid dissolution of the 10 and 50 mg tablet. In accordance with this, in vitro dissolution at a pH 1.2, 4.5

and 6.8 has been submitted, showing very rapid dissolution, i.e. >85% within 15 minutes of the 10 and 50 mg tablets in all 3 media, supporting the biowaiver.

4. Summary of product safety and efficacy

[TB383 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product.

The clinical safety of [TB383 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 [TB383 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB383 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, [TB383 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 [TB383 trade name] was acceptable for the following indication: for the treatment and prevention of isoniazid-induced peripheral neuropathy in patients at risk of the condition, and would allow inclusion of [TB383 trade name], manufactured at Macleods Pharmaceuticals Limited, Unit 2, Plot No. 25-27, Survey No 366, Premier Industrial Estate, Kachigam, Daman, India in the list of prequalified medicinal products.