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	[TB401 trade name][*]
Manufacturer of Prequalified Product	S Kant Healthcare Ltd. Plot No. 1802-1805, G.I.D.C. Phase III, Vapi-396 195, Gujarat, India
Active Pharmaceutical Ingredient(s) (API)	Pyridoxine hydrochloride
Pharmaco-therapeutic group (ATC Code)	Pyridoxine: other plain vitamin preparations (A11HA02)
Therapeutic indication	[TB401 trade name] is indicated for the treatment and prevention of isoniazid-induced peripheral neuropathy in patients at risk of the condition.

1. Introduction

[TB401 trade name] is indicated for the treatment of isoniazid-induced peripheral neuropathy.

Pyridoxine is also indicated for preventing isoniazid toxicity in all children receiving high-dose isoniazid regimens for the treatment of drug-resistant tuberculosis.

Pyridoxine can be used for preventing isoniazid-induced peripheral neuropathy in patients at risk of the condition but other formulations of pyridoxine (e.g. tablets containing 10 mg) are more suitable.

In children, to prevent isoniazid toxicity:

- pyridoxine is indicated for all children aged from 4 years treated for drug-resistant tuberculosis with high-dose isoniazid regimens;
- pyridoxine can be given to children aged from 4 years treated with isoniazid regimens for severe forms of tuberculosis such as tuberculous meningitis and osteoarticular tuberculosis.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

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. Though the API is highly soluble in water, a test for particle size has been included

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

as an additional parameter in the API specifications of the FPP manufacturer since a direct compression process is used for manufacture of the tablets.

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 core tablet formulation include microcrystalline cellulose, colloidal anhydrous silica, sodium starch glycolate and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, polyethylene glycol, talc and titanium dioxide. None of the excipients are derived from human or animal origin. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off white, round, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has a break line on one side and is plain on the other side. The break line 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 clear plastic (PVC/PVDC) on aluminium foil blister cards.

The objective of the product development was to obtain a stable and robust formulation of pyridoxine hydrochloride tablets. The quality target product profile for the multisource product was decided based on literature and requirement of the dosage form and the critical quality attributes for the tablets defined. The selection of excipients in the formulation of pyridoxine hydrochloride tablets was based on compatibility studies with the API and the manufacturer's previous formulation experience. Direct compression manufacturing process which is useful for the moisture and heat-sensitive pyridoxine hydrochloride API was selected 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 the API (UV and HPLC), diameter, thickness, disintegration time, water content, dissolution (UV detection), assay (HPLC), related substances (HPLC), uniformity of dosage units (by weight variation), subdivision of tablets (by mass 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 storage 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. For pyridoxine tablets it is only required to provide dissolution profiles in pH 1.2, 4.5, and 6.8 media using the paddle apparatus at 50 rpm or basket apparatus at 100 rpm that demonstrate very rapid or rapid dissolution for the product. In vitro dissolution

data were provided for 12 units per pH condition. At pH 1.2, 4.5 and 6.8, the tablets exhibited rapid dissolution, i.e., > 85% within 15 min, which fulfils the requirements.

4. Summary of product safety and efficacy

[TB401 trade name] has been shown to conform to the relevant standards of quality, efficacy and safety.

The clinical safety of [TB401 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 [TB401 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB401 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, [TB401 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 [TB401 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 [TB401 trade name], manufactured at S Kant Healthcare Ltd., Plot No. 1802-1805, G.I.D.C. Phase III, Vapi-396 195, Gujarat, India, in the list of prequalified medicinal products.