SCIENTIFIC DISCUSSION

This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	Diethylcarbamazine Citrate Tablets 100 mg USP*
Manufacturer of the Prequalified Product:	Eisai Co., Ltd
Active Pharmaceutical Ingredient (API):	Diethylcarbamazine citrate
Pharmaco-therapeutic group (ATC Code):	Anthelmintics (P02CB02)
Therapeutic indication:	Diethylcarbamazine citrate 100 mg tablets are indicated, in combination with albendazole, for large scale preventative chemotherapy interventions for the control of lymphatic filariasis in adults and in children over 2 years.

* Trade names are not prequalified by WHO. This is the local Drug Regulatory Authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Diethylcarbamazine Citrate Tablets 100 mg USPare tablets containing 100 mg diethylcarbamazine citrate equivalent to 50.9 mg of diethylcarbamazine. It is indicated for the preventative chemotherapy interventions for the control of lymphatic filariasis in adults and in children over 2 years following the recommendations of the WHO Global Programme to Eliminate Lymphatic Filariasis.

2. Assessment of Quality

Introduction

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active Pharmaceutical Ingredient (API)

Diethylcarbamazine citrate is described in the Ph.Int., Ph.Eur. and the USP. It is manufactured from N-methylpiperazine, anhydrous citric acid and N,N-diethylcarbamoyl chloride as starting materials. The data provided indicate that diethylcarbamazine citrate is highly soluble in aqueous medium over the pH range 1.2 to 8.8.

The API specifications are pharmacopoeial based and include tests for description, melting point, solubility, identification of the API and citrates, water content, residue on ignition, heavy metals, chromatographic purity (HPLC) and related substances (TLC), assay (HPLC), residual solvents 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 packaging.

Other ingredients

Other ingredients include lactose monohydrate, corn starch, povidone, magnesium stearate and talc. Magnesium stearate is obtained from vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The tablet is white to off-white, uncoated, circular, flat and bevelled edged, debossed with "Є" on one side, and plain with a break-line on the other side. The score line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are supplied in a white HDPE bottle with a white polypropylene cap having an induction seal and with the inclusion of two 2 gram silica gel desiccant packets.

The development of the final composition of the multisource product was mainly based on prior experience with a similar product and analysis of the comparator product, Supatonin® 50 mg tablets. The excipients selected are similar to those of the comparator product, with povidone (K-30) additionally included. Chemical and physical compatibility between the API and povidone (K-30) has been demonstrated.

The tablets are manufactured via a six sequential processes of mixing, wet granulation, drying, milling, lubrication, and tableting. In the manufacturing process development, risk assessment was performed according to the method of failure mode effect analysis (FMEA). The process parameters were optimised to obtain tablets of desired characteristics. The multisource product showed dissolution profiles similar to those of the comparator product. Satisfactory in-process controls have been established.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification, chromatographic purity (HPLC) and related substances (TLC), dissolution (HPLC), uniformity of dosage units, assay (HPLC), loss on drying and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The data showed that the product is quite stable, and no negative trend was evident at both storage conditions. Based on the available stability data, the proposed shelf life, storage conditions and the in-use period after first opening of the bottle as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2012 according to internationally accepted guidelines.

Bioequivalence study of a 100-mg tablet (new formulation) and two 50-mg tablets (Reference formulation) of diethylcarbamazine under fed conditions in healthy subjects. (study no. DEC-E044-001).

The objective of the study was to compare the rate and extent of absorption of the stated diethylcarbamazine citrate 100 mg tablets (Eisai Co Ltd., Tokyo) with the same dose of Supatonin® 50 mg tablets (Mitsubishi Tanabe Pharma Corp., Japan). The comparison was performed as a randomized, two-treatment, two-period, single-dose, open label, crossover study in healthy male and female subjects under fed conditions. Subjects were assigned to receive the following two treatments:

Treatment T:	Test – Diethylcarbamazine citrate 100 mg tablets (diethylcarbamazine citrate 100 mg) Batch no. PEP11015
Treatment R:	Reference – 2 x Supatonin® 50 tablets (diethylcarbamazine citrate 100 mg) Batch no. S001B

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics AUC_{0-t}, AUC_{0-inf}, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for diethylcarbamazine in plasma were analyzed using a validated LC/MS/MS method. The limit of quantification was stated to be 2 ng/ml for diethylcarbamazine.

The study was performed with 14 participants, data generated from a total of 14 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic means (± SD), geometric means (AUC, C_{max}) for diethylcarbamazine as well as statistical results are summarised in the following table:

Diethylcarbamazine

Pharmacokinetic Parameter	Test formulation (T) arithm.mean (± SD)	Reference (R) arithm. mean (± SD)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	2.25 ± 1.17 (2.50)	2.36 ± 1.13 (1.75)	-	-
C_{max} (ng/ml)	598 ± 84 (593)*	619 ± 148 (603)*	98.3	93.9 – 102.8
AUC_{0-t} (ng.h/ml)	7950 ± 1660 (7800)*	7800 ± 2170 (7530)*	103.6	98.2 – 109.3
AUC_{0-inf} (ng.h/ml)	8090 ± 1740 (7920)*	7920 ± 2230 (7650)*	103.6	98.2 – 109.3

* geom. mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding diethylcarbamazine. Accordingly, the test product Diethylcarbamazine citrate 100 mg tablets (Eisai Co Ltd., Tokyo), meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference, Supatonin® 50 mg tablets (Mitsubishi Tanabe Pharma Corp., Japan).

4. 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 Diethylcarbamazine Citrate Tablets 100 mg USP is used in accordance with the conditions as stated in the SmPC.

Bioequivalence

Diethylcarbamazine Citrate Tablets 100 mg USP has shown to be bioequivalent with Supatonin by Mitsubishi Tanabe Pharma Corp., Japan..

Efficacy and Safety

Regarding clinical efficacy and safety, Diethylcarbamazine Citrate Tablets 100 mg USP 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of Diethylcarbamazine Citrate Tablets 100 mg USP was acceptable for the following indication:**for preventative chemotherapy interventions for the control of lymphatic filariasis in adults and in children over 2 years following the recommendations of the WHO Global Programme to Eliminate Lymphatic Filariasis,** and has advised that the quality, efficacy and safety of Diethylcarbamazine Citrate Tablets 100 mg USP allow inclusion of Diethylcarbamazine Citrate Tablets 100 mg USP, manufactured at Eisai Pharmatechnology & Manufacturing Pvt. Ltd., Formulation Block, Eisai Knowledge Centre, Ramky Pharma City (SEZ), Parawada-531019, Visakhapatnam District, Andhra Pradesh, India, in the list of prequalified medicinal products.