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	[NT007 trade name]*
Manufacturer of Prequalified Product	Laboratorios Liconsa, S.A. Avda. Miralcampo, No 7, Polígono Industrial Miralcampo 19200 Azuqueca de Henares Guadalajara 19200 Spain
Active Pharmaceutical Ingredient(s) (API)	Ivermectin
Pharmaco-therapeutic group (ATC Code)	Anthelminthics: avermectines (P02CF01)
Therapeutic indication	[NT007 trade name] is indicated in the treatment of helminthiases and ectoparasitic infestations.

1. Introduction

[NT007 trade name] is indicated in the treatment of helminthiases and ectoparasitic infestations, as detailed in the summary of product characteristics.

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)

Ivermectin is a semi-synthetic product from fermentation of avermectins B1 and B2. It is a mixture comprising about 90% ivermectin B1a (5-O-demethyl-22,23-dihydroavermectin A1a; also referred to as component H2B1a) and 10% ivermectin B1b (5-O-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl)-22,23-dihydroavermectin A1a; also referred to as component H2B1b).

The APIMF of ivermectin, has been accepted through WHO's APIMF procedure. The manufacture of ivermectin entails fermentation, extraction and purification processes to obtain avermectin. Avermectin is further processed through some few chemical steps into ivermectin. The crystalline, same single polymorphic form, controlled by XRPD is consistently produced.

The API specifications are pharmacopoeia based, and include tests for description, identification (IR and HPLC), water content, appearance of solution, specific optical rotation, sulphated ash, related substances (HPLC), assay (HPLC), residual solvents (GC) and particle size distribution.

* 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, pregelatinized starch, citric acid, butylhydroxyanisole (E 320) and magnesium stearate, all being pharmacopoeia controlled. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a round, white tablet with no marks, of approximately 5mm in diameter. The tablets are packaged in aluminium-aluminium blister cards or white HDPE bottles with white polypropylene screw caps. Each screw cap also contains a capsular desiccant.

The aim of the formulation development strategy was to obtain a stable multisource product bioequivalent to the WHO recommended comparator product, Stromectol® 3mg Tablets. The selection of the excipients was primarily based on the excipients used in the comparator product and API-excipient compatibility studies performed during the pre-formulation stage. Following characterization of the comparator product a quality target product profile was defined. Direct compression technology was chosen as an appropriate manufacturing method to reduce the risk on the critical quality attributes of the product. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain tablets of desired characteristics, including dissolution profile similarity with the comparator product. Satisfactory in-process controls have been established.

According to a risk evaluation by the applicant, the FPP has no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC and UV), assay (HPLC), uniformity of dosage units (content uniformity), dissolution (HPLC detection), related substances (HPLC), identification of butylhydroxyanisole (HPLC), butylhydroxyanisole content (HPLC), water content and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with little degradation observed. 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

The following bioequivalence study has been performed in 2018 according to internationally accepted guidelines.

A randomized, open label, balanced, two-treatment, four period, two sequence, single dose, fully replicate, crossover, bioequivalence study of Ivermectin tablets 3 mg manufactured by Laboratorios Liconsa S.A., Spain, for Chemo Research, S.L., with Stromectol® (ivermectin) 3 mg tablets

manufactured by MSD France in normal, healthy, adult, male and female human subjects under fasting conditions (study no. ARL/17/488).

The objective of the study was to compare the bioavailability of the stated ivermectin 3 mg tablet manufactured by/for Laboratorios Liconsa S.A., Spain (test drug) with the reference formulation Stromectol® (MSD) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, fully replicate crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments twice in a randomized fashion:

Treatment T: Test – 1 tablet Ivermectin 3 mg (ivermectin 3 mg) Batch no. DG1802151

Treatment R: Reference – 1 tablet Stromectol® 3 mg (ivermectin 3 mg) Batch no. N005843.

A 7-10 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 72 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for ivermectin were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.2 ng/mL for ivermectin (H2B1a).

The study was performed with 48 participants. Data generated from a total of 28 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for ivermectin as well as statistical results are summarised in the following table:

Ivermectin

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	4.38 ± 1.24	4.23 ± 1.06	-	-
C_{max} (ng/mL)	16.5 ± 5.9 (16.3)	16.6 ± 6.9 (14.8)	109.7	97.8 – 123.1
AUC_{0-t} (ng·h/mL)	289 ± 107 (280)	288 ± 123 (265)	105.7	94.8 – 117.7
AUC_{0-inf} (ng·h/mL)	374 ± 144 --	379 ± 170 --	-	-

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding ivermectin. Accordingly, the test Ivermectin 3 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Stromectol® (MSD).

4. Summary of product safety and efficacy

[NT007 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 and bioavailability, [NT007 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Stromectol® (MSD), for which benefits have been

proven in terms of clinical efficacy. The clinical safety of [NT007 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 [NT007 trade name] is used in accordance with the SmPC.

Bioequivalence

[NT007 trade name] has been shown to be bioequivalent with Stromectol® of MSD.

Efficacy and Safety

Regarding clinical efficacy and safety, [NT007 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 [NT007 trade name] was acceptable for the following indication: 'treatment of helminthiases and ectoparasitic infestations' and would allow inclusion of [NT007 trade name], manufactured at Laboratorios Liconsa, S.A., Avda. Miralcampo, No 7, Polígono Industrial Miralcampo, 19200 Azuqueca de Henares, Guadalajara 19200, Spain, in the list of prequalified medicinal products.