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.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	VERMOX CHEWABLE[1]
Manufacturer of Prequalified Product:	Lusomedicamenta Sociedade Técnica Farmacêutica S.A. Estrada Consiglieri Pedroso, 69 – B Queluz de Baixo 2730-055 Barcarena Portugal
Active Pharmaceutical Ingredient (API):	Mebendazole
International Nonproprietary Name:	Mebendazole 500mg Chewable Tablets
Pharmaco-therapeutic group (ATC Code):	Anthelmintic for oral administration, benzimidazole derivatives ATC code: P02CA01
Therapeutic indication:	Mebendazole 500 mg chewable tablets is indicated for large scale preventive chemotherapy interventions for the control of soil-transmitted helminth infections caused by *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), *Necator americanus* and *Ancylostoma duodenale* (hookworms).

[1]Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Mebendazole 500 mg chewable tablets is indicated for large scale preventive chemotherapy interventions for the control of soil-transmitted helminth infections (see Part 4 for full indications).

Mebendazole 500 mg chewable tablets should be administered by a health care provider experienced in the management of soil-transmitted helminth infections.

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.

Mebendazole is critically insoluble (of BCS low solubility across the physiological pH range), hence particle size distribution (PSD) and polymorphism are considered critical parameters and form part of the FPP manufacturer's API specifications. Mebendazole exhibits polymorphism with 3 polymorphs identified and referred to as polymorphs A, B, and C. It has been demonstrated that the manufacturing process consistently yields polymorphic form C, which is the form required by the Ph.Int. for mebendazole chewable tablets. The acceptance criteria for PSD were set on information obtained for the API lot used in the FPP clinical batch.

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 used in the tablet formulation include povidone, microcrystalline cellulose, crospovidone, magnesium stearate, sucralose and strawberry flavour. None of the excipients used in the manufacture of the tablets are of human or animal origin. Although the flavour excipient is non-compendial, it is composed of ingredients that are widely used in pharmaceutical preparations and are listed in USFDA′s Inactive Ingredient list for approved pharmaceutical products at or below the levels proposed for oral administration.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Mebendazole 500mg Chewable Tablets are round, flat radius-edged white to yellowish chewable tablets, debossed with "M" over "500" on one side and "J" on the other side. The tablets are presented in HDPE bottles.

The dosage form is a rapidly disintegrating chewable tablet, specifically designed to provide a single, age-appropriate formulation for children one to 16 years of age. The product can be either chewed or administered to younger children in the form of a "soft mass" by spoon. The ability to form a soft mass is a function of the characteristics of the formulation and is achieved by adding a small amount of water to a suitably sized spoon and placing a single tablet into the water and allowing the tablet to disintegrate. This soft mass can be ingested by a small child with a substantially reduced risk of choking. The excipients selected are well characterized and widely used in pharmaceutical preparations, supported by API-excipient compatibility studies. The ability of the excipients to perform their function within a certain concentration range of the proposed commercial formulation was demonstrated through a formulation robustness study. In addition, the formulation was optimised for taste by addition of sucralose as a sweetener and strawberry as a flavour.

The API has poor flow characteristics, therefore a direct compression tablet manufacturing process was not feasible. The chewable tablets are manufactured using conventional fluid bed granulation, screening, blending and compression processes. A stress stability study conducted on

the tablets revealed that exposure to heat and high moisture levels triggers conversion of polymorph C to form A. To reduce the potential for conversion of form C to A, the water content in the tablets is controlled at low levels. A science-based criticality analysis approach was used to determine the critical controls for manufacturing processes and to establish appropriate target settings and ranges.
The registration stability batches, one of which was used to supply the phase 3 clinical study, were manufactured at the commercial manufacturing site using the intended commercial process, equipment train and scale.

Specifications

The finished product specifications include tests for tablet appearance, identification of the API (HPLC and UV), assay (HPLC), chromatographic impurity (HPLC), uniformity of dosage units (by mass variation), dissolution (HPLC detection), disintegration time, polymorph A content (NIR; ≤ 12% during shelf life), water content (KF) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 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 results for all parameters at these storage conditions were within agreed acceptance criteria and no negative trend was observed. The polymorphic form remained unchanged. Based on the available stability data, the proposed shelf-life and storage condition of the unopened bottles as stated in the SmPC are acceptable. The in-use storage period after first opening of the bottle is based on in-use stability data.

Conclusion
The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

Not applicable.

4. Summary of Product Safety and Efficacy

WHO guidelines for treatment of soil-transmitted helminth (STH) infestations state that a 500 mg chewable formulation is appropriate for all ages ≥1 year, with no adjustment in dosage needed based on age, weight, or body surface area.
The WHO also recommends that only chewable deworming tablets should be given to children under 5 years old, and that chewable tablets be mixed with water in children under 3 years old (WHO 2006. Preventive chemotherapy in human helminthiasis: coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers.)

Currently, a single dose 500 mg solid oral tablet formulation of mebendazole that can be swallowed is available for children 5 years of age and older. For younger children, prior to the development of this formulation, that tablet needed to be crushed and mixed with water. A recent study (Kernell et al, PLoS NTD 22 June 2018) documented a considerable risk of adverse swallowing events when such an approach is used in young children.

Safety and efficacy data were derived from the following sources:

1) the information contained in US New Drug Application 208398, VERMOX CHEWABLE 500 mg tablets, which included
2) a comprehensive literature review of the use of mebendazole in deworming programmes; and
3) the US FDA review of NDA 208398 (available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208398, accessed April 13, 2019).

Assessment of the efficacy of this chewable formulation was based on one pivotal phase 3 study, GAI3003, which enrolled 295 subjects aged 1-15 years. A total of 278 subjects completed the study. Cure rates showed a statistically significant difference compared to placebo (84% vs 11% for Ascaris, 34% vs 8% for Trichuris). ERR (egg reduction rates) were also statistically significantly better than placebo (98% vs 19% for Ascaris, and 60% vs 11% for Trichuris). Inclusion of hookworm in the product label was based on the published literature which showed a mebendazole cure rate in eight placebo controlled studies of 20% vs 7%, and an ERR of 61% vs 18%.

After administration of the 500 mg chewable tablet, mebendazole absorption is low and the majority of the dose is available in the gastrointestinal tract for the local anthelmintic effect. A high fat breakfast increased AUC and Cmax by 2.9- and 4.1-fold, respectively. This increase in systemic exposure is considered not clinically relevant, and therefore the tablet can be taken without regard of food intake.

The plasma protein binding of mebendazole is 90 to 95%.
The volume of distribution is 1 to 2 L/kg.

Mebendazole is extensively metabolized primarily by the liver into an amino metabolite by hydrolysis and into a hydroxylated metabolite by due to reduction. The metabolites do not contribute to the activity.

Mebendazole and its metabolites undergo some degree of enterohepatic recirculation.
The apparent elimination half-life after an oral dose ranges from 3 to 6 hours. Less than 2% of an oral dose is excreted in urine and the remainder in the feces as unchanged drug or its metabolites.

An impaired hepatic function, impaired metabolism, or impaired biliary elimination may result in higher plasma levels of mebendazole.

The AUC in peadiatric patients aged 1 to <3 years is about 3-fold higher compared to older children, adolescents and adults.

Assessment of the safety of this chewable formulation in study GAI3003 showed that both placebo and mebendazole were safe and well tolerated by the study population. There were no deaths, serious adverse events, or adverse events leading to study agent discontinuation reported, and the formulation was easily swallowed with 2 (1.4%) adverse swallowing events reported of the 144 children in the mebendazole arm.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are considered. Reference is made 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 Mebendazole 500 mg chewable tablets is used in accordance with the Summary of Product Characteristics.

Efficacy and Safety

Study GAI3003 supports the use of this 500 mg chewable mebendazole formulation in the conduct of WHO-supported mass drug administration programmes for the control of soil transmitted helminths. This formulation is as efficacious as the previously deployed 500 mg mebendazole tablet, while improving the ease and safety of administration in children aged 3 and younger, who are at greatest risk of adverse effects from a heavy infestation of intestinal worms.
Regarding clinical efficacy and safety, Mebendazole 500 mg chewable tablets 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, safety and efficacy the team of assessors considered that the benefit–risk profile of mebendazole 500 mg chewable tablets was acceptable for the following indication:**"for the mass treatment of subjects one year of age and older with gastrointestinal infections caused by *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), *Necator americanus* and *Ancylostoma duodenale* (hookworms)"** and has advised that the quality, efficacy and safety of Mebendazole 500 mg chewable tablets allow inclusion of Mebendazole 500 mg chewable tablets, manufactured at Lusomedicamenta Sociedade Técnica Farmacêutica S.A.; Barcarena, Portugal in the list of prequalified medicinal products.