COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Atovaquon/Proguanil HCl Amarox 62.5 mg/25 mg and 250 mg/100 mg, film-coated tablets

(atovaquone and proguanil hydrochloride)

NL/H/4278/001-002/DC

Date: 20 August 2019

This module reflects the scientific discussion for the approval of Atovaquon/Proguanil HCl Amarox 62.5 mg/25 mg and 250 mg/100 mg, film-coated tablets. The procedure was finalised at 19 March 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Atovaquon/Proguanil HCl Amarox 62.5 mg/25 mg and 250 mg/100 mg, film-coated tablets from Hetero Europe S.L.

The 62.5 mg/25 mg product strength is indicated for:

- Prophylaxis of *Plasmodium falciparum* malaria in adults and children weighing 11-40 kg.
- Treatment of acute, uncomplicated *Plasmodium falciparum* malaria in adults and in children weighing ≥5 kg and <11 kg.

The 250 mg/100 mg product strength is indicated for:

- Prophylaxis of *Plasmodium falciparum* malaria in adults and in children weighing more than 40 kg.
- Treatment of acute, uncomplicated *Plasmodium falciparum* malaria in adults and in children weighing 11 kg or more.

Official guidelines and local information on the prevalence of resistance to antimalarial drugs should be taken into consideration. Official guidelines will normally include WHO and public health authorities' guidelines.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Malarone 62.5 mg/125 mg and 250 mg/100 mg film-coated tablets which has been registered in the United Kingdom by GlaxoSmithKline UK since 15 July 2002 and 21 October 1996 respectively. In the Netherlands, Malarone Junior 62.5 mg/25 mg film-coated tablets has been registered since 5 March 2003 by GlaxoSmithKline B.V. through procedure UK/H/0170/002. Malarone 250 mg/100 mg, film-coated tablets was registered by GlaxoSmithKline B.V. since 25 July 2000 in the Netherlands through procedure UK/H/0170/001.

The concerned member states (CMS) involved in this procedure were Germany and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Atovaquon/Proguanil HCl Amarox is a pink, round, biconvex film-coated tablet:
62.5 mg/25 mg - debossed with 'I' on one side and '11' on the other side.
250 mg/100 mg - debossed with 'H' on one side and '175' on the other side.

The tablets contain as active substance 62.5 mg or 250 mg of atovaquone and 25 mg or 100 mg of proguanil hydrochloride.

The film-coated tablets are packed in clear Alu-PVC blisters, Aluminium/Aluminium blisters and HDPE containers

The excipients are:
Tablet core - poloxamer188, microcrystalline cellulose (E460), low-substituted hydroxypropyl cellulose (E463), povidone K30 (E2101), sodium starch glycolate (Type A), magnesium stearate (E572), and silica colloidal anhydrous (E551)
Film-coating - hypromellose (E464), titanium dioxide (E171), macrogol 400 (E1521), macrogol 8000 (E1521), and iron oxide red (E172)

The two tablet strengths are dose proportional.

II.2 Drug Substances

The active substances are atovaquone and proguanil hydrochloride, established active substances described in the European Pharmacopoeia (Ph.Eur.). Atovaquone is a yellow coloured powder which is practically insoluble in water. Proguanil hydrochloride is a white crystalline powder and is sparingly soluble in water. Atovaquone shows polymorphism, and polymorphic Form A is used, the polymorphic form is controlled in the drug substance specification. There are no literature reports on polymorphic forms of proguanil hydrochloride.

The CEP procedure is used for the active substances. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
CEP's have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification for atovaquone is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. It includes additional specifications for identification, heavy metals, residual solvents, particle size, and microbiological examination.
The drug substance specification for proguanil hydrochloride is also considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and CEP. It includes additional specifications for residual solvents, particle size distribution, and microbiological examination.

Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance
Atovaquone is stable for 36 months when stored under the stated conditions. Proguanil hydrochloride is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP's and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process have been justified and are acceptable. The pharmaceutical development of the product has been adequately performed.

The results of one bioequivalence study have been submitted. Comparable dissolution characteristics, between the reference product and the test product were shown and the results support the results obtained in the bioequivalence study with the 250 mg/100 mg strength.

Comparative dissolution data were also provided for the two strengths of the test product, to support the requested biowaiver of strengths, in which one tablet of the 250 mg/100 mg strength was compared with four tablets of the 62.5 mg/25 mg tablet strength. This same dose comparison is acceptable as the solubility of atovaquone in aqueous solutions is very poor. For proguanil, the dissolution profiles in 0.1N HCl, pH 4.5 and pH 6.8 dissolution media are comparable as >85% is dissolved within 15 minutes. In the QC-medium the calculated F2 value is 50, and thereby the dissolution profiles are comparable. For atovaquone, the dissolution is very poor (<15% after 60 min.) in all three media (0.1N HCl, pH 4.5 and pH 6.8), however, the profiles of both strength are comparable, on a visual basis. Also in the QC-

medium, the dissolution profiles are comparable based on the calculated F2 value of 55. As the dissolution profiles of both drug substances in all dissolution media, for both strengths are comparable, the requested biowaiver of strengths is accepted.

Manufacturing process

The manufacturing process consists of sifting, binder solution preparation, dry mixing, wet granulation, drying, sifting and milling, extra granular material sifting, pre-lubrication, lubrication, compression, coating, analytical testing, and packing. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product, with 1.5% coating, has been presented for three batches, for each strength, as well as three batches of the 250 mg/100 mg strength, also with 1.5% coating. Process validation for full scaled batches, with 3% coating, will be performed post authorisation. The product is manufactured using conventional manufacturing techniques.

Control of excipients

All excipients comply with the specifications in their corresponding pharmacopoeia monographs, except Opadry Pink which complies with manufacturer's specifications. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average weight, water content, hardness, dissolution, uniformity of dosage units, related substances, assay, microbiological examination and identification of colourants. The release and shelf-life limits for water content and hardness are not identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from two production scale batches of the 62.5 mg/25 mg strength and three production scale batches of the 250 mg/100 mg strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided on three batches of each strength stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. No clear up- or downward trends are seen in the provided stability data, under long term conditions (25°C/60% RH) nor under accelerated conditions (40°C/75% RH), and independent of the primary packaging. Based on the provided stability data, a shelf-life was granted of three years (36 months), without any special storage condition is acceptable.
Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Atovaquon/Proguanil HCl Amarox has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Atovaquon/Proguanil HCl Amarox is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Malarone which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Atovaquone and proguanil hydrochloride are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

A recent Art 31 EMA's Committee for Medicinal Products for Human Use (CHMP) concluded that the studies conducted at one of the two study sites cannot be accepted in marketing authorisation applications in the EU. Thus, no medicines can be approved on the basis of this studies. Therefore one of the two bioequivalence studies is completely ignored for this application.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Atovaquon/Proguanil HCl Amarox 250 mg/100 mg, film-coated tablets (Hetero Europe S.L., Spain) is compared with the pharmacokinetic profile of the reference product Malarone 250 mg/100 mg, film-coated tablets (Glaxo Wellcome, Spain).

The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH proposed a waiver for the lower tablet strength (Atovaquone/Proguanil HCl 62.5 mg/25 mg), with reference to the Guideline on the Investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1, on the following grounds:

- the pharmaceutical products are manufactured by the same manufacturing process
- the qualitative composition of the different strengths is the same
- the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all strengths
- appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing

Bioequivalence study

Design

An open label, randomized, two-treatment, two-sequence, two-period, cross-over, single dose, comparative bioequivalence study was carried out under fed conditions in 48 healthy male subjects, aged 20-43 years. Each subject received a single dose (250 mg atovaquone and 100 mg proguanil) of one of the two formulations. The tablet was orally administered with 240 ml water after a high fat high calorie breakfast. There were two dosing periods, separated by a washout period of 26 days.

Blood samples were collected at 0.50, 1.00, 1.50, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.33, 5.67, 6.00, 6.50, 7.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00, 60.00 and 72.00 hours after administration of the products.

The design of the study is acceptable. The wash-out period is long enough, sampling period is long enough, and sampling scheme is adequate to estimate the parameters. A single-dose study under fed conditions is appropriate as the SmPC prescribes that the product should be taken with food.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All subjects completed the study. Therefore 48 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of atovaquone under fed conditions.

Treatment N=48	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	52333 ± 1912	2258 ± 695	4.3 (3.3 - 5.7)
Reference	56960 ± 21128	2541 ± 985	4.3 (2.0 - 7.0)
***Ratio (90% CI)**	0.92 (0.85 - 1.00)	0.91 (0.83 – 1.00)	--
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration			

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of proguanil under fed conditions.

Treatment N=48	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	1886 ± 498	124 ± 30	4.3 (2.3 - 8.0)
Reference	1787 ± 505	118 ± 25	4.3 (2.7 - 8.0)
***Ratio (90% CI)**	1.06 (1.02 - 1.10)	1.05 (0.99 – 1.10)	--
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration			

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Atovaquon/Proguanil HCl Amarox 250 mg/100 mg, film-coated tablets is considered bioequivalent with Malarone 250 mg/100 mg, film-coated tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Atovaquon/Proguanil HCl Amarox.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	--
Important potential risks	--
Missing information	• The safety and effectiveness of atovaquone-proguanil for the treatment of malaria in paediatric patients who weigh less than 5 kg and prophylaxis of malaria in paediatric patients who weigh less than 11 kg has not been established. • The safety of atovaquone-proguanil when administered in human pregnancy has not been established.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Malarone. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Malarone 250 mg/100 mg film-coated tablets (content) and Levetiracetam Hetero 750 mg film-coated tablets (layout; PT/H/515/01-04/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Atovaquon/Proguanil HCl Amarox 62.5 mg/25 mg and 250 mg/100 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Malarone 62.5 mg/25 mg and 250 mg/100 mg, film-coated tablets. Malarone is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Atovaquon/Proguanil HCl Amarox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 May 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse