CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Atovaquon/Proguanil HCl Teva 250/100 m, film-coated tablets Atovaquon/Proguanil HCl Teva 62.5/25 mg, film-coated tablets Teva Nederland B.V., the Netherlands

atovaquon/proguanil hydrochloride

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2612/001-002/DC
Registration number in the Netherlands: RVG 111742, 111744

7 October 2013

Pharmacotherapeutic group:	antimalarials
ATC code:	P01BB51
Route of administration:	oral
Therapeutic indication:	prophylaxis and treatment of *P. falciparum* malaria
Prescription status:	prescription only
Date of authorisation in NL:	23 September 2013
Concerned Member States:	Decentralised procedure with BE, DE, ES, FR, LU, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

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 Teva 250/100 mg and Atovaquon/Proguanil HCl Teva 62.5/25 mg, film-coated tablets from Teva Nederland B.V. The date of authorisation was on 23 September 2013 in the Netherlands.

The 62.5/25 mg product is indicated for:
- Prophylaxis of P. falciparum malaria in individuals weighing 11-40 kg.
- Treatment of acute, uncomplicated *P. falciparum* malaria in children weighing 5 kg and <11 kg.

The 250/100 mg product is indicated for:
- Prophylaxis of *P. falciparum* malaria in adults and in children weighing at least 40 kg
- Treatment of acute, uncomplicated *P. 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 SPC.

Atovaquon/Proguanil HCl Teva is a fixed dose combination of atovaquone and proguanil hydrochloride, which acts as a blood schizonticide and also has activity against hepatic schizonts of *Plasmodium falciparum.*
The constituents of the product, atovaquone and proguanil hydrochloride, interfere with two different pathways involved in the biosynthesis of pyrimidines required for nucleic acid replication. The mechanism of action of atovaquone against *P. falciparum* is via inhibition of mitochondrial electron transport, at the level of the cytochrome bc1 complex, and collapse of mitochondrial membrane potential. One mechanism of action of proguanil, via its metabolite cycloguanil, is inhibition of dihydrofolate reductase, which disrupts deoxythymidylate synthesis. Proguanil also has antimalarial activity independent of its metabolism to cycloguanil. Proguanil, but not cycloguanil, is able to potentiate the ability of atovaquone to collapse mitochondrial membrane potential in malaria parasites. This latter mechanism may contribute to the antimalarial synergic effect.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Malarone film-coated tablets, which have been registered in Luxembourg by The Welcome Foundation since 1994. In the Netherlands, Malarone 250/100 mg (NL License RVG 25386) and Malarone Junior 62.5/25 mg (NL RVG 28319) have been registered by GlaxoSmithKline B.V. since 25 July 2000 and 5 March 2003, respectively.
In addition, reference is made to Malarone authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Malarone 250 mg/100 mg film-coated tablets, registered in the Netherlands. A bioequivalence study is the widely accepted means of demonstrating that difference

of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substances
The active substances are atovaquone and proguanil HCl. Proguanil HCl is described in the European Pharmacopoeia (Ph.Eur.*). The active substance atovaquone is not described in the European Pharmacopoeia, however a USP* monograph is available. Atovaquone is a yellow coloured powder, which is freely soluble in tetrahydrofuran, soluble in chloroform and sparingly soluble in acetone. Proguanil HCl is a white or almost white, crystalline powder, which is slightly soluble in water, sparingly soluble in ethanol and practically insoluble in methylene chloride.
There are no literature reports on polymorphic forms of proguanil HCl. Atovaquone exhibits polymorphism. The polymorph manufactured is crystalline Form-A.

The Active Substance Master File (ASMF) procedure is used for both active substances. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Atovaquone and proguanil HCl are both manufactured in four stages. No class I solvents or heavy metal catalysts are used in either of these processes. All starting materials, solvents and reagents used are considered acceptable.

Quality control of drug substance
The drug substance specifications of the MAH are in line with the specifications of the DMF-holders.
Batch analytical data demonstrating compliance with the drug substance specifications have been provided for six (atovaquone) or three (proguanil HCl) batches.

Stability of drug substance
For atovaquone stability studies were conducted on six full-scale batches stored at 25°C/60% RH (36, 24, 12 or 3 months) and 40°C/75% RH (6 months). The stability results showed an increase in the content of sum of all other related compounds and of sum of all related compounds at accelerated conditions. However, all tested parameters remained within the specifications. The claimed retest period of 48 months and the proposed storage condition of "store below 30°C" are justified.
For proguanil HCl stability studies were conducted on three full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). Stability results showed no changes or trends in any of the parameters tested when stored under long-term and accelerated conditions.

The claimed retest period of 36 months and the proposed storage condition of “no special storage condition is required” are justified.

** Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA respectively.*

Medicinal Product

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

The film-coated tablets are packed in clear Alu-PVC blister, Aluminium/Aluminium blister and HDPE containers with 38mm PP child-resistant closure.

The excipients are:
Tablet core – poloxamer 188, microcrystalline Cellulose (E460), low-substituted hydroxypropyl cellulose (E463), povidone K30 (E2101), sodium starch glycolate (Type A), magnesium stearate (E572), colloidal anhydrous silica (E551)
Coating – hypromellose (E464), titanium dioxide (E171), macrogol 400, macrogol 8000, iron oxide red (E172).

The two strengths are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients justified and their functions explained. All excipients used are well known. The choices of the packaging and manufacturing process are justified.
The manufacture and composition of the bio-batches used in the bioequivalence study is identical to the final formulation. The MAH applies for a biowaiver for the 62.5 mg/25 mg strength. Similarity between the 62.5 mg/25 mg test product and the 250 mg/100 mg test product used in the bioequivalence study was adequately demonstrated. Sufficient comparable dissolution data have been provided. From a quality point of view there are no objections against the biowaiver for the lower strength.

Manufacturing process
The manufacturing process consists of dry mixing followed by wet granulation and compression of lubricated blend and can be considered a standard process. Process validation data on the product has been presented for three full-scale batches. The manufacturing process has been adequately validated according to relevant European guidelines for these batches.

Control of excipients
The excipients comply with their respective Ph.Eur. monographs. Opadry specifications are set according to the manufacturer. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, average weight, water content, hardness, dissolution, uniformity of dosage units, related substances, assay, identification of colourants and microbiological examinations. The release and shelf-life limits for all tests are the same except for the limits for water content and hardness. All specifications are acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production-scale batches of each strength, demonstrating compliance with the release specifications.

Stability of drug product

Stability data on the product has been provided for three pilot-scale batches of each strength stored at 25°C/60% RH (24 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 Alu-Alu blisters, Alu-PVC blisters and HDPE containers (30's and 100's count). Stability results showed that all tested parameters remained within the specifications. The drug product has been shown to be photostable in a study performed in conformity with ICH topic Q1B. The proposed shelf-life of 36 months and the proposed storage condition "This medicinal product does not require any special storage conditions" are justified.
For the HDPE container in-use stability data have been provided in accordance with "The note for guidance on in-use stability testing of human medicinal products" (CPMH/QWP/2934/99. Two batches stored in HDPE containers (100 tablets) of each strength were tested towards the end of shelf-life. The results showed no changes or trends in any of the parameters tested after 30, 60 or 90 days. Based on the provided data an in-use stability period of 90 days can be granted.

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.2 Non-clinical aspects

This product is a generic formulation of Malarone, which is available on the European market. 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.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of atovaquone or proguanil hydrochloride released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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 a bioequivalence study in which the pharmacokinetic profile of the test product Atovaquon/Proguanil HCl Teva 250/100 mg (Teva Nederland B.V., NL) is compared with the pharmacokinetic profile of the reference product Malarone 250 mg/100 mg film-coated tablets (GlaxoSmithKline BV, NL).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 44 healthy male subjects, aged 19-40 years. Each subject received a single dose (250/100 mg) of one of the 2 atovaquone/proguanil HCl formulations. The tablet was orally administered with 240 ml water, 30 min after start of intake of a high fat breakfast. The breakfast consisted of 240 ml milk (155 kcal), 10 g sugar (40 kcal), toast (bread 50 g and butter 10; 211

kcal), omelette 100 g (261 kcal) and vegetable cutlet 170 g (278 kcal). There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.33, 4.67, 5.0, 5.5, 6.0, 7.0, 8.0, 12.0, 16.0, 24.0, 36.0, 48.0, 60.0 and 72.0 hours after administration of the products.

A single-dose, crossover study under fed conditions to assess bioequivalence for atovaquone and proguanil is considered adequate. Considering the long elimination half-life of atovaquone as well as for proguanil, evaluation of the extent of absorption based upon $AUC_{0\text{-}72h}$ is acceptable. The length of the washout period was also acceptable.

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
Three subjects were withdrawn due to vomiting in period I. One subject was withdrawn before period II due to an adverse event (hypocalcaemia). Four subjects did not report for check in for period II and one subject was withdrawn due to vomiting in period II. Thirty-five subjects completed the study and were included in the analysis.

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

Treatment N=35	**$AUC_{0\text{-}72}$** ng.h/ml	**$AUC_{0\text{-}\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	88475 ± 28263	--	3104 ± 959	5.1 ± 1.2	76 ± 27
Reference	89431 ± 36089	--	3248 ± 1066	4.8 ± 1.4	77 ± 35
***Ratio (90% CI)**	0.99 (0.92 - 1.06)	--	0.94 (0.87 - 1.02)	--	--
CV (%)	16.7	--	18.9	--	--

$AUC_{0\text{-}\infty}$ area under the plasma concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$ area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

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

Treatment N=35	**$AUC_{0\text{-}72}$** ng.h/ml	**$AUC_{0\text{-}\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2004 ± 579	--	130 ± 31	4.6 ± 1.3	19 ± 6
Reference	1928 ± 517	--	125 ± 31	4.8 ± 1.1	18 ± 4
***Ratio (90% CI)**	1.04 (1.00 - 1.08)	--	1.04 (0.99 - 1.10)	--	--

CV (%)	9.9	--	12.2	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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
$t_{1/2}$ half-life
**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of atovaquone and proguanil under fasted conditions, it can be concluded that Atovaquon/Proguanil HCl Teva 250/100 mg and Malarone 250 mg/100 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

In studies with HIV-infected patients, the absolute bioavailability of a 750 mg single dose of atovaquone tablets taken with food is 23% with an inter-subject variability of about 45%. Dietary fat taken with atovaquone increases the rate and extent of absorption, increasing AUC 2-3 times and C_{max} 5 times over fasting. Patients are recommended to take the tablets with food or a milky drink. Proguanil hydrochloride is rapidly and extensively absorbed regardless of food intake. In view of this, the bioequivalence study under fed conditions is considered appropriate.

Biowaiver
The formulations are dose-proportional and are manufactured by the same manufacturer and manufacturing process.
Dissolution tests at different pH values have shown comparable dissolution between the 250/100 mg and the 62.5/25 mg strengths. Considering the fact that atovaquone is a low solubility drug and the support of linear pharmacokinetics up to a dose of 750 mg and the linear pharmacokinetics of proguanil, the use of the highest strength is acceptable. A biowaiver for the 62.5/25 mg strength has been granted.

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).

Risk management plan
The combination of atovaquone and proguanil was first approved in 1994, and there is now more than 10 years post-authorisation experience with the active substances. The safety profile of atovaquone and proguanil can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Malarone.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants,

followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The leaflet scored 100% for locating the information necessary to answer the questions very easily or easily and 100% for understanding of this information. The leaflet passed the defined success criteria and did not need revision. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Atovaquon/Proguanil HCl Teva 250/100 mg and Atovaquon/Proguanil HCl 62.5/25 mg Teva, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Malarone 250/100 mg and Malarone Junior 62.5/25 mg 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Teva 250/100 mg and 62.5/25 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 29 May 2013. Atovaquon/Proguanil HCl Teva 250/100 mg and Atovaquon/Proguanil HCl Teva 62.5/25 mg, film-coated tablets were authorised in the Netherlands on 23 September 2013.

The date for the first renewal will be: 29 May 2018.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to perform process validation on three maximum scale batches of each of the product strengths.
- The MAH committed to evaluate the specification limit for hardness test in shelf-life (stability) upon the completion of the stability study.
- The MAH committed to finish the ongoing stability studies.
- The MAH committed to place the first two production batches for each of the strengths on stability studies for 6 months at accelerated conditions and over the proposed shelf life at normal conditions.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached