Public Assessment Report

Scientific discussion

Atovaquon Glenmark 750 mg/5 ml oral suspension

(atovaquone)

NL/H/3762/001/DC

Date: 12 March 2018

This module reflects the scientific discussion for the approval of Atovaquon Glenmark 750 mg/5 ml oral suspension. The procedure was finalised on 5 January 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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
EDMF	European Drug Master File
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 Glenmark 750 mg/5 ml oral suspension from Glenmark Pharmaceuticals Europe Limited.

The product is indicated for acute treatment of mild to moderate Pneumocystis pneumonia (PCP, caused by Pneumocystis jiroveci, formerly classified as P. carinii) (alveolar - arterial oxygen tension difference [(A-a) DO2] < 45 mmHg (6 kPa) and oxygen tension in arterial blood (PaO2) ≥ 60 mmHg (8 kPa) breathing room air) in patients who are intolerant of co-trimoxazole therapy.

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 Wellvone 750 mg/5 ml, oral suspension (NL license RVG 21070) which has been registered in the Netherlands by GlaxoSmithKline B.V. since 24 March 1997 through mutual recognitions procedure FR/H/0112/001.

The concerned member state (CMS) involved in this procedure was 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 Glenmark is a bright yellow liquid. Each ml of suspension contains 150 mg atovaquone and a unit dose of 5 ml contains 750 mg atovaquone.

The oral suspension is packed in a 250 ml high density polyethylene bottle with a child resistant polypropylene closure. A 5 ml measuring spoon (polypropylene) is included.

The excipients are: benzyl alcohol, xanthan gum, poloxamer 188, hypromellose, saccharin sodium dihydrate, citric acid monohydrate, sodium citrate dihydrate, purified water and Tutti Frutti Flavour (051880 AP0551) containing flavouring substances, maize maltodextrin, propylene glycol and alpha-tocopherol.

II.2 Drug Substance

The active substance is atovaquone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a yellow, crystalline powder and insoluble in water and very slightly soluble in 0.1N sodium hydroxide. Atovaquone exists as crystalline form-I, form-II and form-III. For this product, the form III is produced. The drug substance exhibits isomerism. There is a chiral centre for exhibiting enantiomerism. For this product, the trans-isomer is produced. Atovaquone is non-hygroscopic.

The Active Substance Master File (ASMF) procedure is used for the active substance. 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
The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional tests for solubility, heavy metals, identification, residual solvents, polymorphic identification and a microbiological limit test. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for 4 full scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. No significant changes, trends or out of specification results were observed. The active substance is stable for 30 months when stored under the stated conditions.

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 main development studies performed concern the particle size distribution of the atovaquone in the suspension, and the optimisation of the excipients concentrations. The excipients are well known and the choices of the packaging and manufacturing process are justified. The composition of the clinical batches is in accordance with the final composition and the manufacturing process is conform the process described. The batch size of the biobatch is full scaled. In all except 0.1M NaOH dissolution media 0% was dissolved for both test and reference product. In NaOH dissolution was found to be similar, more than 85% was dissolved within 15 minutes. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of 10 steps has been validated according to relevant European guidelines. Process validation data on the product have been presented for 3 full scale batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. with exception of the tutti frutti flavour. In addition to the pharmacopoeial tests, the excipients xanthan gum, poloxamer 188 and hypromellose are also subject to in-house tests. The specifications are acceptable. The composition of the flavouring and specification have been provided. Information that the used flavouring is save by claiming compliance with Regulation 1334/2008 and Commission Regulation (EU) No 231/2012 has been provided.

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 appearance, identity, deliverable volume, pH, sedimentation, viscosity, related substances, dissolution, assay, preservative content, particle size, uniformity of mass of delivered doses from multi-dose containers and microbiological tests. The release and shelf-life limits are identical with exception of viscosity. 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 for 3 full scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided from 3 full scaled stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months) in accordance with the ICH stability guideline. The batches were stored in the proposed packaging. At accelerated conditions no trends or out-of-specifications results are observed. At long term conditions a decrease in pH was observed. Given this decrease in pH the applicant tightened the release specification as requested in order to prevent out-of-

specifications results at the end of shelf life when released at the lower pH limit. Based on the provided data the proposed shelf life of 24 months can be granted. A photostability study, performed in line with the ICH Note for Guidance, demonstrated no light sensitivity of the drug product. As Atovaquon Glenmark is a multi-dose product, in-use stability testing has been performed. In the in-use stability studies no changes are observed. The in-use shelf life of 21 days can be granted.
The storage condition: 'This medicinal product does not require any special storage conditions. Do not refrigerate or freeze.' is acceptable.

Specific measures for 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 Glenmark 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 Glenmark 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 Wellvone 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 is a well-known active substance 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 which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Atovaquon Glenmark 750 mg/5 ml oral suspension (Glenmark Pharmaceuticals Europe Limited, UK) is compared with the pharmacokinetic profile of the reference product Wellvone 750 mg/5 ml, oral suspension (GlaxoSmithKline B.V, NL).

The choice of the reference product in the bioequivalence studies is accepted.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out high-fat fasted conditions in 38 healthy male subjects, aged 22-44 years. Each subject received a single dose (750 mg/5 ml) of one of the 2 atovaquone formulations. The oral suspension was orally administered with 240 ml water after a high calorie, high fat breakfast. The breakfast consisted of toast, omelette, chicken cutlets and milk. There were 2 dosing periods, separated by a washout period of 33 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00, and ambulatory at 72.00, 96.00, 120.00, 168.00, 216.00, 264.00 and 336.00 after administration of the products.

The design of the study is acceptable. The wash-out period of 33 days is considered sufficient in light of the reported t1/2 of 2 to 3 days. 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

One subject discontinued on his own accord and one subject was withdrawn from the study due to protocol non-compliance. Therefore, 36 subjects completed the study and 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=36	**AUC_{0-72}** µg.h/ml	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	338 ± 112	765 ± 210	833 ± 195*	9.23 ± 2.19	5.0 3.0 – 12.0	101 ± 28*
Reference	343 ± 115	787 ± 236	867 ± 277**	9.52 ± 2.47	4.5 4.5 – 12.0	95 ± 22**
***Ratio (90% CI)**	0.99 (0.93 - 1.05)	0.97 (0.92 - 1.04)	0.99*** (0.93 - 1.05)	0.98 (0.91 - 1.06)	--	--

$AUC_{0-\infty}$ 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
* N=32 & ** N=30 & *** N=28, as subjects with residual area > 20% were excluded

**ln-transformed values*

Conclusion on bioequivalence studies:

The 90% confidence intervals calculated for AUC_{0-72}, AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Atovaquon Glenmark 750 mg/5 ml oral suspension is considered bioequivalent with Wellvone 750 mg/5 ml, oral suspension.

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 Glenmark.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hypersensitivity - Lower atovaquone plasma levels associated with diarrhoea or difficulty taking with food - Interaction with other medicinal products and other forms of interaction
Important potential risks	None
Missing information	- Use in pregnancy and lactation - Use in children - Use in elderly - Use in patients having renal and hepatic impairment

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 Wellvone. 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

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 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Atovaquon Glenmark 750 mg/5 ml oral suspension has a proven chemical-pharmaceutical quality and is a generic form of Wellvone 750 mg/5 ml, oral suspension. Wellvone 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 Glenmark with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 January 2018.

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