COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Hydroxychloroquinesulfaat DOC 200 mg, film-coated tablets

(hydroxychloroquine sulphate)

NL/H/4266/001/DC

Date: 5 September 2019

This module reflects the scientific discussion for the approval of Hydroxychloroquinesulfaat DOC 200 mg, film-coated tablets. The procedure was finalised at 15 January 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

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 Hydroxychloroquinesulfaat DOC 200 mg, film-coated tablets from DOC Generici S.r.l.

The product is indicated in adults for:
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Discoid lupus erythematosus
- Dermatological conditions caused or aggravated by sunlight
- Prevention and treatment of uncomplicated malaria caused by *Plasmodium vivax*, *P. Falciparum*, *P. ovale* and *P. malariae*

The product is indicated in children for:
- Juvenile idiopathic arthritis (in association with other treatments)
- Systemic lupus erythematosus
- Discoid lupus erythematosus
- Treatment of acute attacks and prophylaxis of malaria caused by *Plasmodium vivax*, *P. falciparum*, *P. ovale* and *P. malariae*.

Chloroquine-resistant *P. falciparum*, and increasingly chloroquine-resistant *P. vivax*, occur in many regions, which limits the usability of hydroxychloroquine in these regions.

Official guidelines and local information about the occurrence of anti-malarial drug resistance need to be taken into account. Examples of this include WHO and public safety 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 Plaquenil 200 mg film-coated tablets which has been registered in Denmark by Sanofi-Aventis Denmark A/S since 5 May 1958. In the Netherlands, Plaquenil 200 mg film-coated tablets has been registered since 21 November 1966 (NL License RVG 00853).

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

II. QUALITY ASPECTS

II.1 Introduction

The product is a white, round, biconvex film-coated tablet embossed with "200" on one side and plain on the other side.

Each film-coated tablet contains 200 mg of hydroxychloroquine sulphate, which corresponds to 154.8 mg of hydroxychloroquine.

The product is packed in transparent PVC/aluminium blister packs.

The excipients are:
Tablet core – maize starch, calcium hydrogen phosphate dihydrate (E341), colloidal anhydrous silica (E551), polysorbate 80 (E433), dried maize starch, talc (E553b) and magnesium stearate (E470b).
Tablet coating - hypromellose (E464), macrogol 6000, titanium dioxide (E171) and talc (E553b).

II.2 Drug Substance

The active substance is hydroxychloroquine sulphate an established active substance described in the European Pharmacopoeia (Ph. Eur.). It is a white or almost white crystalline powder. Hydroxychloroquine sulphate is freely soluble in water and practically insoluble in ethanol (96%) and ether. The drug substance is not hygroscopic and the same polymorphic form is manufactured consistently.

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.

<u>Manufacturing process</u>
The manufacturing process consists of two stages followed by blending. The starting materials, intermediates and reagents are adequately characterised. The process is regarded to be sufficient to ensure full control of the quality of the final substance and is therefore considered suitable.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. It meets the requirements of the monograph in the Ph. Eur. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three commercial scale batches stored at 25°C/60% RH (five years) and 40°C/75% RH (six months). All values remain well within the proposed limits. On the basis of the stability data the claimed retest period of 60 months.

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. For maize starch an overage is used. The overage has been adequately justified by the MAH. Several development formulations were tried in order to obtain a tablet with comparable dissolution characteristics as the reference product Plaquenil. The pharmaceutical development of the product has been adequately performed.

One bioequivalence study was submitted to demonstrate bioequivalence between Hydroxychloroquinesulfaat DOC and the reference medicinal product, Plaquenil. The test batch shows deviating dissolution characteristics compared to the reference product at pH 1.2, 4.5 and 6.8, with the exception of the release medium water. The possible reasons for the observed discrepancies in the *in vitro* dissolution between test and reference product have been addressed and justified. In this case the outcome of the bioequivalence study prevails.

Manufacturing process
The manufacturing process consists of mixing, granulation, sifting and sizing, drying, lubrication, compressing, film-coating and packing. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for six batches, three with the minimum commercial batch size and three with the maximum commercial batch size, in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the European Pharmacopoeia (Ph.Eur.). 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 appearance, identity, assay, average weight, related substances, dissolution, uniformity of dosage units, and microbiological

quality. The release and shelf-life requirements/limits are 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 six batches, three with the minimum commercial batch size and three with the maximum commercial batch size, 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 for six commercial scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. No significant changes are observed in any of the parameters tested. The drug product remains stable throughout the test period. The proposed shelf-life of three years, when stored in the original package in order to protect from light, is justified.

Photostability testing was performed on the drug product according to ICH Guidelines for direct exposure and in the blister packaging as proposed for marketing. It can be concluded from the study that the drug product is photo-stable in the proposed packaging.

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 Hydroxychloroquinesulfaat DOC 200 mg, film-coated tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. One post-approval commitment was made:

- The ASMF-holder committed to update the specification and test method of Hydroxychloroquine Sulfate with inclusion of non routine control of two solvents in the final API release specification immediately after analytical method validation activities and method transfer activities are completed. The finished product manufacturer confirmed that it will include the solvents in the finished product manufacturer's API specifications, as part of the variation to update the ASMF.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Hydroxychloroquinesulfaat DOC 200 mg, film-coated tablets 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 Plaquenil 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

Hydroxychloroquine sulfate 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 Hydroxychloroquinesulfaat DOC 200 mg, film-coated tablets (DOC Generici S.r.l., Italy) is compared with the pharmacokinetic profile of the reference product Plaquenil 200 mg film-coated tablets (Sanofi Aventis, Denmark).

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.

Bioequivalence study

Design

An open label, randomised, single-period, two-treatment, parallel, balanced, single dose bioequivalence study was carried out in 112 healthy male subjects, aged 18-44 years. 56 subjects were included in each arm. Each subject received a single dose (200 mg) of one of the two hydroxychloroquine formulations. The tablet was orally administered with 240 ml water 30 minutes after serving of standardised high-calorie and high-fat breakfast. There was one dosing period.

Blood samples were collected pre-dose and at 0.50, 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, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design of the study is acceptable. A parallel design was chosen, as the elimination half-life of hydroxychloroquine is very long (about 50 days)

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

Two subjects were discontinued post dose on medical ground, due to the adverse event of vomiting. One subject was dosed with the reference product; the other was dosed with the test product. Therefore 110 subjects (55 subjects per arm) were eligible for pharmacokinetic analysis.

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

Treatment N=55 per arm	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	4104 ± 1159	202 ± 68	4.5 ± 1.1
Reference	4098 ± 1227	211 ± 67	4.6 ± 1.1
*Ratio (90% CI)	1.01 (0.91 – 1.11)	0.95 (0.85 – 1.05)	--
CV (%)	30.2	34.6	--

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 Hydroxychloroquinesulfaat DOC 200 mg, film-coated tablets is considered bioequivalent with Plaquenil 200 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 Hydroxychloroquinesulfaat DOC.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Overdose - Severe hypoglycaemia - Visual disturbance - Gastrointestinal effects
Important potential risks	- Patients with hepatic and renal insufficiency - Cardiac conduction disorders - Haematological effects - Musculoskeletal effects - Medical dermatitis - Use in pregnancy - Use in breastfeeding
Missing information	None

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 Plaquenil. 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 (PL) 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 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Hydroxychloroquinesulfaat DOC 200 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Plaquenil 200 mg film-coated tablets. Plaquenil 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 Hydroxychloroquinesulfaat DOC with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 January 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
NL/H/4266/IA/001/G	- Change in the batch size (including batch size ranges) of the finished product; up to 10-fold compared to the originally approved batch size - Change in the specification parameters and/or limits of the finished product; deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	-	23-04-2019	Approved	-
NL/H/4266/IA/002/G	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance: • addition of a new specification parameter to the specification with its corresponding test method • Change in the specification parameters and/or limits of the finished product; deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	-	25-07-2019	Approved	-