

Public Assessment Report

National Procedure

Hydroxychloroquine Sulphate 200mg Film-coated Tablets

Quinoric 200mg Film-Coated Tablets

PL 17907/0017

Bristol Laboratories Ltd

LAY SUMMARY

Hydroxychloroquine Sulphate 200mg Film-coated Tablets Quinoric 200mg Film-Coated Tablets

This is a summary of the public assessment report (PAR) for Hydroxychloroquine Sulphate 200mg Film-coated Tablets/Quinoric 200mg Film-Coated Tablets. It explains how Hydroxychloroquine Sulphate 200mg Film-coated Tablets/Quinoric 200mg Film-Coated Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Hydroxychloroquine Sulphate 200mg Film-coated Tablets/Quinoric 200mg Film-Coated Tablets. Hydroxychloroquine Sulphate 200mg Film-coated Tablets and Quinoric 200mg Film-Coated Tablets are identical to each other apart from the difference in product names and will be collectively referred to as Hydroxychloroquine Sulphate 200mg Film-coated Tablets in the remainder of this report.

For practical information about using Hydroxychloroquine Sulphate 200mg Film-coated Tablets patients should read the package leaflet or contact their doctor or pharmacist.

What are Hydroxychloroquine Sulphate 200mg Film-coated Tablets and what are they used for?

Hydroxychloroquine Sulphate 200mg Film-coated Tablets is a 'generic medicine'. This means that Hydroxychloroquine Sulphate 200mg Film-coated Tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Plaquenil 200mg Film-coated Tablets (Zentiva).

Hydroxychloroquine Sulphate 200mg Film-coated Tablets can be used to treat rheumatoid arthritis (inflammation of the joints), juvenile idiopathic arthritis (in children), discoid and systemic lupus erythematosus (a disease of the skin or the internal organs) and skin problems which are sensitive to sunlight.

How do Hydroxychloroquine Sulphate 200mg Film-coated Tablets work?

Hydroxychloroquine Sulphate 200mg Film-coated Tablets work by reducing inflammation in people with autoimmune diseases (this is where the body's immune system attacks itself by mistake).

How are Hydroxychloroquine Sulphate 200mg Film-coated Tablets used?

Hydroxychloroquine Sulphate 200mg Film-coated Tablets should be swallowed whole with a meal or a glass of milk. The tablets should not be crushed or chewed.

The recommended dose in adults, including the elderly, is one or two tablets each day. Children and adolescents should take one tablet each day. This medicine is only suitable for children who weigh more than 31 kg (around 5 stones).

This medicine can only be obtained with a prescription.

What benefits of Hydroxychloroquine Sulphate 200mg Film-coated Tablets have been shown in studies?

Because Hydroxychloroquine Sulphate 200mg Film-coated Tablets is a generic medicine, studies in patients have been limited to tests to determine that Hydroxychloroquine Sulphate 200mg Film-coated Tablets are bioequivalent to the reference medicine, Plaquenil 200mg Film-coated Tablets. Two medicines are bioequivalent when they produce the same levels of active substance in the body.

What are the possible side effects of Hydroxychloroquine Sulphate 200mg Film-coated Tablets?

Because Hydroxychloroquine Sulphate 200mg Film-coated Tablets is a generic medicine, its benefits and possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Hydroxychloroquine Sulphate 200mg Film-coated Tablets, see section 4 of the package leaflet. For the full list of restrictions, see the package leaflet.

Why is Hydroxychloroquine Sulphate 200mg Film-coated Tablets approved?

It was concluded that, in accordance with EU requirements, Hydroxychloroquine Sulphate 200mg Film-coated Tablets have been shown to be comparable to Plaquenil 200mg Film-coated Tablets. Therefore, the MHRA decided that, as for Plaquenil 200mg Film-coated Tablets, the benefits of Hydroxychloroquine Sulphate 200mg Film-coated Tablets are greater than their risks.

What measures are being taken to ensure the safe and effective use of Hydroxychloroquine Sulphate 200mg Film-coated Tablets?

Suitable safety information has been included in the Summary of Product Characteristics and the package leaflet for Hydroxychloroquine Sulphate 200mg Film-coated Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Hydroxychloroquine Sulphate 200mg Film-coated Tablets

The Marketing Authorisation for Hydroxychloroquine Sulphate 200mg Film-coated Tablets was granted on 15 February 2007.

This summary was last updated in July 2015.

The full PAR for Hydroxychloroquine Sulphate 200mg Film-coated Tablets follows this summary.

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I Introduction

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Hydroxychloroquine Sulphate 200mg Film-coated Tablets (PL 17907/0017) could be approved on 15 February 2007. This prescription only medicine (POM) is used in adults for the treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight and in the paediatric population for the treatment of juvenile idiopathic arthritis (in combination with other therapies), discoid and systemic lupus erythematosus.

This application was made under Article 10(1) of Directive 2001/83/EC, as amended, as a so-called generic application. The reference medicinal product for this application is Plaquenil 200mg Film-coated Tablets (PL 17780/0748), which is currently authorised to Zentiva but was first authorised to Sterling Winthrop Group Limited, UK on 5 January 1973. The reference product has been authorised in the EEA for at least 10 years, therefore, the legal basis of this application is acceptable.

Antimalarial agents like chloroquine and hydroxychloroquine have several pharmacological actions which may be involved in their therapeutic effect in the treatment of rheumatic disease, but the role of each is not known. These include interaction with sulphadryl groups, interference with enzyme activity (including phospholipase, NADH- cytochrome C reductase, cholinesterase, proteases and hydrolases), DNA binding, stabilisation of lysosomal membranes, inhibition of prostaglandin formation, inhibition of polymorphonuclear cell chemotaxis and phagocytosis, possible interference with interleukin 1 production from monocytes and inhibition of neutrophil superoxide release.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

No new non-clinical data were submitted, which is acceptable given that the application is for a generic version of an originator product that has been in clinical use for over 10 years.

A bioequivalence study comparing the proposed product to Plaquenil 200mg Film-coated Tablets was submitted with the application. Assurance has been provided that the study has been conducted according to the principles of Good Clinical Practice (GCP).

The RMS considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder

has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The lack of a Risk Management Plan (RMP) with this application is acceptable as the application was submitted on 7 March 2014.

Since Hydroxychloroquine Sulphate 200mg Film-coated Tablets are intended for generic substitution, their use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

The MHRA considered that the application could be approved and a Marketing Authorisation was granted on 5 February 2007.

II Quality aspects

II.1 Introduction

The tablets are white, circular, biconvex film coated tablets embossed with 'BL' on one face and '200' on the other.

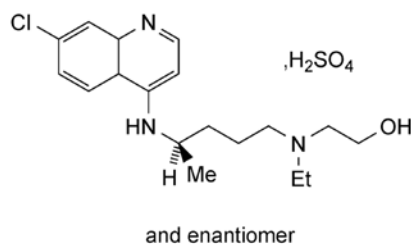
The excipients in the medicinal products are maize starch, calcium hydrogen phosphate dihydrate, colloidal anhydrous silica, polysorbate 80, purified talc, magnesium stearate, hypromellose, titanium dioxide and macrogol 6000.

The tablets are presented in Al/PVC blisters or HDPE tablet containers. Pack sizes of 60 tablets have been authorised for the Al/PVC blister packs and pack sizes of 100, 500 and 1000 tablets have been authorised for the HDPE tablet containers. Not all pack sizes may be marketed.

II.2 Drug Substance

Chemical name: *RS*-2-*N*-[4-(7-chloro-4-quinolylamino)pentyl]-*N*-ethylaminoethanol sulfate

Structure:



Molecular formula: $C_{18}H_{26}ClN_3O, H_2SO_4$

Molecular weight: 434.0

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with

the relevant specifications. Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Acceptable certificates of analysis have been provided for all reference standards used.

Batch analysis data have been provided and comply with the proposed specification.

Specifications have been provided for all aspects of the container-closure system used to store the active substance. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated to support the proposed retest period.

II.3 Medicinal Product

Pharmaceutical development

The aim of the pharmaceutical development of Hydroxychloroquine Sulphate 200mg Film-coated Tablets was to develop a generic version of the innovator product, Plaquenil 200mg Film-coated Tablets.

All excipients comply with their European Pharmacopoeia monographs. Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients contain materials of animal or human origin.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability of the product

Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years. The storage precaution 'store in the original package' applies to product stored in the blister packs and 'store in the original container' and 'keep the container tightly closed' apply to product stored in the HDPE tablet containers.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a Marketing Authorisation is recommended.

II.5 SmPC, PIL and labelling

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following product labelling was approved:

Blister:

HYDROXYCHLOROQUINE SULPHATE 200 mg FILM-COATED TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501	HYDROXYCHLOROQUINE SULPHATE 200 mg FILM-COATED TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501	FXXX EXP.
HYDROXYCHLOROQUINE SULPHATE 200 mg FILM-COATED TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501	HYDROXYCHLOROQUINE SULPHATE 200 mg FILM-COATED TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501	FXXX B.No.
HYDROXYCHLOROQUINE SULPHATE 200 mg FILM-COATED TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501	HYDROXYCHLOROQUINE SULPHATE 200 mg FILM-COATED TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501	FXXX EXP.
HYDROXYCHLOROQUINE SULPHATE 200 mg FILM-COATED TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501	HYDROXYCHLOROQUINE SULPHATE 200 mg FILM-COATED TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501	FXXX B.No.

Carton:



☒ No special storage precautions required. Store in the original package.
CHILDREN.
KEEP OUT OF THE REACH AND SIGHT OF patient information leaflet.
For further information please read the enclosed Take as directed by the physician.
For oral administration only.
ingredient.
Hydroxychloroquine Sulphate as the active Each film-coated tablet contains 200 mg Film-coated Tablets
Hydroxychloroquine Sulphate 200 mg Film-coated Tablets

PLACE DISPENSARY LABEL HERE

BN :
EXP: :

PL 17907/0017 **POM**
Code: BL 501
PL Holder:
Bristol Laboratories Ltd.,
Berkhamsted, Herts, HP4 1EG, UK.

Labels:

Each film-coated tablet contains 200 mg Hydroxychloroquine Sulphate as the active ingredient.

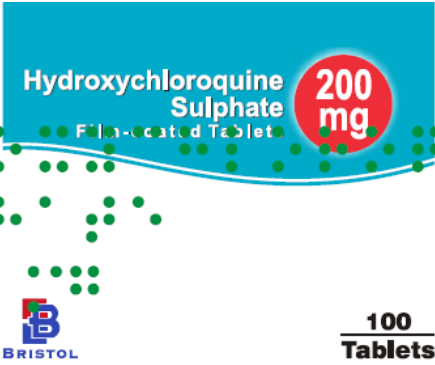
For oral administration only.
Take as directed by the physician.

For further information please read the patient information leaflet provided.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

No special storage precautions required.

Store in the original container, tightly closed.



BN :
EXP :
PL 17907/0017
Code: **BL 501** **POM**
PL Holder:
Bristol Laboratories Ltd.,
Berkhamsted, Herts, HP4 1EG, UK.

Each film-coated tablet contains 200 mg Hydroxychloroquine Sulphate as the active ingredient.

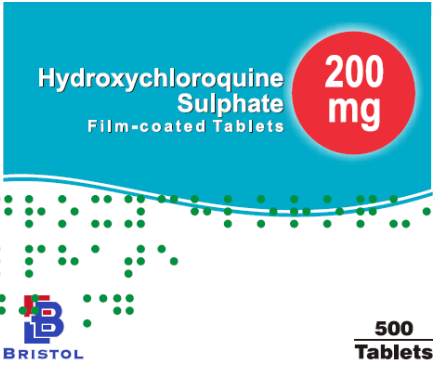
For oral administration only.
Take as directed by the physician.

For further information please read the patient information leaflet provided.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

No special storage precautions required.

Store in the original container, tightly closed.



BN :
EXP :
Code: **BL 501**
POM
PL 17907/0017
PL Holder:
Bristol Laboratories Ltd.,
Berkhamsted, Herts, HP4 1EG, UK.

Each film-coated tablet contains 200 mg Hydroxychloroquine Sulphate as the active ingredient.


For oral administration only.
Take as directed by the physician.

For further information please read the patient information leaflet provided.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

No special storage precautions required.

Store in the original container, tightly closed.



BN :
EXP :
PL 17907/0017
Code: **BL 501** **POM**
PL Holder:
Bristol Laboratories Ltd.,
Berkhamsted, Herts, HP4 1EG, UK.

III Non-clinical aspects

III.1 Introduction

No new non-clinical data have been submitted and none are required for applications of this type. The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory.

III.2 Pharmacology

No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology

No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since the formulation of Hydroxychloroquine Sulphate 200mg Film-coated Tablets is intended for generic substitution, it will not lead to an increased exposure to the environment. An ERA is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

The grant of a Marketing Authorisation is recommended.

IV Clinical aspects

IV.1 Introduction

The applicant has submitted a bioequivalence study in support of this application. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

A randomised, one-way parallel, open-label, single dose, fasting, bioequivalence study of Hydroxychloroquine Sulphate 200mg Film-coated Tablets versus Plaquenil[®] 200mg tablets was conducted in healthy, non-smoking, male subjects. The Plaquenil[®] 200mg tablets that were used in the study were authorised to Sanofi-Synthelabo, which was the Marketing Authorisation Holder of the reference product at the time of the study.

The use of a one-way parallel design is acceptable due to the long elimination half-life for the drug.

The results of the study are as follows:

Parent drug

	Test (Least squares mean)	Reference (Least squares mean)
C _{max} (ng/mL)	144.58	158.00
AUC ₀₋₇₂ (ng.h/mL)	3329.62	3333.33
AUC _∞ (ng.h/mL)	Not Provided	Not Provided
T _{max} (h)*	4.28	3.86

C_{max} is within the range 135-422ng/mL and T_{max} is within range 1.5-7.0h.

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals

	Parent drug
C _{max} (ng/mL)	90.8 (90% CI: 79.3; 104)
AUC ₀₋₇₂ (ng.h/mL)	99.5 (90% CI: 87.4; 113)
AUC _∞ (ng.h/mL)	Not Provided

The 90% confidence intervals for test/reference lie within the acceptance criteria

Based on the submitted bioequivalence data, it can be considered that the applicant's Hydroxychloroquine Sulphate 200mg Film-coated Tablets is a generic medicinal product to Plaquenil 200mg Film-coated Tablets.

IV.3 Pharmacodynamics

No new pharmacodynamic data are required for this application and none have been submitted.

IV.4 Clinical efficacy

No new clinical efficacy data are required for this application and none have been submitted.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data are presented for this application and none is required. No new or unexpected safety issues arose during the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The lack of a Risk Management Plan (RMP) with this application is acceptable as the application was submitted on 3 March 2004.

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended.

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, as amended.

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

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with hydroxychloroquine sulphate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

VII Steps taken for assessment

1	The MHRA received the marketing authorisation application on 3 March 2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 7 November 2005
3	Following assessment of the application the MHRA requested further information relating to the clinical dossier on 6 December 2005 and the quality dossier on 23 February 2006
4	The applicant responded to the MHRA's requests, providing further information on clinical dossier on 8 March 2006 and the quality dossier on 29 August 2006
5	Following assessment of the responses the MHRA requested further information relating to the clinical dossier on 6 October 2006 and the quality dossier on 24 October 2006
6	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 23 November 2006 and the clinical dossier on 7 January 2007
7	Following assessment of the responses the MHRA requested further information relating to the clinical dossier on 12 January 2007
8	The applicant responded to the MHRA's request, providing further information on the clinical dossier on 14 February 2007
9	The application was determined on 15 February 2007

VIII Steps taken after initial authorisation

Date submitted	Application type	Scope	Outcome
29/01/2008	Type IB variation	To add the brand name 'Quinoric 200mg Film-Coated Tablets' on the product licence for	Approved - 18/09/2008

		Hydroxychloroquine Sulphate 200mg Film-Coated Tablets.	
18/04/2011	Type IA variation	1) To register other change(s) to the DDPS that do not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes, update of acronyms, naming changes of functions/procedures. 2) To register the change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH.	Approved - 31/07/2011
14/09/2011	Renewal	Renewal of Marketing Authorisation	Approved - 12/10/2011
09/06/2010	Type II variation	To update sections 4.4 (Special warnings), 4.8 (Undesirable effects), 4.9 (Emergency procedures), 5.3 (Preclinical safety) and 6.2 (Incompatibilities) of the SmPC in line with the innovator SmPC (Plaquenil tablets).	Approved - 22/12/2011
13/02/2012	Type IB variation	To update sections 4.4 (Special Warnings) and 4.8 (Undesirable effects) of the SmPC to include Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrosis (TEN) in line with the PhVWP recommendation. As a consequence, the leaflet has been updated.	Approved - 19/04/2012
13/07/2012	Type IA variation	1) To register a change in the contact details of the QPPV. 2) To register other changes to the DDPS that does not impact on the operation of the pharmacovigilance system.	27/10/2012
28/08/2012	Type IB variation	To update the SmPC and leaflet, in line recommended wording hydroxychloroquine	07/11/2012

		products following the publication of PdAR for an EU Art 45 WS procedure on 04 June 2012.	
15/07/2013	Type IA variation	To introduce a new PSMF and a summary of Pharmacovigilance System.	29/07/2013
22/11/2013	Type IA variation	To register an update of 4.4, 4.8 of SmPC and PIL to bring in line with recent PRAC recommendations (EMA/PRAC/550442/2013) published on 3 October 2013 by the European Medicines Agency.	10/12/2013
24/10/2014	Label and leaflet - self certification	This notification is submitted under article 61(3) of Council Directive 2001/83/EC. 1) Change in the trademark sign from TM to ® 2) The statement 'keep out of the reach and sight of children' has been amended to 'keep out of the sight and reach of children' in carton mock-up to keep in line with QRD template.	30/10/2014
07/03/2014	Type II variation	To introduce a new bioequivalence study for this product prior to initiation of a Mutual Recognition Procedure.	15/06/2015

Annex 1 – Variation assessment report

Type of application:	National variation
Reference product used in the bioequivalence studies:	Plaquenil 200mg Film-coated Tablets Sanofi-Aventis Denmark
Original product:	Plaquenil 200mg Film-coated Tablets Marketing authorisation holder: Sanofi Syntelabo Ltd First authorisation in EU: 1973/01/05, UK

Introduction

This is a Type II, national variation application for Hydroxychloroquine Sulphate 200mg Film-coated Tablets of Bristol Laboratories Ltd. The aim of this variation is to introduce a new bioequivalence study for this product prior to initiation of a Mutual Recognition Procedure.

In support of this variation application, an open label, randomised, single-period, two-treatment, parallel, balanced, single dose oral bioequivalence study of Hydroxychloroquine Sulphate 200mg Film-coated Tablets and Plaquenil 200mg Film-coated Tablets in healthy adult human subjects was conducted under fed conditions.

As the tablets are to be taken with food, conducting the study under fed conditions is appropriate.

Due to the very long half life of hydroxychloroquine (>40 hours) a parallel design rather than the standard cross-over design with AUC truncated at 72 hours was used in the bioequivalence study.

Subjects were housed in the clinical facility at least 8 hours before dosing. Study drug was taken orally with water after a supervised high-fat, high-calorie breakfast. Blood samples were collected prior to drug administration and at intervals up to 72 hours post dose.

112 healthy male volunteers were enrolled in the study. Two subjects were replaced after randomisation but prior to dosing. All except two subjects (dropped-out after dosing due to vomiting) completed the study and were included in the pharmacokinetic and statistical analysis. No major protocol deviations were reported. Inclusion and exclusion criteria were presented and were acceptable for a BE study and for the product under investigation.

Drop outs: Two subjects due to vomiting.

Pharmacokinetic variables and statistical methods:

The pharmacokinetic parameters C_{max} , AUC_{0-72} , T_{max} were determined. Primary variables were considered to be AUC_{0-72} and C_{max} . PK parameters for each individual were tabulated and graphically presented. AUC_{0-72} was calculated using the linear trapezoidal rule. None of the pre-dose samples contained detectable levels of hydroxychloroquine.

Criteria for conclusion of bioequivalence:

For both, AUC_{0-72} and C_{max} , the 90% confidence interval for the ratio of test/reference for the population means derived from logarithmically transformed data should lie between the conventional 0.80 and 1.25 limits.

Assessor's comment:

The pharmacokinetic parameters calculated are appropriate for a single dose study. Standard bioequivalence criteria are proposed for AUC_{0-72} and C_{max} .

Results

PK evaluation:

Table 2: Test & Reference Geometric mean, Ratio, 90% Confidence Intervals, Inter-Subject CV (%) and Power based on Log-transformed data for Hydroxychloroquine (n=110) (55 subjects per treatment arm)

Pharmacokinetic parameter	Geometric mean (Test)	Geometric mean (Reference)	Ratio (%)
AUC_{72} (ng.hr/ mL)	3946.197	3921.033	100.64
C_{max} (ng/ mL)	190.743	201.328	94.74

Pharmacokinetic parameter	90% Confidence Intervals	Inter-Subject CV (%)	Power
AUC_{72} (ng.hr/ mL)	(91.66%;110.51%)	30.221	0.9883
C_{max} (ng/ mL)	(85.19%;105.36%)	34.552	0.9646

Safety evaluation:

No serious adverse events (AEs) were reported during the study. A total of six AEs occurred and three were considered possibly related to the study drugs. These were mild in nature and related to raised liver enzymes.

Assessor's comment:

The study design, analytical and statistical methods are considered acceptable.

None of the subjects had measurable pre-dose plasma concentrations of hydroxychloroquine. None of the subjects reached C_{max} at the first sampling time point indicating that sampling time schedule was adequate.

The pharmacokinetic variables for hydroxychloroquine are comparable between test and reference product.

Both formulations were equally well tolerated in the study.

The 90% confidence intervals for the test and reference mean ratio of the log-transformed pharmacokinetic variables C_{max} , and AUC_{0-72} , were within the conventional bioequivalence range of 80% to 125%.

Pharmacokinetic conclusion:

Based on the submitted bioequivalence study, as stated above, hydroxychloroquine test tablets can be considered bioequivalent to the reference product.

3.3 Benefit-Risk assessment

The benefit-risk assessment is favourable.

Hydroxychloroquine Sulphate 200mg Film-coated Tablets are pharmaceutically equivalent to the reference product. No specific risks are related to hydroxychloroquine as an active ingredient.

Granted: 15 June 2015