HYDROXYCHLOROQUINE SULPHATE 200MG FILM-COATED TABLETS
PL 33271/0001

UKPAR

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>3</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>12</td>
</tr>
<tr>
<td>Steps taken after authorisation – summary</td>
<td>13</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>14</td>
</tr>
<tr>
<td>Product Information Leaflet</td>
<td>19</td>
</tr>
<tr>
<td>Labelling</td>
<td>21</td>
</tr>
</tbody>
</table>
HYDROXYCHLOROQUINE SULPHATE 200MG FILM-COATED TABLETS
PL 33271/0001

LAY SUMMARY

On 15\textsuperscript{th} September 2011, the MHRA granted Blackrock Pharmaceuticals Limited a Marketing Authorisation (licence) for Hydroxychloroquine sulphate 200mg film-coated Tablets.

Hydroxychloroquine sulphate 200mg film-coated Tablets contain the active ingredient hydroxychloroquine sulphate.

Hydroxychloroquine sulphate 200mg film-coated Tablets are used to treat inflammatory diseases such as rheumatoid arthritis and juvenile chronic arthritis.

They are also used to treat discoid and systemic lupus erythematosus (a disease where the immune system attacks the body causing tissue damage and inflammation) and also in problems with the skin that are triggered or worsened by sunlight.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of Hydroxychloroquine sulphate 200mg film-coated Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
HYDROXYCHLOROQUINE SULPHATE 200MG FILM-COATED TABLETS
PL 33271/0001

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction ........................................... Page 4
Pharmaceutical assessment ......................... Page 5
Non-clinical assessment .............................. Page 8
Clinical assessment (including statistical assessment) .... Page 9
Overall conclusions and risk benefit assessment .... Page 11
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Hydroxychloroquine sulphate 200mg film-coated Tablets (PL 33271/0001) to Blackrock Pharmaceuticals Limited on 15th September 2011. This prescription only medicine is used in the treatment of:

- rheumatoid arthritis,
- juvenile chronic arthritis,
- discoid and systemic lupus erythematosus,
- dermatological conditions caused or aggravated by sunlight.

This application for Hydroxychloroquine sulphate 200mg film-coated Tablets is submitted according to Article 10.a of Directive 2001/83/EC, a ‘well established use’ application.

Hydroxychloroquine has 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 sulphhydryl 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.

No non-clinical studies have been performed and none are required for this bibliographic application as the use of hydroxychloroquine sulphate is well-established.

A bioequivalence study was performed to compare the pharmacokinetics of the product against the UK brand leader Plaquenil Tablets 200mg, originally approved and granted to Smithkline Beecham (SWG) Limited (as Hydroxychloroquine Sulphate Tablets BP) on 16th February 1990 (PL 00071/0341). This then underwent changes of ownership to Sanofi-Synthelabo Limited on 30th September 1994 (PL 11723/0150) and Aventis Pharma Limited on 22nd July 2010 (PL 04425/0621). No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for this application.

A satisfactory justification has been provided for the absence of a Risk Management Plan.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Hydroxychloroquine sulphate 200mg film-coated Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

INN/Ph.Eur name: Hydroxychloroquine sulphate
Chemical name: 2-[[4-[(7-Chloro-4-quinolyl) amino] pentyl] ethylamino] ethanol sulphate (1:1)

Structural formula:

![Structural formula of Hydroxychloroquine sulphate]

Physical form: A white or almost white, crystalline powder
Solubility: Freely soluble in water

Molecular formula: C_{18}H_{26}ClN_{3}O\cdot H_{2}SO_{4}
Molecular weight: 1699.9

Hydroxychloroquine sulphate is the subject of a British Pharmacopoeia monograph.

Synthesis of the active 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. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
DRUG PRODUCT

Other ingredients
Other ingredients are the pharmaceutical excipients lactose monohydrate, maize starch, hypromellose, croscarmellose sodium, magnesium stearate, talc, titanium dioxide, macrogol 6000, Iron Oxide Yellow E172 and polysorbate 80.

With the exception of Iron Oxide Yellow E172, all excipients comply with their respective European Pharmacopoeia monographs.

Iron Oxide Yellow E172 complies with suitable in-house specifications.

None of the excipients used contain material of human origin. The suppliers of the excipients have provided declarations that neither the excipients nor any material used in the production of the excipients pose a TSE risk. The supplier of magnesium stearate has confirmed that it is of vegetable origin.

The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Product development
A suitable product development section has been provided. Valid justification for the use and amount of each excipient is provided. Comparative *in vitro* dissolution profiles have been provided for the proposed and brand leader product.

Manufacture
A description and flow-chart of the manufacturing method has been provided. Satisfactory batch formulae have been provided for the manufacture of the products. The manufacturing process has been validated and has shown satisfactory results. In-process controls are satisfactory based on batch data and controls on the finished products. Process validation data on batches have been provided and are satisfactory.

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

Container-Closure System
The tablets are packaged in polyvinyl chloride (PVC) and aluminium blisters which hold 10 tablets. The blister packs are packed in cardboard cartons and come in pack sizes of 28, 30 and 60 film-coated tablets.

Specifications and Certificates of Analysis have been provided. All primary product packaging complies with EU legislation regarding contact with food.
Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years for the product has been set with the storage instructions ‘Do not store above 25°C’.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SmPC)
This is pharmaceutically satisfactory.

Labelling
This is pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The user testing results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
This is pharmaceutically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application from a quality point of view.
NON-CLINICAL ASSESSMENT

This application for Hydroxychloroquine sulphate 200mg film-coated Tablets is submitted according to Article 10.a of Directive 2001/83/EC, a ‘well established use’ application. The pharmacodynamics, pharmacokinetics and toxicological properties of hydroxychloroquine sulphate are well-known. The applicant has not provided any new non-clinical data and none are required.

The overview based on literature review is appropriate.

Satisfactory justification was provided for the absence of an Environmental Risk Assessment.

It is recommended that a Marketing Authorisation is granted for this application from a non-clinical point of view.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support this application, the Marketing Authorisation Holder has included a single bioequivalence study. This was to ensure that the product was a generic hydroxychloroquine product, interchangeable with other marketed hydrochloroquine products. This was in view of the risk of irreversible ocular toxicity and other serious side-effects.

An open-label, balanced, randomised, two-treatment, single period, single dose bioequivalence study comparing the pharmacokinetics of Hydroxychloroquine sulphate 200mg film-coated Tablets (Test) versus Plaquenil (hydroxychloroquine sulphate) Tablets 200mg (Reference) in healthy volunteers under fed conditions.

Blood sampling was performed pre-dose and up to 72 hours post dose in each treatment period. Pharmacokinetic parameters were calculated and statistically analysed.

Results from this study are presented below as non-transformed values:

Geometric Least Mean Squares and 90% Confidence Interval
Pharmacokinetic parameters of hydroxychloroquine sulphate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-72} (ng.h/mL)</th>
<th>C_{max} (ng/mL)</th>
<th>T_{max} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>4862.376 ± 1134.9197</td>
<td>245.573 ± 69.8259</td>
<td>4.000</td>
</tr>
<tr>
<td>Reference</td>
<td>5008.638 ± 1252.0479</td>
<td>251.455 ± 84.5687</td>
<td>5.000</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>97.4</td>
<td>98.2</td>
<td>-</td>
</tr>
<tr>
<td>90% Confidence Interval</td>
<td>(89.85 – 105.50)</td>
<td>(89.18 – 108.12)</td>
<td>-</td>
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</table>

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
T_{max} time to peak concentration (represented in median value)
* log transformed values

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-72} and C_{max} for hydroxychloroquine sulphate lie within the normal 80.00 - 125.00 % limits. Bioequivalence has been shown between the test and brand leader product.

EFFICACY
The clinical overview provides an adequate summary of the efficacy of hydroxychloroquine sulphate.

SAFETY
The clinical overview provides an adequate summary of the safety of hydroxychloroquine sulphate. No clinically relevant safety findings were found during the bioequivalence study.

EXPERT REPORTS
The clinical overview has been written by a suitably qualified person and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
These are clinically satisfactory.
MARKETING AUTHORISATION APPLICATION FORM (MAA form)
This is satisfactory.

DISCUSSION
The applicant has satisfactorily demonstrated bioequivalence between the test and brand leader product.

CONCLUSION
The bioequivalence study submitted, together with the additional data provided has shown that Hydroxychloroquine sulphate 200mg film-coated Tablets can be considered interchangeable with the brand leader product Plaquinil Tablets 200mg.

It is recommended that a Marketing Authorisation is granted for this application from a clinical point of view.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Hydroxychloroquine sulphate 200mg film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. A literature review is therefore appropriate. The pharmacology, pharmokinetics and toxicology of hydroxychloroquine sulphate are well-known. No new or unexpected safety concerns arise from this application.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Hydroxychloroquine sulphate 200mg film-coated Tablets and the brand leader product Plaquenil Tablets 200mg.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study concluded that the applicant’s product and the brand leader product are bioequivalent. Extensive clinical experience with hydroxychloroquine sulphate is considered to have demonstrated its therapeutic value. The benefit/risk for the indications proposed is therefore considered to be positive.
**HYDROXYCHLOROQUINE SULPHATE 200MG FILM-COATED TABLETS**  
PL 33271/0001

**STEPS TAKEN FOR ASSESSMENT**

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<thead>
<tr>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 16(^{th}) April 2009.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 14(^{th}) May 2009.</td>
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</table>
| 3 | Following assessment of the application, the MHRA requested further information relating to the quality dossier on 7\(^{th}\) September 2009, 18\(^{th}\) March 2010, 13\(^{th}\) August 2010, 24\(^{th}\) June 2011 and 9\(^{th}\) August 2011.  
   The MHRA requested further information relating to the clinical dossier on 21\(^{st}\) September 2009 and 12\(^{th}\) May 2011. |
| 4 | The applicant responded to the MHRA’s requests, providing further information on 17\(^{th}\) March 2010, 27\(^{th}\) July 2010, 12\(^{th}\) May 2011, 27\(^{th}\) June 2011 and 14\(^{th}\) August 2011 for the quality section.  
   Further information was provided on 11\(^{th}\) January 2010 and 12\(^{th}\) May 2011 for the clinical section. |
| 5 | The application was determined on 15\(^{th}\) September 2011. |
HYDROXYCHLOROQUINE SULPHATE 200MG FILM-COATED TABLETS
PL 33271/0001

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Hydroxychloroquine sulphate 200mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Hydroxychloroquine Sulphate 200mg

3 PHARMACEUTICAL FORM
Film Coated Tablet

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Treatment of rheumatoid arthritis, juvenile chronic arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults (including the elderly)
The minimum effective dose should be employed. This dose should not exceed 6.5mg/kg/day (calculated from ideal body weight and not actual body weight) and will be either 200mg or 400mg per day.

In patients able to receive 400mg daily:
Initially 400mg daily in divided doses. The dose can be reduced to 200mg when no further improvement is evident. The maintenance dose should be increased to 400mg daily if the response lessens.

Children
The minimum effective dose should be employed and should not exceed 6.5mg/kg/day based on ideal body weight. The 200mg tablet is therefore not suitable for use in children with an ideal body weight of less than 31kg.
Each dose should be taken with a meal or glass of milk. Hydroxychloroquine is cumulative in action and will require several weeks to exert its beneficial effects, whereas minor side effects may occur relatively early. For rheumatic disease treatment should be discontinued if there is no improvement by 6 months. In light-sensitive diseases, treatment should only be given during periods of maximum exposure to light.

The tablets are for oral administration.

4.3 CONTRAINDICATIONS
- hypersensitivity to hydroxychloroquine or to any of the excipients
- known hypersensitivity to 4-aminoquinoline compounds
- pre-existing maculopathy of the eye
- pregnancy (see section 4.6 Pregnancy and lactation)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General
• The occurrence of retinopathy is very uncommon if the recommended daily dose is not exceeded. The administration of doses in excess of the recommended maximum is likely to increase the risk of retinopathy, and accelerate its onset.

• All patients should have an ophthalmological examination before initiating treatment with Hydroxychloroquine sulphate. Thereafter, ophthalmological examinations must be repeated at least every 12 months.

The examination should include testing visual acuity, careful ophthalmoscopy, fundoscopy, central visual field testing with a red target, and colour vision.
This examination should be more frequent and adapted to the patient in the following situations:

- daily dosage exceeds 6.5mg/kg lean body weight. Absolute body weight used as a guide to dosage could result in an overdosage in the obese.

- renal insufficiency
- visual acuity below 6/8
- age above 65 years
- cumulative dose more than 200 g.

Hydroxychloroquine sulphate should be discontinued immediately in any patient who develops a pigmentary abnormality, visual field defect, or any other abnormality not explainable by difficulty in accommodation or presence of corneal opacities. Patients should continue to be observed for possible progression of the changes.

Patients should be advised to stop taking the drug immediately and seek the advice of their prescribing doctor if any disturbances of vision are noted, including abnormal colour vision.

Hydroxychloroquine sulphate should be used with caution in patients taking medicines which may cause adverse ocular or skin reactions. Caution should also be applied when it is used in the following:

- patients with hepatic or renal disease, and in those taking drugs known to affect those organs.

Estimation of plasma hydroxychloroquine levels should be undertaken in patients with severely compromised renal or hepatic function and dosage adjusted accordingly.

- patients with severe gastrointestinal, neurological or blood disorders.

Although the risk of bone marrow depression is low, periodic blood counts are advisable as anaemia, aplastic anaemia, agranulocytosis, a decrease in white blood cells, and thrombocytopenia have been reported. Hydroxychloroquine sulphate should be discontinued if abnormalities develop.

Caution is also advised in patients with a sensitivity to quinine, those with glucose-6-phosphate dehydrogenase deficiency, those with porphyria cutanea tarda which can be exacerbated by hydroxychloroquine and in patients with psoriasis since it appears to increase the risk of skin reactions.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Small children are particularly sensitive to the toxic effects of 4-aminoquinolines; therefore patients should be warned to keep Hydroxychloroquine sulphate out of the reach of children.

All patients on long-term therapy should undergo periodic examination of skeletal muscle function and tendon reflexes. If weakness occurs, the drug should be withdrawn.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Hydroxychloroquine sulphate has been reported to increase plasma digoxin levels: serum digoxin levels should be closely monitored in patients receiving combined therapy.

Hydroxychloroquine sulphate may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared. These include: potentiation of its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics; inhibition of its metabolism by cimetidine which may increase plasma concentration of the antimalarial; antagonism of effect of neostigmine and pyridostigmine; reduction of the antibody response to primary immunisation with intradermal human diploid-cell rabies vaccine.

As with chloroquine, antacids may reduce absorption of hydroxychloroquine so it is advised that a 4 hour interval be observed between Hydroxychloroquine sulphate and antacid dosaging.

As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.

4.6 PREGNANCY AND LACTATION

Pregnancy:

Hydroxychloroquine crosses the placenta. Data are limited regarding the use of hydroxychloroquine during pregnancy. It should be noted that 4-aminoquinolines in therapeutic doses have been associated with central nervous system damage, including ototoxicity (auditory and vestibular toxicity, congenital deafness), retinal hemorrhages and abnormal retinal pigmentation. Therefore Hydroxychloroquine sulphate should not be used in pregnancy.
Lactation:
Careful consideration should be given to using hydroxychloroquine during lactation, since it has been shown to be excreted in small amounts in human breast milk, and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Impaired visual accommodation soon after the start of treatment has been reported and patients should be warned regarding driving or operating machinery. If the condition is not self-limiting, it will resolve on reducing the dose or stopping treatment.

4.8 UNDESIRABLE EFFECTS

• Ocular effects:
Retinopathy with changes in pigmentation and visual field defects can occur, but appears to be uncommon if the recommended daily dose is not exceeded. In its early form it appears reversible on discontinuation of Hydroxychloroquine sulphate. If allowed to develop, there may be a risk of progression even after treatment withdrawal.

Patients with retinal changes may be asymptomatic initially, or may have scotomatous vision with paracentral, pericentral ring types, temporal scotomas and abnormal colour vision.

Corneal changes including oedema and opacities have been reported. They are either symptomless or may cause disturbances such as haloes, blurring of vision or photophobia. They may be transient and reversible on stopping treatment.

Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible may also occur.

• Dermatologic effects:
Skin rashes sometimes occur; pruritus, pigmentary changes in skin and mucous membranes, bleaching of hair and alopecia have also been reported. These usually resolve readily on stopping treatment.

Bullous eruptions including very rare cases of erythema multiforme and Stevens-Johnson syndrome, photosensitivity and isolated cases of exfoliative dermatitis have been reported. Very rare cases of acute generalised exanthematous pustulosis (AGEP) has to be distinguished from psoriasis, although hydroxychloroquine may precipitate attacks of psoriasis. It may be associated with fever and hyperleukocytosis. Outcome is usually favourable after drug withdrawal.

• Gastrointestinal effects:
Gastrointestinal disturbances such as nausea, diarrhoea, anorexia, abdominal pain and, rarely, vomiting may occur. These symptoms usually resolve immediately on reducing the dose or on stopping treatment.

• CNS effects:
Less frequently, dizziness, vertigo, tinnitus, hearing loss, headache, nervousness, emotional lability, toxic psychosis and convulsions have been reported with this class of drugs.

• Neuromuscular effects:
Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups have been noted. Myopathy may be reversible after drug discontinuation, but recovery may take many months.
Associated mild sensory changes, depression of tendon reflexes and abnormal nerve conduction may be observed.

• Cardio-vascular effects:
Cardiomyopathy has been rarely reported.
Chronic toxicity should be suspected when conduction disorders (bundle branch block/atrioventricular heart block) as well as biventricular hypertrophy are found. Drug withdrawal may lead to recovery.

• Hematologic effects:
Rarely, there have been reports of bone-marrow depression. Blood disorders such as anaemia, aplastic anaemia, agranulocytosis, a decrease in white blood cells and thrombocytopenia have been reported. Hydroxychloroquine may precipitate or exacerbate porphyria.

• Liver effects:
Isolated cases of abnormal liver function tests have been reported; rare cases of fulminant hepatic failure have also been reported.

• Allergic reactions:
  Urticaria, angioedema and bronchospasm have been reported.

4.9 OVERDOSE
Overdosage with the 4-aminoquinolines is dangerous particularly in infants, as little as 1-2g having proved fatal.

The symptoms of overdosage may include headache, visual disturbances, cardiovascular collapse, convulsions, hypokalaemia, and rhythm and conduction disorders, followed by sudden and early respiratory and cardiac arrest. Since these effects may appear soon after taking a massive dose, treatment should be prompt and symptomatic. The stomach should be immediately evacuated, either by emesis or by gastric lavage. Activated charcoal in a dose at least five times of the overdose may inhibit further absorption if introduced into the stomach by tube following lavage and within 30 minutes of ingestion of the overdose.

Consideration should be given to administration of parenteral diazepam in cases of overdosage; it has been shown to be beneficial in reversing chloroquine cardiotoxicity.

Respiratory support and shock management should be instituted as necessary.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES

ATC Code: P01BA02
Pharmacotherapeutic group: Anti rheumatic

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 sulphydryl 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.

5.2 PHARMACOKINETIC PROPERTIES
Hydroxychloroquine has actions, pharmacokinetics and metabolism similar to those of chloroquine. Following oral administration, hydroxychloroquine is rapidly and almost completely absorbed. In one study, mean peak plasma hydroxychloroquine concentrations following a single dose of 400mg in healthy subjects ranged from 53-208ng/ml with a mean of 105ng/ml. The mean time to peak plasma concentration was 1.83 hours. The mean plasma elimination half-life varied, depending on the post-administration period, as follows: 5.9 hours at Cmax-10 hours), 26.1 hours (at 10-48 hours) and 299 hours (at 48-504 hours). The parent compound and metabolites are widely distributed in the body and elimination is mainly via the urine, where 3% of the administered dose was recovered over 24 hours in one study.

5.3 PRECLINICAL SAFETY DATA
There are no preclinical safety data of relevance to the prescriber, which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Lactose Monohydrate
Maize Starch
Hypromellose
Croscarmellose Sodium
Magnesium Stearate
Talc
Titanium Dioxide
Macrogol 6000
Iron Oxide Yellow E172
Polysorbate 80
6.2 INCOMPATIBILITIES
No incompatibilities are known.

6.3 SHELF LIFE
3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER
250µm clear PVC/20µm aluminium foil blister pack containing 10 tablets.
The blister packs are packed in a outer cardboard carton containing 28, 30 or 60 tablets. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
None

7 MARKETING AUTHORITY/HOLDER
Blackrock Pharmaceuticals Ltd.
Vandervell House
Vanwall Business Park
Maidenhead, Berkshire SL6 4UB
United Kingdom

8 MARKETING AUTHENTICATION NUMBER(S)
PL 33271/0001

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
15/09/2011

10 DATE OF REVISION OF THE TEXT
15/09/2011
UKPAR Hydroxychloroquine sulphate 200mg film-coated Tablets

PL 33271/0001

PACKAGE LEAFLET: INFORMATION FOR THE USER
Hydroxychloroquine Sulphate 200mg Film Coated Tablets
(referred to as Hydroxychloroquine Sulphate Tablets in the remainder of the leaflet)

Hydroxychloroquine sulphate

Read all of this leaflet carefully before you start to take this medicine.
- Keep this leaflet. You may need to read it again while you are receiving your treatment.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Hydroxychloroquine Sulphate Tablets are and what they are used for
2. Before you take Hydroxychloroquine Sulphate Tablets
3. How to take Hydroxychloroquine Sulphate Tablets
4. Possible side effects
5. How to store Hydroxychloroquine Sulphate Tablets
6. Further information

1. What Hydroxychloroquine Sulphate Tablets are and what they are used for

The name of your medicine is Hydroxychloroquine Sulphate Tablets; the active ingredient is hydroxychloroquine sulphate. These tablets are used in the treatment of inflammatory diseases such as rheumatoid arthritis and juvenile chronic arthritis.

They are also used to treat discoid and systemic lupus erythematosus (a disease where the immune system attacks the body causing tissue damage and inflammation) and also in problems with the skin that are triggered or worsened by sunlight.

2. Before you take Hydroxychloroquine Sulphate Tablets

Do not take Hydroxychloroquine Sulphate Tablets if you:
- are allergic (hypersensitive) to hydroxychloroquine sulphate or to any of the other ingredients in Hydroxychloroquine Sulphate Tablets (see section 6. Further information)
- are allergic (hypersensitive) to 4-aminoquinoline compounds (e.g. chloroquine, amodiaquine)
- suffer from maculopathy (a disease of the eye)
- are pregnant.

Before starting this medicine your doctor should arrange for you to have a thorough eye test.
- this should be repeated at least once every year while you are taking this medicine
- the elderly, those with kidney or previous eye problems and those taking more than one tablet per day may need more frequent eye tests.

Talk to your doctor before taking Hydroxychloroquine Sulphate Tablets if you:
- suffer from liver or kidney disease
- suffer from severe problems with your gastrointestinal system or nervous system
- suffer from severe problems with your blood or bone marrow
- suffer from porphyria (a disease of blood proteins that can affect the skin, gut and nervous system)
- have the inherited condition glucose-6-phosphate dehydrogenase (G6PD) deficiency (an enzyme deficiency which increases the risk of developing anaemia)
- suffer from psoriasis (a skin condition causing scaly skin patches over the body)
- have eye or eyesight problems
- are allergic to quinine (a medicine used to treat malaria).

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, tell your doctor if you are taking any of the following medicines:

The following medicines may increase the chance of you getting side effects when taken with Hydroxychloroquine Sulphate Tablets:
- medicines used to treat myasthenia gravis – a disease of the muscles and nerves (e.g. neostigmine and pyridostigmine)
- aminoglycoside antibiotics (used to treat bacterial infections)
- cimetidine (used to treat heartburn and stomach ulcers)
- medicines that affect the skin or the eyes
- medicines that may affect the kidney or liver.

The following medicines can change the way Hydroxychloroquine Sulphate Tablets work or Hydroxychloroquine Sulphate Tablets may affect the way some of these medicines work:
- medicines used to treat diabetes (e.g. insulin and anti-diabetic tablets)
- digoxin (used to treat abnormal heart rhythms and heart failure)
- rabies vaccine
- antacids (medicines used to treat indigestion) – you should wait at least four hours between taking antacids and Hydroxychloroquine Sulphate Tablets.

Taking Hydroxychloroquine Sulphate Tablets with food and drink
Hydroxychloroquine Sulphate Tablets should be taken with a meal or a glass of milk.

Pregnancy and breast-feeding
Do not take this medicine if you are pregnant.
If you are breast-feeding you should discuss with your doctor before taking this medicine.

Driving and using machinery
When you first start treatment with Hydroxychloroquine Sulphate Tablets you may get blurred vision. If this happens do not drive a car or operate machinery. If this continues or you get other visual problems see your doctor immediately. There is more information on this in section 4.

Important information about some of the ingredients in Hydroxychloroquine Sulphate Tablets
This medicine contains lactose, if you have been told by your doctor that you have an intolerance to some sugars contact your doctor before taking this medicine.

3. How to take Hydroxychloroquine Sulphate Tablets

Always take Hydroxychloroquine Sulphate Tablets as your doctor has told you. Your doctor will decide the right dose for you; this will be on the pharmacist’s label. Check this carefully, it will tell you how many tablets to take and how often to take them. You should check with your doctor or pharmacist if you are not sure.

Taking this medicine
- swallow the tablets whole with a meal or a glass of milk
- the doctor will work out the dose depending on your body weight
- if you are being treated for a skin disease that is sensitive to sunlight light, then you should use this medicine during periods of high exposure to light

Continued overleaf...
UKPAR Hydroxychloroquine sulphate 200mg film-coated Tablets
PL 33271/0001

- while you are taking this medicine your doctor may arrange for blood tests to monitor your response to treatment
- if you have been taking this medicine for more than 6 months for the treatment of rheumatoid arthritis and you do not feel that it is helping you, speak to your doctor as it may be decided to stop treatment with this medicine.

How much to take
Adults (including the elderly)
- the usual dose is one tablet taken daily or one tablet taken morning and night
- your doctor may alter your dose depending on your response to treatment.

Children and Adolescents
- one tablet each day
- this medicine is only suitable for children who weigh more than 31kg.

It may be several weeks before you notice an improvement in your condition with this medicine.

If you take more Hydroxychloroquine Sulphate Tablets than you should
If you (or anybody else), takes more Hydroxychloroquine Sulphate Tablets than you should contact your nearest hospital casualty department or doctor immediately. Always take the blister pack of tablets and this leaflet with you.

Young children and babies are particularly at risk if they accidentally take Hydroxychloroquine Sulphate Tablets. Take the child to hospital straight away.

Symptoms that could indicate someone has taken too much are headache, visual disturbances, breathing difficulties, problems with your heart, low blood pressure and fits.

If you forget to take Hydroxychloroquine Sulphate Tablets
If you forget a dose, take another as soon as you remember. If it is almost time for your next dose, then do not take the missed dose at all. NEVER take a double dose to make up for the one missed.

4. Possible side effects
Like all medicines, Hydroxychloroquine Sulphate Tablets can cause side effects, although not everybody gets them.

As can happen with any medicine, a few people may develop an allergic reaction. If you experience any of the following, seek medical help immediately:
- rash, itching and/or difficulty breathing
- rapid swelling of the skin around the face, particularly the mouth

If you experience any of the following symptoms then stop taking the medicine and seek medical help immediately:
- any visual disturbance including persistent blurring of vision, changes to your colour vision, or sensitivity to light
- any muscle weakness, particularly of the upper arms or legs, muscle spasms or cramps, or changes in sensation of your skin. If you take this medicine over a long time your doctor will occasionally check your muscles and tendons to ensure they are not affected
- blistering of the skin, particularly the mouth, face, nose and genitails, fever and flu-like symptoms. This could be a serious reaction called Stevens - Johnson syndrome
- other skin changes including the formation of numerous small pustules or itchy pink-red blotches or generalised scaling of the skin

You should tell your doctor or pharmacist if you have any of the following side effects, or if you think Hydroxychloroquine Sulphate Tablets are making you feel unwell in any other way. Side effects reported with this medicine include:
- visual disturbances
- headaches
- feeling or being sick
- loss of appetite
- dizziness
- ringing in the ears
- headache
- mood swings
- fits
- spasm of airways
- muscle weakness
- decreased reflexes
- low platelets
- bone marrow depression
- abnormal nerve conduction
- abnormal liver function seen on blood tests
- symptoms of a condition called Porphyria, which may include stomach pain, being sick, constipation, fits, rashes or blisters, itching, pain or weakness in back, arms and legs
- weakening of the heart muscle (cardiomyopathy) resulting in difficulty breathing, chest pain, an irregular or abnormal heartbeat, feeling dizzy or tired, swelling of feet, ankles and legs

Talk to your doctor or pharmacist if you experience any side effects or feel that the medicine is affecting you badly or if you experience any side effects not listed in this leaflet.

5. How to store Hydroxychloroquine Sulphate Tablets
Keep out of the reach and sight of children.

- Do not store above 25°C. Store in the original packaging; do not transfer your tablets to another container
- Do not take after the expiry date on the label; the expiry date refers to the last day of the month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Further information
What Hydroxychloroquine Sulphate Tablets contain
The active ingredient is: 200mg hydroxychloroquine sulphate.
The other ingredients are: lactose monohydrate, maize starch, hypromellose, croscarmellose sodium, magnesium stearate, talc, titanium dioxide, macrogol 6000, iron oxide yellow E172 and polysorbate 80.

What Hydroxychloroquine Sulphate Tablets look like and the contents of the pack
Hydroxychloroquine Sulphate Tablets are round, light yellow tablets with a score line on one side and Incepta inscribed on the reverse. They are supplied in blister pack of 10 tablets, with an outer cardboard carton, and are available in pack size of 28, 30 or 60 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Blackrock Pharmaceuticals Ltd., Vandervell House, Vanwell Business Park, Maidenhead, Berkshire, SL6 4UB, UK.

Manufacturer:
Blackrock Pharmaceuticals Ltd., Vandervell House, Vanwell Business Park, Maidenhead, Berkshire, SL6 4UB, UK.

Product Licence Number: PL 33271/0001
Leaflet Prepared: May 2011

Blackrock Pharmaceuticals
Hydroxychloroquine Sulphate film coated Tablets
For oral administration

Each Tablet contains:
Hydroxychloroquine Sulphate 200 mg

List of excipients:
Lactose monohydrate, Maize starch, Hypromellose, Croscarmellose Sodium, Magnesium Stearate, Talc, Titanium Dioxide, Macrogol 6000, Iron Oxide Yellow (E172) and Polysorbate 80

To be taken as directed by your doctor
Read the package leaflet before use

Instructions on use: Swallow the tablet as a whole with a meal or a glass of milk

Warning: Keep out of the reach and sight of children.

Special storage condition:
Do not store above 25°C
Keep in the original packaging

Marketing authorization holder:
Blackrock Pharmaceuticals Ltd
Vanderwell House, Vanwell Business Park,
Maidstone SL6 4BB, United Kingdom
PL 33271/0001

Manufactured by:
Blackrock Pharmaceuticals Ltd
UKPAR Hydroxychloroquine sulphate 200mg film-coated Tablets

60 Tablets

Hydroxychloroquine Sulphate
cell coated Tablets
For oral administration

Each Tablet contains:
Hydroxychloroquine Sulphate 200 mg

List of excipients:
Lactose monohydrate, Maize starch, Hypromellose, Croscarmellose
Sodium, Magnesium Stearate, Talc, Titanium Dioxide, Macrogol 6000, Iron
Oxide Yellow (E172) and Polysorbate 80.

To be taken as directed by your doctor.
Read the package leaflet before use.

Instructions on use: Swallow the tablet as a whole
with a meal or a glass of milk.

Warning: Keep out of the reach and sight of children.

Special storage conditions:
Do not store above 25°C.
Keep in the original packaging.

Marketing authorization holder:
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Vanderwell House, Vanwell Business Park,
Maidenhead SL6 4UB, United Kingdom
PL 33271/0001

Manufactured by
Blackrock Pharmaceuticals Ltd