Public Assessment Report

UKPAR

Quinine Sulfate 200mg Tablets

(Quinine sulfate)

UK Licence No: PL 13606/0200

Strides Shasun (UK) Ltd.
LAY SUMMARY

Quinine Sulfate 200mg Tablets
(Quinine sulfate, film-coated tablet, 200 mg)

This is a summary of the Public Assessment Report (PAR) for Quinine Sulfate 200mg Tablets (PL 13606/0200). It explains how Quinine Sulfate 200mg 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 Quinine Sulfate 200mg Tablets.

The product will be referred to as Quinine Sulfate Tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Quinine Sulfate Tablets patients should read the package leaflet or contact their doctor or pharmacist.

What are Quinine Sulfate Tablets and what are they used for?
Quinine Sulfate Tablets are used to:
- Treat malaria
- Treat and prevent nocturnal (night-time) leg cramps in adults and the elderly when sleep is regularly disturbed.

The reference medicine for this application is Quinine Sulphate Tablets BP 300mg (PL 13606/0059).

The company (Strides Shasun (UK) Ltd) that makes Quinine Sulphate Tablets BP 300mg (PL 13606/0059) has agreed that its scientific data can be used as a basis for the grant of a licence for Quinine Sulfate Tablets (informed consent).

How do Quinine Sulfate Tablets work?
This medicine contains the active ingredient called quinine sulfate which belongs to a group of medicines called antiprotozoal agents.

How are Quinine Sulfate Tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure. These tablets should be swallowed with some water.

Malaria:
Adults (including the elderly) and adolescents over 12 years:
600mg at 8 hour intervals for 7 days.

Children under 12 years:
10mg/kg at 8 hour intervals for 7 days.
Quinine Sulphate 200mg Tablets are not suitable for children weighing less than 20kg or less than 5 years old.
Nocturnal leg cramps:
Adults (including elderly people):
200mg at bedtime. The maximum dose is 300mg.

The patient must not take more than the prescribed dose.

It may take up to 4 weeks before the patient notices any reduction in the frequency of leg cramps.

Please refer to section 3 of the package leaflet for information on how to use this medicine.

This medicine can only be obtained with a prescription.

For further information on how Quinine Sulfate Tablets are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

What benefits of Quinine Sulfate Tablets have been shown in studies?
Quinine Sulfate Tablets are considered similar to previously authorised Quinine Sulphate Tablets BP 300mg (PL 13606/0059), with the same benefits and risks. So no new studies have been provided for Quinine Sulfate Tablets but reference is made to the data and studies for Quinine Sulphate Tablets BP 300mg (PL 13606/0059). The company provided suitable justification for the results and conclusions of the studies for Quinine Sulphate Tablets BP 300mg (PL 13606/0059) to be extended to this application for the medicinal product Quinine Sulfate Tablets.

What are the possible side effects from Quinine Sulfate Tablets?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Quinine Sulfate Tablets are considered similar to the previously authorised application for Quinine Sulphate Tablets BP 300mg (PL 13606/0059) with the same benefits and risks.

For a full list of all the side effects reported with Quinine Sulfate Tablets see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

Why are Quinine Sulfate Tablets approved?
The MHRA decided that the benefits of Quinine Sulfate Tablets are greater than their risks and recommended that they be approved for use.

What measures are being taken to ensure the safe and effective use of Quinine Sulfate Tablets?
A Risk Management Plan has been developed to ensure that Quinine Sulfate Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Quinine Sulfate Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Quinine Sulfate Tablets
A Marketing Authorisation was granted in the UK on 25 October 2016.
The full PAR for Quinine Sulfate Tablets follows this summary.

For more information about treatment with Quinine Sulfate Tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2017.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Introduction</td>
<td>6</td>
</tr>
<tr>
<td>II Quality aspects</td>
<td>7</td>
</tr>
<tr>
<td>III Non-clinical aspects</td>
<td>8</td>
</tr>
<tr>
<td>IV Clinical aspects</td>
<td>8</td>
</tr>
<tr>
<td>V User consultation</td>
<td>9</td>
</tr>
<tr>
<td>VI Overall conclusion, benefit/risk assessment and recommendation</td>
<td>9</td>
</tr>
</tbody>
</table>
I INTRODUCTION
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Strides Shasun (UK) Ltd a Marketing Authorisation for the medicinal product Quinine Sulfate Tablets (PL 13606/0200) on 25 October 2016. The product is a prescription only medicine (POM) indicated:

- For the treatment of chloroquine resistant falciparum malaria in adults and children aged 5 years or older (and ≥ 20kg)
- For the treatment and prevention of nocturnal leg cramps in adults and the elderly, when cramps cause regular disruption of sleep (see section 4.2 and Section 4.4 of the SmPC).

This application was submitted as a simple abridged (informed consent) application according to Article 10c of Directive 2001/83/EC, as amended, for a line extension.

The application cross-refers to Quinine Sulphate Tablets BP 300mg, which was first authorised to Strides Shasun (UK) Ltd (PL 13606/0059) on 18 February 1998. The applicant requested a waiver from performing a bioequivalence study on the basis of a comparison between the 300mg and 200mg strength products; they have a similar formulation to a reference product and also demonstrate similar dissolution profiles.

Quinine is a rapidly acting blood schizontocide with activity against Plasmodium falciparum, P. vivax, P. ovale and P. malariae. It is active against the gametocytes of P. malariae and P. vivax but not against P. falciparum gametocytes. It has no activity against exoerythrocytic forms.

The precise mechanism of action of quinine is unclear but it may interfere with lysosome function or nucleic acid synthesis in the malaria parasite. Since it has no activity against exoerythrocytic forms, quinine does not produce a radical cure of malaria caused by plasmodium vivax and plasmodium ovale infections. Its toxicity profile overall is less favourable than chloroquine based on scientific literature.

Quinine has effects on the motor end-plate of skeletal muscle and prolongs the refractory period. Like quinidine, quinine is a sodium channel blocker and, therefore, has local anaesthetic, and both anti-and proarrhythmic activity.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Quinine Sulfate Tablets outweigh the risks and therefore, a Marketing Authorisation was granted.
II  QUALITY ASPECTS

II.1  Introduction
This is an abridged application for Quinine Sulfate Tablets (PL 13606/0200) submitted under Article 10c of Directive 2001/83/EC, as amended, for a line extension.

The application cross-references to Quinine Sulphate Tablets BP 300mg, which was first authorised to Strides Shasun (UK) Ltd (PL 13606/0059) on 18 February 1998. The application is considered valid.

II.2  Drug Substance
Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

II.3  Medicinal Product
Name
The proposed product name for this application is Quinine Sulfate 200mg Tablets. The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack sizes
Each film-coated tablet contains 200 mg quinine sulfate. The finished product is packed in to polyvinyl chloride (PVC) (285µm)/aluminium (25µm) foil blisters in packs of 5, 7, 10, 14, 15, 20, 21, 25, 28, 30, 56, 60, 84, 90, 100, 112, 120, 168, 180, 250 and 500 tablets. Not all pack sizes may be marketed.

The proposed shelf life of the unopened product is 36 months with no special storage conditions.

Legal status
Prescription only medicine (POM).

Marketing Authorisation Holder/Contact Persons/Company
Strides Shasun (UK) Ltd, Unit 4 Metro Centre, Tolpits Lane, Watford, Hertfordshire, WD18 9SS, UK.

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory CV has been provided.

Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative composition
The proposed composition is satisfactory.

Manufacturing process
The proposed manufacturing processes are consistent with the details registered for the cross-reference product and the maximum batch size is stated.

Finished product/shelf-life specification
The proposed finished product specification is satisfactory.

TSE Compliance
None of the excipients contain materials of animal or human origin.
Bioequivalence
The company (Strides Shasun (UK) Ltd) provided suitable justification for the results and conclusions of the studies for Quinine Sulphate Tablets BP 300mg (PL 13606/0059) to be extended to this application for the medicinal product Quinine Sulfate 200mg Tablets (PL 13606/0200). The applicant has requested a waiver from performing a bioequivalence study on the basis of a comparison between the 300mg and 200mg strength products; they have a similar formulation to a reference product and also demonstrate similar dissolution profiles.

Expert Report
The applicant cross-references to the data for Quinine Sulphate Tablets BP 300mg (PL 13606/0059). This is acceptable.

Product Name and Appearance
See Section II.3 ‘Medicinal Product; Name’ for details of the proposed product name. The appearance of the product is a white, biconvex film-coated tablet, plain on both sides.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The data submitted with the application is acceptable. The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS
Introduction
As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, for a line extension, no new non-clinical data have been supplied and none are required.

Ecotoxicity/environmental risk assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is similar to an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS
Introduction
As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, for a line extension, no new clinical data have been supplied and none are required.

The applicant (Strides Shasun (UK) Ltd) provided suitable justification for the data, results and conclusions of the studies for Quinine Sulphate Tablets BP 300mg (PL 13606/0059) to be extended to this application for the medicinal product Quinine Sulfate 200mg Tablets (PL 13606/0200).

Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Quinine Sulfate Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risk(s)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinchonism</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrhythmias, including atrioventricular conduction disturbances, QT interval prolongation, widening QRS complex, T wave flattening &amp; ventricular arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Risk of Acute Hemolytic anaemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency</td>
<td></td>
</tr>
<tr>
<td>Severe respiratory distress in patients with myasthenia gravis</td>
<td></td>
</tr>
</tbody>
</table>

| Important potential risk(s)                                                                  |   |
| Risk of congenital abnormalities while exposure during pregnancy                             |   |

| Missing information                                                                          | Nil |

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

**Discussion on the clinical aspects**
The grant of a Marketing Authorisation is recommended.

**V User consultation**
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the product for Quinine Sulphate Tablets BP 300mg (PL 13606/0059). The bridging report submitted by the applicant is acceptable.

**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 quinine sulfate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels

The Summary of Product Characteristics and Patient Information Leaflet (PIL) are consistent with the details registered for the cross-reference product.

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

The approved labelling for this medicine is presented below: