Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Quinine Sulfate 200mg Tablets B.P.

quinine sulfate

PL 04556/0060

Pharmvit Limited

LAY SUMMARY

Quinine Sulfate 200mg Tablets B.P.
quinine sulfate

This is a summary of the Public Assessment Report (PAR) for Quinine Sulfate 200mg Tablets B.P. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Quinine Sulfate in this lay summary for ease of reading.

For practical information about using Quinine Sulfate, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Quinine Sulfate and what is it used for?
This application is for a medicine that has a well-established use. This means that the use of the active substance in this medicine has been well-established in the UK/European Union for at least 10 years, with recognised efficacy and an acceptable level of safety.

Quinine Sulfate is used to treat:
- Malaria
- and prevent night cramps in adults and the elderly when sleep is regularly disrupted.

How does Quinine Sulfate work?
Quinine Sulfate belongs to a group of medicines called anti-protozoal agents.

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

The patient should swallow the tablets with water.

For uncomplicated malaria (the patient may be given another medicine for malaria with or after the course of quinine**):**

<u>Recommended dose</u>
Adults, the elderly and children over 12 years
Two tablets every eight hours for 7 days.

Children under 12 years
Equivalent of 10mg/kg of body weight every eight hours for 7 days.

Patients with kidney or liver problems
A lower dose than the usual adult dose or increased time between doses should be used if the patient has kidney or liver problems.

For the relief of nocturnal cramps in Adults and the elderly
200mg at bedtime which may be increased maximum to 300mg. It may take up to 4 weeks before the patient notices any reduction in the frequency of leg cramps.

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

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Quinine Sulfate have been shown in studies?
Quinine Sulfate is a line extension of the existing product Quinine sulfate 300 mg Tablets. The data submitted previously for Quinine sulfate 300 mg Tablets and the submitted clinical expert report and clinical overview are sufficient to demonstrate that Quinine Sulfate shows a benefit in the indications listed.

What are the possible side effects of Quinine Sulfate?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Quinine Sulfate 200 mg Tablets B.P. is a line extension of the existing product Quinine sulfate 300 mg Tablets, its benefits and possible side effects are taken as being the same as Quinine sulfate 300 mg Tablets.

Why was Quinine Sulfate approved?
It was concluded that, as Quinine Sulfate 200 mg Tablets B.P. is a line extension of Quinine sulfate 300 mg Tablets, the indications and side effects observed with Quinine sulfate 300 mg Tablets are applicable to the lower strength. Therefore, the MHRA decided that, as for Quinine sulfate 300 mg Tablets, the benefits are greater than the risks and recommended that Quinine Sulfate 200 mg Tablets B.P. can be approved for use.

What measures are being taken to ensure the safe and effective use of Quinine Sulfate?
A Risk Management Plan (RMP) has been developed to ensure that Quinine Sulfate is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

The RMP details the important risks of Quinine Sulfate, how these risks can be minimised, any uncertainties about Quinine Sulfate (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Quinine Sulfate:

Summary of safety concerns	
Important identified risks	• Hypersensitivity reactions, including anaphylaxis • Optic Neuritis • Tinnitus • Use in patients with Myaesthenia gravis • Cardiac disorders • Cinchonism • Thrombocytopenia
Important potential risks	• Use in patients with G6PD Deficiency • Drug-drug interactions, particularly affecting cytochrome P450 CYP3A4 enzymes • Use in pregnancy and breastfeeding • Overdose
Important missing information	• Use in severe renal impairment • Use in severe hepatic impairment

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

Other information about Quinine Sulfate
A marketing authorisation for Quinine Sulfate 200 mg Tablets B.P. was granted in the United Kingdom (UK) on 16 July 2024.

The full PAR for Quinine Sulfate follows this summary.

This summary was last updated in November 2024.

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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 Quinine Sulfate 200mg Tablets B.P. (PL 04556/0060) could be approved.

The product is approved for the following indications:

a) Treatment of uncomplicated attacks of falciparum malaria due to chloroquine or multi drug resistant strains.

b) 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).

Quinine is a rapidly acting blood schizontide 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. Since it has no activity against exoerythrocytic forms quinine does not produce a radical cure in vivax or ovale malarias. Quinine supresses the asexual cycle of development of the malarial parasite in the erythrocytes through interference with its DNA.

On skeletal muscle quinine has dual action; it acts directly on muscle fibre and also effects muscular transmission by increasing the threshold of excitability of the motor end-plate.

This application was submitted under Regulation 54 of The Human Medicines Regulation 2012, as amended (previously Article 10a of Directive 2001/83/EC, as amended), as a well-established use application. No new non-clinical or clinical studies were submitted, as the data submitted for these applications is in the form of literature references. As this application is for a line extension of the existing product Quinine sulfate 300 mg Tablets (PL 04556/0032), the non-clinical and clinical data are identical to those submitted previously.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A national marketing authorisation was granted in the United Kingdom (UK) 16 July 2024.

II QUALITY ASPECTS

II.1 Introduction

The active substance is Quinine Sulfate. Each tablet contains 200mg Quinine Sulfate.

The other ingredients are lactose, maize starch, magnesium stearate, stearic acid, purified talc, sodium croscarmellose, opaglos, sucrose and titanium dioxide.

The finished product is packaged in:

-Plastic securitainer with tamper evident polypropylene lids which are available in pack sizes of 25, 50, 100, 250, 500 & 1000 tablets.

-Blister packs of 0.25mm PVC and 20 microns Aluminium foil which are available in pack sizes of 28 & 56 tablets.

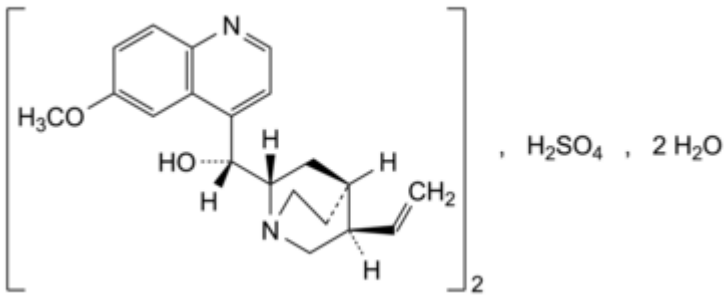
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: quinine sulfate

Chemical Name: bis[(*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol] sulfate dihydrate.

Molecular Formula: $C_{40}H_{50}N_4O_8S,2H_2O$



Chemical Structure:

Molecular Weight: 783

Appearance: White or almost white, crystalline powder or fine, colourless needles.

Solubility: Slightly soluble in water, sparingly soluble in boiling water and in ethanol (96 per cent).

The information related to the active substance was provided in an ASMF. The Active substance is the subject of a Ph.Eur. 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 specifications are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

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

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

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

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose, no excipients of animal or human origin are used in the final products.

The supplier of lactose has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have 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 Specification

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 5 years, with the storage conditions protect from light and moisture and store below 25°C, is acceptable.

Additional storage conditions for the blisters: Do not store above 25°C. Keep the blisters in the outer carton in order to protect from light and moisture.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
This application was submitted under Regulation 54 of The Human Medicines Regulation 2012, as amended, as a well-established use application. No new non-clinical studies were submitted, as the data submitted for these applications is in the form of literature references. As this application are for a line extension of the existing product Quinine sulfate 300 mg Tablets (PL 04556/0032), the non-clinical data are identical to those submitted previously.

III.2 Pharmacology
No new pharmacology data were submitted, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were submitted, and none were required for this application.

III.4 Toxicology
No new toxicology data were submitted, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a product containing an active substance of well-established use that will be used in place of existing products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
As this application are for a line extension of the existing product Quinine sulfate 300 mg Tablets (PL 04556/0032), the clinical data are identical to those submitted previously. Thus, with the exception of the data from the bridging studies, no new clinical data were submitted and none were required.

To support the clinical aspects of this bibliographic application, the applicant has submitted a clinical expert report and a clinical overview. The applicant has also submitted 19 references dated until 2005, some of which are abstracts only. The submitted evidence is summarised in the subsequent sections of this report.

IV. 2 Pharmacokinetics

Absorption

Quinine is readily absorbed orally, mainly from the upper small intestine. Bioavailability is more than 85% in healthy subjects and patients with severe malaria. Quinine is a weak base (pKa 8.4) and is best absorbed at higher pH. In patients with malaria, mean Tmax is increased to 5.9 hours. Mean Cmax and AUC are also increased compared to healthy subjects. Quinine undergoes little first-pass metabolism.

The applicant refers to a randomised cross-over bioavailability study of three oral formulations and one intravenous formulation of quinine as a single 600 mg dose in 6 healthy adult male subjects. Absolute bioavailability was around 65% for a quinine sulfate capsule and a quinine hydrochloride tablet, respectively. The third oral formulation contained no quinine. In another crossover bioavailability study in 12 healthy adult male volunteers, average Tmax was 2.7 hours for both oral formulations (capsule and tablet). Average absolute bioavailability was 73% and 39% for capsule and tablet, respectively.

Distribution

Malaria is associated with a reduction in apparent volume of distribution of quinine, proportional to disease severity. Quinine is 70-80% protein bound, predominantly to alpha 1-acid glycoprotein; the binding is increased in malaria to around 90%. Volume of distribution is 1.5 L/kg in healthy subjects. The volume of distribution is reduced in patients with malaria (1.2 L/kg), and in children and pregnant women. Plasma and red blood cell (RBC) concentrations appear to be similar before infection; however, during a malaria attack, plasma concentrations are higher than RBC concentrations. Quinine does not freely cross the blood-brain barrier; the cerebrospinal fluid to plasma ratio is approximately 2-7%. Quinine crosses the placenta and is distributed into breast milk; peak concentrations are reached in breast milk approximately 90 minutes after oral administration.

Elimination

Malaria is associated with a reduction in systemic clearance of quinine. This is proportional to disease severity. In healthy adults, plasma elimination half-life is 11 hours. The plasma elimination half-life is prolonged by 50% in patients with malaria. In children 1 - 12 years of age, the plasma elimination half-life of quinine reportedly averages 11 - 12 hours in those with malaria and 6 hours in those convalescing from the disease.

Systemic clearance is predominantly by hepatic biotransformation to more polar metabolites (80% of dose). The formation of 3-hydroxyquinine via CYP3A4 is the major metabolic pathway. Inhibitors selective for CYP1A1/2, CYP2D6, CYP2E1, CYP2C9/10 or CYP2C19 had little or no effect on quinine 3-hydroxylation. There is evidence that hepatic metabolism is impaired for patients with malaria, based on the ratio of parent to metabolite. Around 20% of the dose is excreted as unchanged drug in the urine. The metabolites are excreted in the urine, mainly as hydroxy derivatives. Excretion is more rapid when urine is acidic.

Special populations

The impact of renal impairment is not significant, since only 20% of the drug is excreted unchanged in urine. The pharmacokinetics (PK) of quinine in eight patients with severe renal failure on regular haemodialysis has been compared to the PK in eight healthy subjects after a single 300 mg oral dose. In haemodialysis patients, Cmax was higher and total clearance was reduced by 43%. The free fraction of quinine was also reduced, probably due to an increased serum concentration of alpha 1-acid glycoprotein, and free clearance (mainly hepatic) was increased. The authors postulate that this may lead to reduced efficacy.

Interactions

An *in vitro study* tested for interactions of 21 drugs with CYP3A4-catalysed 3-hydroxylation of quinine by human liver microsomes. According to the respective mean IC_{50} values, the inhibitory rank order of the drugs was: ketoconazole > troleandomycin (with preincubation) > doxycycline > omeprazole > primaquine > tetracycline = troleandomycin (without preincubation) > nifedipine > erythromycin > verapamil > cimetidine > diltiazem > oleandomycin > hydralazine. The authors conclude that tetracycline, doxycycline, omeprazole, ketoconazole, nifedipine, troleandomycin and erythromycin are likely to be inhibitors of quinine metabolism *in vivo*, based on likely plasma concentrations. In another *in vitro* study of human liver microsomes, quinine inhibited the metabolism of etoposide via inhibition of CYP3A4. In addition, etoposide inhibited the metabolism of quinine via inhibition of CYP3A4.

In vivo, adverse drug interactions include marked reduction in the clearance of digitalis glycosides, reduction in the clearance of flecainide, and potentiation of oral anticoagulants.

The applicant has conducted an up-to-date literature search for additional evidence to support the clinical pharmacokinetics. This is summarised below.

Oral quinine is rapidly and almost completely absorbed with a Tmax of 1-3 hours. Quinine is widely distributed including to CSF, breast milk and placenta. Volume of distribution is reduced in the presence of malaria. Plasma-protein binding (mainly to ∝1-acid glycoprotein) increases from about 80%, in healthy subjects to 90% in patients with malaria.

Quinine undergoes extensive hepatic biotransformation mainly via CYP3A4 enzymes. The main metabolite is 3-hydroxyquinine which contributes approximately 10% of the antimalarial activity of the parent compound. Up to 20% of the administered drug is excreted unchanged by the kidneys. Clearance is reduced in the presence of malaria. The elimination half-life is approximately 11 hours in healthy subjects but may be prolonged in patient with malaria.

Half-life is increased in patients with hepatic impairment, with risk of accumulation. In severe renal impairment, exposure to the main metabolite is increased by 45%. In pregnancy, exposure is generally lower. Higher concentrations are observed in children <2 years.

Inhibitors of CYP3A4 such as erythromycin, ciprofloxacin, cimetidine and ritonavir, have been shown to increase exposure to quinine. Rifampicin, a CYP3A4 inducer, reduces exposure to quinine.

Quinine reduces exposure to penicillins, possibly due to delayed gastric emptying. Quinine inhibits the metabolism of halofantrine, phenytoin and carbamazepine, and increases exposure to ritonavir. Quinine reduces the clearance of digoxin via biliary excretion, resulting in increased digoxin exposure. Quinine may increase the effects of anticoagulants, neuromuscular blockers and hypoglycaemics, due to pharmacodynamic interactions.

The applicant has adequately reviewed the bibliographic evidence to support the PK of quinine. The PK aspects are adequately reflected in sections 4.2, 4.5 and 5.2 of the SmPC, which is in line with the applicant's approved Quinine Sulphate 300mg Tablets (PL 04556/0032).

IV.3 Pharmacodynamics

Malaria

Quinine is a highly active blood schizonticide and suppresses the asexual cycle of development of malaria parasites in the erythrocytes. Quinine interferes with parasite metabolism of heme, a toxic product of haemoglobin digestion. Quinine is maximally active on the mature trophozoite stage of parasite development (roughly the middle third of the cycle).

Nocturnal leg cramps

Quinine is thought to act by decreasing the excitability of the myoneuronal plate and by increasing the refractory period of striated muscle.

Relationship between plasma concentration and effect

The applicant refers to a pharmacokinetic-pharmacodynamic (PK-PD) study in 30 adult males with uncomplicated acute *P. falciparum.* All patients were treated with a 7-day course of oral quinine (10 mg/kg/day), alone or on combination with rifampicin (n=8). All patients recovered. Mean parasite clearance time (PCT) was 73 hours. PCT correlated positively with quinine AUC over 0-7 days. During a 28-day monitoring period, six patient had recrudescent infections, of which four had also received rifampicin. Low AUC over days 3-7 was associated with an increased risk of recrudescence. Rifampicin may have increased the chance of treatment failure by inducing cytochrome P450. The mean minimum inhibitory concentration (MIC) was estimated to be 0.68 μg/ml (95% CI, 0.65 to 0.71) and the mean minimum parasiticidal concentration (MPC) was estimated to be 7.25 μg/ml (95% CI, 3.12 to 3.41). The authors conclude that it is necessary to maintain concentrations of quinine above the MPC for the entire 7-day treatment course, equivalent to 4 parasite asexual cycles.

The applicant has conducted an up-to-date literature search for additional evidence to support the clinical pharmacodynamics as detailed below.

Quinine kills large ring and trophozite asexual parasites and is gametocytocidal against *P.vivax, P.ovale* and *P.malariae* but not *P.falciparum* malaria. The mechanism of action is not clearly understood, although it is thought to involve inhibition of the parasite's ability to detoxify haem inside the food vacuole. When the parasite digests haemoglobin in the erythrocyte, an accumulation of iron(III)protoporphyrin IX occurs in the parasite's digestive vacuole. The parasite then eliminates the heme-complex into the cytoplasm and converts it into hemozoin. Quinoline-based antimalarial compounds block the formation of hemozoin resulting in an accumulation of the heme-complex and subsequent toxicity to the pathogen.

Quinine also reduces the excitability of the motor end plates to nerve stimulation.

The applicant has adequately reviewed the bibliographic evidence to support the pharmacodynamics of quinine.

IV.4 Clinical efficacy

Nocturnal leg cramps

A meta-analysis of randomised clinical trials evaluating its efficacy for the relief of nocturnal leg cramps supports its use for this indication. A meta-analysis included six randomised double-blind placebo-controlled cross-over trials of quinine for nocturnal leg cramps, in a total of 107 predominantly elderly ambulatory patients. Doses were 200 mg to 300 mg per day over 2-4 weeks. For five trials that reported absolute change in number of cramps, the combined absolute reduction in number of night cramps over 4 weeks (vs placebo) was 8.83

(95% CI: 4.16 to 13.49). The 2-week trials did not demonstrate a benefit. Two trials (n=51) reported on number of nights with cramps. There was a 27.5% reduction (95% CI: -30.6 to -24.4). There was no evidence of a reduction in cramp severity or duration.

A later meta-analysis (1997) added unpublished data. This was a meta-analysis of eight randomised double-blind placebo-controlled trials, seven of which had a crossover design. A total of 695 ambulatory patients with regular nocturnal cramps were included. Pooled data demonstrated that there was a 3.60 (95% CI: 2.15, 5.05) reduction in number of cramps over 4 weeks compared to placebo. The relative risk reduction was 21% (95% CI: 12%, 30%). There was also a statistically significant reduction in severity of 0.13 units (95% CI: 0.05, 0.21) when severity was converted to a 3-point scale (1 = mild, 2 = moderate, 3 = severe).

The 1997 meta-analysis provides evidence for the efficacy of quinine at the 200 mg daily dose, for the treatment and prevention of nocturnal leg cramps.

The applicant has conducted an up-to-date literature search for additional evidence to support the clinical efficacy of the proposed product in the malaria and nocturnal leg cramp indications.

The applicant refers to a recent review of the management of nocturnal leg cramps in older people, which concludes that quinine is the only drug shown to reduce the frequency and intensity of leg cramps. This review refers to the 2015 Cochrane Review of quinine for muscle cramps. The Cochrane review considered 23 randomised controlled trials with 1586 participants, mostly older patients with idiopathic nocturnal leg cramps. Quinine (200 mg to 500 mg daily) was compared with placebo or active control. The most frequent dose was 300 mg daily. Compared to placebo, quinine reduced cramp numbers over a 2-week period by 28% (absolute difference of about 2.5 cramps). Cramp intensity, measured on a scale from 1 (mild) to 3 (severe), was reduced by 0.12 (10% reduction). There was insufficient evidence to judge the optimal dosage or duration of quinine treatment. The review concluded that there is low quality evidence that quinine significantly reduces the frequency of cramps, and moderate quality evidence that quinine reduces cramp intensity.

The applicant has adequately reviewed the bibliographic evidence to support the clinical efficacy of quinine in the treatment and prevention of nocturnal leg cramps. The proposed indication and posology are in line with that of the applicant's approved Quinine Sulphate 300mg Tablets (PL 04556/0032). The provision of a 200 mg strength product will facilitate prescription of the recommended dose (200 mg at bedtime).

<u>Treatment of malaria</u>
The applicant has provided the UK malaria treatment guidelines 2016. Uncomplicated P. falciparum malaria should be treated with an artemisinin combination therapy (ACT). Quinine or atovaquone/proguanil can be used if an ACT is not available. Quinine is highly effective but poorly-tolerated in prolonged treatment and should be used in combination with an additional drug, usually oral doxycycline.

Uncomplicated falciparum malaria in the first trimester of pregnancy should usually be treated with quinine and clindamycin. Quinine and clindamycin can also be used during the second and third trimesters although ACT is considered the treatment of choice. Children with uncomplicated malaria should be treated with an ACT as first line treatment. Quinine with doxycycline or clindamycin, or atovaquone/proguanil can also be used.

The applicant also refers to the WHO Guidelines for the treatment of malaria which recommends quinine and clindamycin when treating uncomplicated *P. falciparum* (or chloroquine resistant *P. vivax* malaria) during the first trimester of pregnancy. Quinine is regarded as safe in the first trimester at therapeutic doses and there was no evidence of effects on uterine contractions following its use in cases of uncomplicated and severe malaria. In the second and third trimesters, meta-analyses showed the risk of stillbirth and congenital abnormalities are the same for quinine-based treatments and artemisinin-based treatments. Doses of 10mg/kg/dose three times a day in pregnant patients are administered, with or without clindamycin, for 7 days.

The recommended posology in adults is oral quinine sulfate 600 mg 8 hourly for 5-7 days. However pregnant women may be candidates for parenteral therapy following specialist advice. In children, the recommended posology is 10 mg/kg 8 hourly for 7 days.

The applicant has adequately reviewed the bibliographic evidence to support the clinical efficacy of quinine in the treatment of malaria. High quality evidence from clinical trials is not expected, since quinine has been in well-established use for centuries. Instead, the applicant refers to recent reviews and guidelines, which is appropriate.

Artemisinin combination therapy (ACT) is the treatment of choice in uncomplicated falciparum malaria. Superior efficacy to quinine has been demonstrated, in part due to poor compliance with quinine, which has to be taken for longer and can cause cinchonism (nausea, deafness, tinnitus). However, quinine remains an effective treatment option, if combined with doxycycline (or clindamycin in children under 12).

Quinine in combination with clindamycin is the recommended first-line treatment of uncomplicated falciparum malaria during the first trimester of pregnancy.

The proposed indication and posology are in line with that of the applicant's approved Quinine Sulphate 300mg Tablets (PL 04556/0032). The restriction to uncomplicated falciparum malaria is appropriate, since severe or complicated malaria necessitates parenteral therapy. Chloroquine and sulfadoxine/ pyrimethamine are no longer recommended for the treatment of falciparum malaria due to widespread resistance i.e. most falciparum malaria strains are considered chloroquine or multi-drug resistant. However, since resistance to ACTs is now emerging[1], the reference to chloroquine or multi-drug resistant strains can be accepted.

The proposed posology is in line with the recommendations of the latest UK guideline and is acceptable.

IV.5 Clinical safety

A meta-analysis included 6 randomised double-blind placebo-controlled cross-over trials of quinine for nocturnal leg cramps, in a total of 107 predominantly elderly ambulatory patients. Doses were 200 mg to 300 mg per day over 2-4 weeks. One subject experienced nausea, myalgia, leucopenia and thrombocytopenia that resolved 3 days after quinine discontinuation. A small number of subjects reported minor adverse effects.

A later meta-analysis (1997) added unpublished data. This was a meta-analysis of 8 randomised double-blind placebo-controlled trials, 7 of which had a crossover design. A total

of 695 ambulatory patients with regular nocturnal cramps was included. This included patients from an unpublished parallel group study sponsored by a pharmaceutical company. Tinnitus was reported with a significantly higher frequency by subjects taking quinine, compared to placebo.

Cinchonism, comprising tinnitus, deafness, headache, nausea, and visual disturbance, affects most conscious malaria patients with therapeutic levels. Quinine stimulates release of insulin and may precipitate hypoglycaemia.

Certain patient groups are at particular risk of severe AEs (including the elderly, the very young, glucose-6-phosphate dehydrogenase (G6PD)-deficient people and HIV positive people).

Ototoxicity
Ototoxicity was monitored by audiogram during a clinical study which included healthy volunteers and patients with malaria. Nine of the 12 healthy subjects who received a single dose of IV quinine 300 mg suffered hearing losses especially in the high frequencies, although in most cases these transient hearing impairments remained unnoticed by the subjects. Nine patients with falciparum malaria who received IV quinine 600 mg TID for 3 days and were also evaluated. They showed indications of hearing impairment on the 3rd day of infusion with standard audiometry. They all reported impaired hearing and tinnitus, but eventually recovered.

Cardiotoxicity
In the study described under ‘ototoxicity’, subjects were also monitored for electrocardiographic changes. No changes were observed in healthy subjects after a single 300 mg dose. For the malaria patients (600 mg TID for 3 days), there was an increase in QTc from a mean (± SD) of 0.390 (± 0.04) seconds to a mean of 0.470 (± 0.04) seconds.

Hypersensitivity
Hypersensitivity reactions are uncommon and involve rashes, thrombocytopenia, leukopenia, disseminated intravascular coagulation, haemolytic-uremic syndrome, bronchospasm and pancytopenia.

Overdose
A 1996 report for the UK National Poisons Unit has been submitted. Quinine is noted to be highly toxic in overdose. Quinine causes nausea, vomiting, tremor, tinnitus and deafness. Blurred vision may proceed to complete (sometimes irreversible) blindness within a few hours. Tachycardia, dysrhythmias, hypotension and ECG conduction abnormalities may precede cardiac arrest. Oliguria and acute renal failure from intravascular haemolysis may occur, as well as coma and convulsions (especially in children). There is a higher risk of visual loss and cardiac complications when plasma concentrations of quinine exceed 15 mg/l at any stage of overdosage. The average fatal dose for an adult is about 8 g although deaths have been reported from as little as 1.5 g in an adult and 900 mg in a child.

Activated charcoal increases the clearance of quinine.

The applicant has conducted an up-to-date literature search for additional evidence to support the clinical safety of the proposed product, this is provided below.

The applicant refers to ‘Meyler’s side effects of drugs’ which lists nausea, tinnitus, dizziness

as common ADRs. More serious ADRs relate to pro-dysrhythmic effects, hypoglycaemia, hepatic injury, renal impairment, psychosis and hypersensitivity. Quinine crosses the placenta and is found in high concentrations in cord blood. It is also excreted in breastmilk. However, reports of teratogenicity at therapeutic doses are scarce.

The applicant also refers to a 2016 systematic review of 383 publications on adverse reactions to quinine. As well as cinchonism (nausea, deafness, tinnitus) and cardiac abnormalities (QRS or QT interval increases), the review identified immune-mediated reactions (particularly with prior quinine exposure), thrombocytopenia and thrombotic microangiopathy. The WHO Guidelines mention severe ADRs including loss of vision, and warns about the importance of recognising hypoglycaemia, particularly in pregnant women and children. The high tone hearing loss associated with cinchonism is dose dependent and reversible on drug withdrawal.

The applicant refers to a systematic review of 177 clinical trials was conducted in a study to determine the nature of the arrhythmogenic cardiotoxicity of quinoline or structurally related antimalarials. Quinine was included in 51 of these trials which included 2,611 participants, 2,320 of which had ECGs. The review concluded that a variety of generally non-serious, self-limiting cardiac rhythm abnormalities were described, and no sudden deaths were noted. Serious cardiovascular events were rare.

Regarding use at lower doses to prevent or treat nocturnal cramps, the Cochrane Review 2015 concludes that a significantly greater number of people suffered minor adverse events on quinine than placebo (risk difference 3%, 95% confidence interval 0% to 6%), mainly gastrointestinal symptoms. In the included trials there was no significant difference in major adverse events compared with placebo. One participant suffered from thrombocytopenia (0.12% risk) on quinine. There is moderate quality evidence that with use up to 60 days, the incidence of serious adverse events is not significantly greater than for placebo in the identified trials.

The applicant has adequately reviewed the bibliographic evidence to support the clinical safety of quinine in the treatment of malaria, and the treatment and prevention of nocturnal leg cramps.

IV.6 Risk Management Plan (RMP)

The Applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

The applicant has provided appropriate literature references (including contemporary references), and these are summarised in a clinical overview. Taken in conjunction with the well-established use of this medicine the clinical overview was considered sufficient to support an understanding of the safety, and efficacy of the product. The quality of the product has been supported by the information and data in the relevant module of the dossier.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

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 from the literature. Extensive clinical experience with quinine sulfate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**