Prescribing Information (Summary of Product Characteristics)

1. NAME OF THE MEDICINAL PRODUCT

S-QUIN (Quinine Dihydrochloride Intravenous Infusion BP 600 mg/2 ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NOT FOR USE IN NEONATES

CONTAINS BENZYL ALCOHOL

QUALITATIVE DECLARATION

Quinine Dihydrochloride BP
Benzyl Alcohol BP
Sodium Hydroxide BP
Water for Injections BP

QUANTITATIVE DECLARATION

Each ml contains:
Quinine Dihydrochloride BP.....300 mg
Benzyl Alcohol BP.....0.5% w/v (As Preservative)
Water for Injections BP.....q. s

3. PHARMACEUTICAL FORM

Solution for Injection

Description: Light Yellow colour clear liquid

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

For the treatment of acute attacks of malaria, including attacks due to chloroquine-resistant or multi-drug-resistant strains of Plasmodium falciparum.

Quinine is used Parenterally for cerebral, severe or complicated malaria, or when vomiting prevents retention of an orally administered drug. Quinine dihydrochloride is the salt usually employed for the preparation of injections.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

General

NOTE: CONTAINS BENZYL ALCOHOL (see PRECAUTIONS).

Adult Dosage:
Usual adult and adolescent dose
Malaria, Plasmodium falciparum, severe (treatment):
Loading dose: 20 mg/kg up to a maximum of 1400 mg given slowly by infusion over 4 hours. Commence the maintenance doses 8 to 12 hours after loading dose.

Maintenance dose: 10 mg/kg up to a maximum of 700 mg over 4 hours given slowly by infusion. Repeat every 8 - 12 hours if necessary.
A loading dose is not required if anti-malarials have been given during the previous 24 hours.

If parenteral therapy is required for more than 48 hours, the maintenance dose of quinine should be reduced by one third to one half to 5 mg/kg to avoid accumulation and drug level monitoring is important.

Alternatively, in Intensive Care Units or if an infusion pump is available, an initial loading dose of 7mg/kg may be given over 30 minutes followed immediately by the first of the maintenance infusions.
Note: The two dosage regimens listed above are equally effective. Either regimen should be administered in conjunction with doxycycline, clindamycin, or Sulfadoxine / pyrimethamine combination.

Treatment should be switched to oral quinine sulfate when the patient can swallow, to complete a seven-day treatment course.

MODE OF ADMINISTRATION
By Slow Infusion or deep IM Injection.
If IV infusion is not possible, quinine dihydrochloride has been given IM route. This can be an irritant, cause pain (quinine dihydrochloride are acidic (pH 2)), focal necrosis and abscess formation, and fatal tetanus has developed in some patients, and there have been concerns regarding its safety and efficacy. The IM route should only be used as a last resort.

IV infusion: The solution should be diluted before administration infused slowly over 4 hours.
Hypotension and cardiac arrest may result from rapid intravenous injection. Intravenous quinine should be given only by infusion, never injection.

Loading dose: max.< 1400mg
Maintenance dose: max. < 700mg
Quinine causes an approximately 10% prolongation of the electrocardiograph QT interval – mainly as a result of slight QRS widening. The effect on ventricular repolarization is much less than that with quinidine.

Dosage and directions to use
In severe or complicated malaria, when the patient is unable to take oral medication, a slow intravenous infusion of quinine is used. In severely ill adults, a loading dose of 20 mg quinine dihydrochloride per kg may be administered by slow, constant rate intravenous infusion diluted in either isotonic fluid or 5% glucose solution (5-10 mL per kg bodyweight depending on the patient's overall fluid balance) over four hours provided that the patient has not received quinine, quinidine or mefloquin during the previous twelve to twenty-four hours, and reliable hospital facilities are available, including cardiac monitoring.

If any of the following happen tell your doctor or nurse immediately or go to the Emergency Department at your local hospital:
• skin rash, itching, swelling of the face, flushing of the skin
• wheezing, difficulty breathing

• irregular heartbeat, chest pain
• symptoms of liver disease such as yellowing of the eyes and skin
• reduced or no urine produced or discoloured urine
• increase in bruising or bleeding
• muscle weakness
• fainting. The above list includes some very serious s

4.3.CONTRAINDICATIONS
Patients hypersensitive to quinidine may be hypersensitive to this medication also.
Medical considerations/Contraindications
The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate) not necessarily inclusive.

Risk-benefit should be considered when the following medical problems exist Blackwater fever, history of (interrupted or recurrent quinine therapy in patients with Plasmodium falciparum infections may predispose them to the complications of black water fever, including anemia and hemolysis with renal failure).

Cardiac arrhythmias, history of, or QT prolongation (a prolonged QT interval has been noted in patients being treated for cerebral malaria, without correlation with plasma quinine concentration; patients with a history of cardiac arrhythmias or QT prolongation may be at risk for arrhythmias while taking quinine).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency (hemolysis or hemolytic anemia may occur in G6PD-deficient patients; however, quinine has been given safely in therapeutic doses to patients with G6PD deficiency).

- Hypersensitivity to quinine or quinidine
- Hypoglycemia (quinine stimulates release of insulin from the pancreas; hypoglycemia may also be a complication of severe P. falciparum malaria, especially in children and during pregnancy)
- Myasthenia gravis (quinine may exacerbate muscle weakness in myasthenia gravis due to its neuromuscular blocking effects) Purpura, thrombocytopenic, or history of (quinine may cause thrombocytopenic purpura, especially in highly sensitive patients or in patients with a previous history of this reaction to quinine)
  Quinine Dihydrochloride Intravenous Infusion is contraindicated for use in premature infants because the formulation contains benzyl alcohol. (See **WARNINGS** and **PRECAUTIONS: Pediatric Use**.)

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings

Quinine must be used with caution in patients with atrial fibrillation or other serious heart disease.

Quinine may aggravate symptoms of myasthenia gravis and should be used with care if at all in such patients.

Quinine may cause Hypoprothrombinaemia and enhance the effects of anticoagulants. Quinine must be stopped immediately if evidence of haemolysis appears.

Antimalarial agents and especially quinine, when given for prolonged periods, have been implicated in precipitating black water fever. However, in some cases deficiency of glucose-6-phosphate dehydrogenase may have been involved. Glucose-6-phosphate dehydrogenase- deficient patients with malaria may be at increased risk of haemolysis during quinine therapy.

Precautions

Check for hypersensitivity to quinine or quinidine before administration. It is important that when given intravenously it should be given by slow infusion and the patient observed closely for signs of cardiotoxicity.

Pulse and blood pressure should be closely monitored and the rate of infusion attenuated if dysrhythmias occur, and blood glucose concentrations should be monitored. Therapy should be changed to oral administration as soon as possible.

If intravenous infusion is not possible, quinine dihydrochloride has been given intramuscularly. This can be an irritant, cause pain, focal necrosis and abscess formation, and fatal tetanus has developed in some patients, and there have been concerns regarding its safety and efficacy. The intramuscular route should only be used as a last resort.

Haemolysis: Quinine dihydrochloride should be stopped immediately and supportive measures instituted if signs of haemolysis appear. Haemolysis with a potential for haemolytic anaemia has been reported when given to patients with G6PD deficiency.
Prothrombin Formation: Quinine dihydrochloride is capable of causing hypoprothrombinaemia and may enhance the effect of anticoagulants.

Atrial Fibrillation: Patients with this condition should be digitilised before receiving quinine as otherwise it may cause an increase in the ventricular rate. **Hypersensitivity:** Reactions include cutaneous flushing, pruritis, rash, fever, facial oedema, GI distress, dyspnoea, tinnitus, and impairment of vision. The most frequently reported hypersensitivity reaction is extreme flushing of the skin with intense pruritis. If evidence of hypersensitivity occurs, quinine therapy should be discontinued.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Digitalis glycosides: Quinine markedly reduces the renal clearance of digoxin and digoxin levels may be doubled.

Flecainide: Quinine reduces the systemic clearance.

Warfarin: Quinine may potentiate warfarin by inhibiting its hepatic metabolism.

Cimetidine: Cimetidine inhibits the hepatic metabolism of quinine. **Hypoglycaemic drugs:** As quinine stimulates the release of insulin from islet cells, diabetic control may be compromised.

Mefloquine: Quinine and Mefloquine are both quinolinemethanols and have similar cardiac adverse effects; consequently, there has been concern about the potentially additive toxicity from the combination. Patients who have taken a therapeutic dose of mefloquine before developing severe malaria may not require a loading dose of quinine.

Pediatric Use
This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome" (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

Although normal therapeutic doses of this product ordinarily delivers amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the hepatic capacity to detoxify the chemical. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

4.6. PREGNANCY AND LACTATION Pregnancy considerations:

The use of anti-malarial for the treatment of life threatening malaria during pregnancy is acceptable, because the small risk to the fetus is outweighed by the benefits to the mother and fetus.
In high doses, quinine causes fetal injuries in the form of deafness, development disturbances, and malformation of the extremities and cranium.

It has the ability to induce uterine contractions and constitutes a risk of abortion.
This product contains benzyl alcohol as a preservative.
Benzyl alcohol can cross the placenta. See **PRECAUTIONS: Pediatric use**.

Quinine should not be withheld from pregnant women with life-threatening malaria if other less hazardous agents are unavailable or inappropriate. Pregnant women seem to be particularly prone to quinine-induced hyperinsulinaemia and hypoglycaemia. Excessive doses may induce abortion, and congenital malformation of the optic and auditory nerves have been reported after failure to induce abortion with quinine.

When administered intravenously to pregnant patients, the infusion rate should not exceed 10 mg/kg every eight **hours.**

Breastfeeding considerations:
Quinine is distributed into breast milk in small amounts. One study suggests that a breast-fed infant will receive approximately 1.5 to 3 mg per day of quinine base from maternal therapy. Problems in humans have not been documented.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None

4.8. UNDESIRABLE EFFECTS

Very common (≥10%)
Gastrointestinal disturbances (abdominal or stomach cramps or pain; diarrhea; nausea; vomiting).

Note: Symptoms of gastrointestinal disturbances, such as nausea and vomiting, may be related to central nervous system (CNS) effects of quinine.

Common (1%-10%)
When quinine is given repeatedly, a group of symptoms known as cinchonism occurs. Cinchonism symptoms include tinnitus, impaired hearing, headache, nausea, disturbed vision, vomiting, abdominal pain, diarrhoea, and vertigo.

Blood dyscrasias such as agranulocytosis, leukopenia, and/or thrombocytopenia (black, tarry stools; blood in urine or stools; cough or hoarseness; fever or chills; lower back or side pain; painful or difficult urination; pinpoint red spots on skin; sore throat; unusual bleeding or bruising; unusual tiredness or weakness) hypoglycemia (anxiety; behavior change, similar to drunkenness; blurred vision; cold sweats; confusion; convulsions or coma; cool pale skin; difficulty in concentrating; drowsiness; excessive hunger; fast heartbeat; headache; nausea; nervousness; nightmares; restless sleep; shakiness; slurred speech; unusual tiredness or weakness).

Note: Hypoglycemia, which may be severe and recurrent, has been reported in some patients with severe malaria caused by Plasmodium falciparum who received quinine therapy, and there was some evidence that quinine-induced insulin secretion may have been one of several possible precipitating factors.
Serious ADR (<1%)

hypersensitivity reactions (abdominal pain; difficulty in breathing and/or swallowing; fever; hives; nausea; reddening of the skin, especially around ears; swelling of eyes, face, or inside of nose; unusual tiredness or weakness) hypoprothrombinemia (unusual bleeding or bruising) visual disturbances (blurred vision; disturbed color perception; double vision; night blindness) **Note:** Hemolytic uremic syndrome (HUS) is a multi-system disorder that is characterized by hemolytic anemia, thrombocytopenia, disseminated intravascular coagulation (DIC), and acute renal failure. This reaction may occur within hours of a single ingestion of quinine. Several case reports have been published describing patients who have had an acute hypersensitivity reaction to quinine that resulted in adult HUS.

Hypoprothrombinemia may be reversed with vitamin K administration.

4.9. OVERDOSE

Poisoning by quinine is usually due to clinical overdose or to hypersensitivity. Symptoms of overdosage include gastro-intestinal, central nervous system, cardiovascular disturbances, and other toxic symptoms mentioned under side- effects to an enhanced degree. Visual disturbances are usually reversible but may be permanent, and may rarely include sudden blindness.

CNS Symptoms
These are noted in more severe grades of poisoning, particularly headache, fever, vomiting, apprehension, excitement, confusion, delirium, and syncope. Respiration is first stimulated and then shallow and depressed.

The skin becomes cold and cyanotic as poisoning progresses, the body temperature and blood pressure fall, weakness is extreme and the pulse is feeble, coma ensues and death occurs from respiratory arrest.

Severe poisoning can produce convulsions, coma, respiratory depression and death.
The average fatal dose in adults has been reported to be about 8 g. Death may result in a few hours or may be delayed for one to two days.

If large doses of quinine or its salts have been recently ingested, the stomach should be emptied by aspiration and lavage.

Measures aimed at enhancing the elimination of quinine such as forced acid diuresis, haemodialysis, and haemoperfusion are largely ineffective because quinine is extensively metabolized in the liver.

Blood pressure should be supported. Signs of haemolytic anaemia may be indicative of a need to treat acute renal failure.

Assisted respiration may be necessary to combat respiratory failure. Cardiac rhythm should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMICS PROPERTIES

Quinine is a blood schizonticidal agent and is active against the asexual erythrocytic forms of P. falciparum, P. malariae, P. ovale and P. vivax. The drug is not active against sporozoites or pre-erythrocytic or exoerythrocytic forms of plasmodia. Quinine is also gametocytocidal for *P. malariae, P. vivax and P. ovale*, but has no direct activity against the gametocytes of *P. falciparum*.

The precise mechanism of the antimalarial activity of quinine is not completely understood. It is thought that pH elevation in the intracellular organelles of the parasites by quinine plays a role in the mechanism. The drug appears to interfere with the function of plasmodial DNA.

Because quinine is active only against the asexual erythrocytic forms of plasmodia, the drug cannot prevent delayed primary attacks or relapse of *P. ovale or P. vivax* malaria and cannot provide a radical cure in malaria caused by these species since they have exoerythrocytic stages. Therefore, primaquine phosphate may be indicated in conjunction with quinine if the drug is used for treatment of *P. vivax* malaria.

Resistance to quinine has been reported rarely in *P. falciparum* malaria. Although cross-resistance has been demonstrated rarely between quinine and 4-aminoquinoline derivatives, quinine may be active against some strains of *P. falciparum* that are resistant to chloroquine and/or sulphadoxine and pyrimethamine.

5.2. PHARMACOKINETIC PROPERTIES

Quinine is also gametocidal for P. vivax and P. malariae but not for P. falciparum, and therefore does not prevent transmission of this infection by the mosquito.

Plasma concentrations of quinine between 8 and 15 mg/liter are effective clinically and are generally non-toxic; such values are usually achieved with the standard therapeutic dose.

Approximately 70% of quinine is bound to proteins in the plasma in healthy subjects, rising to about 90% in patients with malaria. The concentration in cerebrospinal fluid is about 2-5% of that in the plasma. Quinine is extensively metabolized, especially in the liver, and excreted in the urine. Estimates of the proportion of unchanged quinine excreted in the urine vary from less than 5% to 20%.

The metabolites are excreted in the urine; renal excretion of quinine is twice as rapid when the urine is acidic as when it is alkaline.

The elimination half-life in healthy subjects is about eleven hours, but may be prolonged in patients with malaria.

The pharmacokinetics of quinine may be altered significantly by malaria infection, with reductions in both clearance and the apparent volume of distribution.
Quinine crosses the placenta and is excreted in breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENT(S)

Benzyl Alcohol BP
Sodium Hydroxide BP
Water for Injections BP

6.2. INCOMPATIBILITIES

None

6.3. SHELF-LIFE

36 months

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Do not Store above 30^{o}C. Protect from light.
KEEP OUT OF REACH OF CHILDREN.

6.5. NATURE AND CONTENTS OF CONTAINER

2 ml amber USP type I glass Ampoules with printed label and such 10 Ampoules packed in a carton along with plastic tray & Insert.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

For single use. Discard any unused contents.

7. MARKETING AUTHORISATION HOLDER

Swiss Parenterals Limited,
808, 809, 810 Kerala Industrial Estate, G.I.D.C,
Nr. Bavla City, Ahmedabad Dist. Ahmedabad 382 220, Gujarat, India.

8. MARKETING AUTHORISATION NUMBER(S)

TAN 22 HM 0202

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/08/2021

10. DATE OF REVISION OF THE TEXT