SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hydroxychloroquine Sulfate 200 mg Film – Coated Tablets
Quinoric 200mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg Hydroxychloroquine Sulfate B.P.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film coated tablet (tablet)

White, circular, biconvex film coated tablets debossed with ‘200’ on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight.

Paediatric Population
Treatment of juvenile idiopathic arthritis (in combination with other therapies) , discoid and systemic lupus erythematosus.

4.2 Posology and method of administration

Posology

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

In patients able to receive 400mg daily:

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

Paediatric population
The minimum effective dose should be employed and should not exceed 6.5 mg/kg/day based on ideal body weight. The 200 mg tablet is therefore not suitable for use in children with an ideal body weight of less than 31kg.

Method of administration
The tablets are for oral administration.

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.

4.3 Contraindications

- Hypersensitivity to the active substance, 4-aminoquinoline compounds or to any of the excipients listed in section 6.1.
- Pre-existing maculopathy of the eye.
- Pregnancy (see section 4.6).

4.4. Special warnings and precautions for use

Retinopathy
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. Thereafter, ophthalmological examinations must be repeated at least every 12 months.

The examination should include testing visual acuity, careful ophthalmoscopy, fundoscopy and 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.
- concomitant use of hydroxychloroquine sulfate with drugs known to induce retinal toxicity, such as tamoxifen.

Hydroxychloroquine 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.

Extrapyramidal disorders
Extrapyramidal disorders may occur with Hydroxychloroquine sulfate (see section 4.8).

Hypoglycaemia
Hydroxychloroquine has been shown to cause severe hypoglycaemia including loss of consciousness that could be life threatening in patients treated with and without antidiabetic medications. Patients treated with hydroxychloroquine should be warned about the risk of hypoglycaemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycaemia during treatment with hydroxychloroquine should have their blood glucose level checked and treatment reviewed as necessary.

QT interval prolongation
Hydroxychloroquine has the potential to prolong the QTc interval in patients with specific risks factors. Hydroxychloroquine should be used with caution in patients with congenital or documented acquired QT prolongation and/or known risk factors for prolongation of the QT interval such as:

- cardiac disease, e.g., heart failure, myocardial infarction
- proarrhythmic conditions, e.g., bradycardia (< 50 bpm)
- a history of ventricular dysrhythmias
- uncorrected hypokalemia and/or hypomagnesemia
- during concomitant administration with QT interval prolonging agents (see section 4.5) as this may lead to an increased risk for ventricular arrhythmias.

The magnitude of QT prolongation may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded.

Chronic Cardiac toxicity
Cases of cardiomyopathy resulting in cardiac failure, in some cases with fatal outcome, have been reported in patients treated with hydroxychloroquine sulfate (see section 4.8 and 4.9). Clinical monitoring for signs and symptoms of cardiomyopathy is advised and with hydroxychloroquine sulfate should be discontinued if cardiomyopathy develops. Chronic toxicity should be considered when conduction disorders (bundle branch block / atrio-ventricular heart block) as well as biventricular hypertrophy are diagnosed (see section 4.8).

Bone marrow depression
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 should be discontinued if abnormalities develop.

Other monitoring on long term treatments
Patients on long-term therapy should have periodic full blood counts, and hydroxychloroquine should be discontinued if abnormalities develop (See section 4.8).
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 (see section 4.8)

Potential carcinogenic risk
Experimental data showed a potential risk of inducing gene mutations. Animal carcinogenicity data is only available for one species for the parent drug chloroquine and this study was negative (see section 5.3). In humans, there is insufficient data to rule out an increased risk of cancer in patients receiving long-term treatment.

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.
- 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.

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

Dermatological reactions
Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Hydroxychloroquine.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Hydroxychloroquine treatment should be discontinued.

The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS or TEN with the use of Hydroxychloroquine, Hydroxychloroquine must not be re-started in this patient at any time.

Severe cutaneous adverse reactions (SCARs)
Cases of severe cutaneous adverse drug reactions (SCAR), including drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported during treatment with hydroxychloroquine. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. If signs and symptoms suggestive of severe skin reactions appear, hydroxychloroquine should be withdrawn at once and alternative therapy should be considered.

Suicidal behavior and psychiatric disorders
Suicidal behavior and psychiatric disorders have been reported in some patients treated with hydroxychloroquine (see section 4.8). Psychiatric side effects typically occur within the first month after the start of treatment with hydroxychloroquine and have been reported also in patients with no prior history of psychiatric disorders. Patients should be advised to seek medical advice promptly if they experience psychiatric symptoms during treatment.

Carefully consider the benefits and risks before prescribing hydroxychloroquine for any patients taking azithromycin or other macrolide antibiotics, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

Hepatotoxicity
Serious cases of drug-induced liver injury (DILI) including hepatocellular injury, cholestatic liver injury, acute hepatitis, mixed hepatocellular/cholestatic liver injury and fulminant hepatic failure (including fatal cases) have been reported during use of Hydroxychloroquine sulfate.

Risk factors may include pre-existing liver disease, or predisposing conditions such as uroporphyrinogen decarboxylase deficiency or concomitant hepatotoxic medications. Prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury. For patients with significant liver function abnormalities (see section 4.8), physicians should assess the benefits/risk of continuing the treatment.

Hydroxychloroquine sulfate should be used with caution in patients taking medicines which may cause adverse skin reactions.

Hepatitis B reactivation
Reactivation of hepatitis B virus has been reported in patients treated with hydroxychloroquine in combination with other immunosuppressants.

4.5 Interaction with other medicinal products and other forms of interaction

Digoxin
Hydroxychloroquine sulfate has been reported to increase plasma digoxin levels: Serum digoxin levels should be closely monitored in patients receiving concomitant treatment.

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

Drugs known to prolong the QT interval/with potential to induce cardiac arrhythmia
Hydroxychloroquine should be used with caution in patients receiving drugs known to prolong the QT interval, e.g., Class IA and III antiarrhythmics, tricyclic antidepressants, antipsychotics, some anti-infectives (e.g. macrolides including azithromycin) due to increased risk of ventricular arrhythmia (see sections 4.4 and 4.9). Halofantrine should not be administered with hydroxychloroquine. There may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin.

Ciclosporin
An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered.

Tamoxifen
Concomitant use of drugs known to induce retinal toxicity e.g. tamoxifen and hydroxychloroquine, is not recommended (see section 4.4).

Agalsidase
There is a theoretical risk of inhibition of intra-cellular α-galactosidase activity when hydroxychloroquine is co-administered with agalsidase.

Drugs affecting the convulsive threshold
Antimalarials
Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other antimalarials known to lower the convulsion threshold (e.g mefloquine) may increase the risk of convulsions.

Anti-epileptics
Also, the activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine.

Hydroxychloroquine sulfate 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 sulfate and antacid dosing.

Praziquantel
In a single-dose interaction study, chloroquine has been reported to reduce the bioavailability of praziquantel. It is not known if there is a similar effect when hydroxychloroquine and praziquantel are co-administered. Per extrapolation, due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for hydroxychloroquine.

Azithromycin and macrolide antibiotics
Observational data have shown that co-administration of hydroxychloroquine with azithromycin in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing hydroxychloroquine for any patients taking azithromycin. Similar careful consideration of the balance of benefits and risk should also be undertaken before prescribing hydroxychloroquine for any patients taking other macrolide antibiotics, such as clarithromycin or erythromycin, because of the potential for a similar risk when hydroxychloroquine is co-administered with these medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data from a population-based cohort study including 2045 hydroxychloroquine exposed pregnancies suggests a small increase in the relative risk (RR) of congenital malformations associated with hydroxychloroquine exposure in the first trimester (n = 112 events). For a daily dose of ≥ 400 mg the RR was 1.33 (95% CI, 1.08 – 1.65). For a daily dose of < 400 mg the RR was 0.95 (95% CI, 0.60 – 1.50).

Animal studies with the structurally related chloroquine, have shown reproduction toxicity at high maternal exposure (see section 5.3). In humans, hydroxychloroquine crosses the placenta and blood concentrations in the foetus are similar to maternal blood concentrations.

Hydroxychloroquine crosses the placenta. 4-aminoquinolines in therapeutic doses caused damage to the central nervous system, including ototoxicity (auditory and vestibular toxicity, congenital deafness), retinal haemorrhages and abnormal retinal pigmentation.

In animal studies, reproduction toxicity was found with chloroquine, a substance related to hydroxychloroquine, following high maternal exposition (see section 5.3).

Only limited non-clinical data are available for hydroxychloroquine, data on chloroquine have shown developmental toxicity at high supratherapeutic doses and a potential risk of genotoxicity in some test systems (see section 5.3).

Therefore, hydroxychloroquine sulfate should be avoided in pregnancy (see section 4.3) except when, in the judgement of the physician, the individual potential benefits outweigh the potential hazards. If treatment with hydroxychloroquine is necessary during pregnancy, the lowest effective dose should be used. In case of prolonged treatment during pregnancy, hydroxychloroquine safety profile in particular ophthalmological side effects should be taken into account for child monitoring.

Before treatment is started a pregnancy has to be excluded.

Breast-feeding

Hydroxychloroquine is excreted in breast milk (less than 2% of the maternal dose after bodyweight correction). There are very limited data on the safety in the breastfed infant during hydroxychloroquine long- term treatment; the prescriber should assess the potential risks and benefits of use during breastfeeding, according to indication and duration of treatment.

Fertility

Animal studies showed an impairment of male fertility for chloroquine (see section 5.3). There are no data in humans.

Contraception

During treatment with hydroxychloroquine and for at least 3 months after treatment termination, a pregnancy should be strictly avoided.

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

The following CIOMS frequency rating is used, when applicable:
Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100) ; Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (frequency cannot be estimated from the available data).

Tabulated list of adverse reactions

System Organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Not known	Bone-marrow depression, anaemia, aplastic anaemia, agranulocytosis, leucopenia and thrombocytopenia
Immune system disorders	Not known	Urticaria, angioedema, bronchospasm
Metabolism and nutrition disorders	Common	Anorexia
	Not known	Hypoglycaemia (see section 4.4) Hydroxychloroquine may precipitate or exacerbate porphyria
Psychiatric disorders	Common	Affect liability
	Uncommon	Nervousness
	Not known	Suicidal behaviour, psychosis,

		depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders
Nervous system disorders	Common	headache
	Uncommon	dizziness
	Not known	Convulsions have been reported with this class of drugs. Extrapyramidal disorders such as dystonia, dyskinesia, tremor (see section 4.4)
Eye disorders	Common	Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible
	Uncommon	*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 sulfate. 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 are reversible on stopping treatment.
	Not known	Cases of maculopathies and macular degeneration have been reported (the onset ranging from 3 months to several years of exposure to hydroxychloroquine) and may be irreversible
Ear and labyrinth disorders	Uncommon	Vertigo, tinnitus
	Not known	Hearing loss
Skin and subcutaneous tissue disorders	Common	Skin rash, Pruritus
	Uncommon	Pigmentation disorders in skin and mucous membranes, bleaching of hair, alopecia

		These usually resolve readily on stopping treatment.
	Not known	• Bullous eruptions including erythema multiforme • Stevens-Johnson syndrome and toxic epidermal necrolysis • Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome) • Photosensitivity • Sweet's syndrome and Severe cutaneous adverse reactions (SCARs) • exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP). 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 disorders	Very common	Abdominal pain, nausea
	Common	diarrhoea, vomiting These symptoms usually resolve immediately on reducing the dose or on stopping treatment.
Cardiac disorders	Not known	QT interval prolongation in patients with specific risk factors, which may lead to arrhythmia (torsade de pointes, ventricular tachycardia) (see sections 4.4 and 4.9). Cardiomyopathy which may result in cardiac failure and in some cases a fatal outcome (see section 4.4 and 4.9) Chronic toxicity should be considered when conduction disorders (bundle branch block/atrioventricular heart block) as well as biventricular hypertrophy are found. Drug withdrawal may lead to recovery.
Musculoskeletal and connective tissue disorders	Uncommon	Sensory motor disorders
	Not known	Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups.

		Myopathy may be reversible after drug discontinuation, but recovery may take many months. Depression of tendon reflexes and abnormal nerve conduction studies. Phospholipidosis mimicking Fabry disease
Hepatobiliary disorders	Uncommon	Abnormal liver function tests
	Not known	Drug-induced liver injury (DILI) including hepatocellular injury, cholestatic liver injury, acute hepatitis, mixed hepatocellular/cholestatic liver injury and fulminant hepatic failure

Reporting of side effects

Reporting of suspected adverse reactions after the marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

Symptoms

The symptoms of overdose may include headache, visual disturbances, cardiovascular collapse, convulsions and hypokalaemia. Rhythm and conduction disorders, including QT prolongation, Torsade de Pointes, ventricular tachycardia and ventricular fibrillation, width increased QRS complex, bradyarrhythmias, nodal rhythm, atrioventricular block followed by sudden potentially fatal respiratory and cardiac arrest. Immediate medical attention is required, as these effects may appear shortly after the overdose.

Management

The stomach should be immediately evacuated, either by emesis or gastric lavage. Finely powdered 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 overdose; 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

Pharmacotherapeutic group: Antimalarials, Aminoquinolines
ATC Code: P01BA02

Mechanism of action

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 similar to those of chloroquine.

Absorption

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.

Distribution

The parent compound and metabolites are widely distributed in the body.

Metabolism

The metabolism of Hydroxychloroquine is similar to that of Chloroquine.

Elimination

The mean plasma elimination half-life varied, depending on the post-administration period, as follows; 5.9 hours (at C max- 10 hours), 26.1 hours (at 10-48 hours) and 229 hours (at 48-504 hours). 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

Only limited preclinical data are available for hydroxychloroquine, therefore chloroquine data are considered due to the similarity of structure and pharmacological properties between the two products.

Genotoxicity:
There are limited data on hydroxychloroquine genotoxicity. Chloroquine is reported in the literature to elicit both gene mutations and chromosomal/DNA breaks in some *in vitro* systems in others and in *in vivo* studies using rodents when dosed via the intraperitoneal route. Chromosomal effects were not observed *in vivo* when chloroquine was administered orally.

Carcinogenicity:
There are no data on hydroxychloroquine carcinogenicity.
In a limited 2-years study in rats with chloroquine, no increase in neoplastic or proliferative changes was observed.

Development and reproductive toxicity
There are limited data on hydroxychloroquine teratogenicity. Chloroquine is teratogenic in rats after administration at very high, supratherapeutic doses, i.e. between 250 – 1500 mg/kg/day, showing a fetal mortality rate of 25% and ocular malformations (anophthalmia and microophthalmia) in 45% of foetuses in the 1000 mg/kg/day group. Auto-radiographic studies have shown that when administered at the start or the end of gestation, chloroquine accumulates in the eyes and ears of fetuses.

A study in male rats after 30 days of oral treatment at 5 mg/day of chloroquine showed a decrease in testosterone levels, weight of testes, epididymis, seminal vesicles and prostate. The fertility rate was also decreased in another rat study after 14 days of intraperitoneal treatment at 10mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Calcium Hydrogen Phosphate dihydrate
Colloidal anhydrous silica
Polysorbate 80
Purified Talc
Magnesium stearate
Hypromellose
Titanium dioxide
Macrogol 6000

6.2. Incompatibilities

Not applicable

6.3 Shelf life

Containers: 3 years
Blisters: 4 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Al/PVC blister, pack sizes of 30, 60 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd.

Unit 3, Canalside, Northbridge Road,

Berkhamsted, Herts, HP4 1EG,

United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of Renewal of Authorisation: 12th October 2011

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13/03/2024