DATA SHEET

1 PRODUCT NAME

PLAQUENIL 200mg Tablet, film coated

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hydroxychloroquine sulfate 200mg equivalent to 155mg hydrochloroquine.
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film coated tablet.
White to off-white peanut shaped tablets, marked “Plaquenil” in black ink on one face of the tablet.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Acute and chronic rheumatoid arthritis; mild systemic and discoid lupus erythematosus; the suppression and treatment of malaria.

4.2 DOSE AND METHOD OF ADMINISTRATION

Rheumatoid Arthritis

Plaquenil is cumulative in action and will require several weeks to exert its beneficial therapeutic effects, whereas minor side effects may occur relatively early. Several months of therapy may be required before maximum effects can be obtained.
Initial dosage: In adults, a suitable initial dosage is from 400 to 600 mg daily, preferably taken at meal times. In a few patients the side effects may require temporary reduction of the initial dosage. Generally, after five to ten days the dose may be gradually increased to the optimum response level, frequently without return of side effects.

Maintenance dosage: When a good response is obtained (usually in four to twelve weeks) the dose can be reduced to 200 to 400 mg daily (but should not exceed 6 mg/kg per day) and can be continued as maintenance treatment. The minimum effective maintenance dose should be employed. The incidence of retinopathy has been reported to be higher when the maintenance dose is exceeded.

If objective improvement (such as reduced joint swelling or increased mobility) does not occur within six months the drug should be discontinued.

If a relapse occurs after medication is withdrawn, therapy may be resumed or continued on an intermittent schedule if there are no ocular contraindications.

Safe use of Plaquenil for the treatment of juvenile rheumatoid arthritis has not been established.

Use in Combination Therapy: Plaquenil may be used safely and effectively in combination with corticosteroids, salicylates, NSAIDS, and methotrexate and other second line therapeutic agents. Corticosteroids and salicylates can generally be decreased gradually in dosage or eliminated after the drug has been used for several weeks. When gradual reduction of steroid dosage is suggested, it may be done by reducing every four to five days, the dose of cortisone by no more than 5 to 15 mg; of methylprednisolone from 1 to 2 mg and dexamethasone from 0.25 to 0.5 mg. Treatment regimens using agents other than corticosteroids and NSAIDS are under development. No definitive dose combinations have been established.

**Lupus Erythematosus**

In mild systemic and discoid cases, the antimalarials are the drugs of choice.

The dosage of Plaquenil depends on the severity of the disease and the patient's response to treatment. For adults an initial dose of 400-800 mg daily is recommended. This level can be maintained for several weeks and then reduced to a maintenance dose of 200-400 mg daily.

**Malaria**

Plaquenil is active against the erythrocytic forms of P.vivax and P.malariae and most strains of P.falciparum (but not the gametocytes of P.falciparum).

Plaquenil does not prevent relapses in patients with vivax or malariae malaria because it is not effective against exo-erythrocytic forms, nor will it prevent vivax or malariae infection when administered as a prophylactic.

It is effective as a suppressive agent in patients with vivax or malariae malaria, in terminating acute attacks and significantly lengthening the interval between treatment and relapse. In patients with falciparum malaria it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of P.falciparum.
Malaria Suppression

Adults
400 mg (310 mg base) on exactly the same day of each week.

Children
The weekly suppressive dose is 5 mg (base) per kg bodyweight but should not exceed the adult dose regardless of weight.
Suppressive therapy should begin two weeks prior to exposure. Failing this, in adults an initial loading dose of 800 mg (620 mg base), or in children 10 mg base per kg, may be taken in two divided doses, six hours apart. The suppressive therapy should be continued for eight weeks after leaving the endemic area.

Treatment of Acute Attack

Adults
An initial dose of 800 mg followed by 400 mg in six to eight hours and 400 mg on each of two consecutive days. (Total dose of 2 g or 1.55 g base). A single dose of 800 mg (620 mg base) has also proved effective.

Children
The dosage is calculated on the basis of bodyweight. (Total dose of 25 mg base per kg).
First dose - 10 mg base per kg (not exceeding a single dose of 620 mg base).
Second dose - 5 mg base per kg (not exceeding 310 mg base), six hours after first dose.
Third dose - 5 mg base per kg eighteen hours after second dose.
Fourth dose - 5 mg base per kg twenty-four hours after third dose.
For radical cure of vivax and malariae malaria, concomitant therapy with an 8-aminoquinoline is necessary.

4.3 CONTRAINDICTION

Plaquinil is contraindicated in:

• patients with pre-existing maculopathy of the eye
• patients with known hypersensitivity to 4-aminoquinoline compounds, and
• long-term therapy in children
• children under 6 years of age.
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Plaquenil is not effective against chloroquine-resistant strains of P. falciparum.

Patients should be warned to keep Plaquenil out of the reach of children, as small children are particularly sensitive to the 4-aminoquinolines.

Plaquenil should be used with caution or not at all in patients with severe gastrointestinal, neurological or blood disorders. If such severe disorders occur during therapy, the drug should be stopped. Periodic blood counts are advised.

When used in patients with porphyria or psoriasis, these conditions may be exacerbated. Plaquenil should not be used in these conditions unless in the judgement of the physician, the benefit to the patient outweighs the possible risk.

Observe caution in patients with hepatic or renal disease, in whom a reduction in dosage may be necessary, as well as in those taking medicines known to affect these organs. Also observe caution in patients with a sensitivity to quinine, and in glucose-6-phosphate dehydrogenase deficiency.

Chronic Cardiac Toxicity

Cases of cardiomyopathy resulting in cardiac failure, in some cases with fatal outcome, have been reported in patients treated with Plaquenil. Clinical monitoring for signs and symptoms of cardiomyopathy is advised and Plaquenil 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.

Hypoglycaemia

Hydroxychloroquine has been shown to cause severe hypoglycaemia including loss of consciousness that could be life threatening in patients treated with and without anti-diabetic 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.

Ophthalmological

Irreversible retinal damage has been observed in some patients who had received long-term or high-dosage 4-aminoquinolone therapy for discoid and systemic lupus erythematosus, or rheumatoid arthritis. Retinopathy has been reported to be dose related. Exceeding the recommended daily dose sharply increases the risk of retinal toxicity.

If there is any indication of abnormality in the visual field, or retinal macular areas (such as pigmentary changes, loss of foveal reflex), or any visual symptoms (such as light flashes and streaks) which are not fully explainable by difficulties of accommodation or corneal opacities, the drug should be discontinued immediately and the patient closely observed for possible progression. Retinal changes (and visual disturbances) may progress after cessation of therapy.
Concomitant use of hydroxychloroquine with drugs known to induce retinal toxicity, such as tamoxifen, is not recommended.

Before starting a long term treatment, both eyes should be examined (for visual acuity, central visual field and colour vision, and fundoscopy. Wherever possible, optical coherence tomography (OCT) is recommended). Then the examination should be repeated at least annually.

Ophthalmological testing should be more frequent and adapted to the patient, in the following circumstances:

- Dose exceeds 6 mg per kg ideal (lean) body weight per day. Absolute body weight used as a guide to dosage, could result in an overdosage in the obese.
- Significant renal impairment
- Significant hepatic impairment
- Elderly
- Complaints of visual disturbances
- Duration of treatment exceeds 5 years.

The examination should include slit-lamp microscopy (for corneal opacities) and fundus and visual field studies.

Corneal changes often subside on reducing the dose or on interrupting therapy for a short period of time, but any suggestion of retinal change or restriction in the visual field is an indication for complete withdrawal of the drug.

The use of sunglasses in patients exposed to strong sunlight is recommended, as this may be an amplifying factor in retinopathy.

Skin Reactions

Pleomorphic skin eruptions (morbilliform, lichenoid, purpuric), itching, dryness and increased pigmentation sometimes appear after a few months of therapy. The rash is usually mild and transient. If a rash appears, Plaquenil should be withdrawn and only started again at a lower dose. Patients with psoriasis appear to be more susceptible to severe skin reactions than other patients.

Other Monitoring On Long Term Treatments

Patients on long-term therapy should have periodic full blood counts. If evidence of abnormalities such as agranulocytosis, aplastic anaemia, thrombocytopenia or leukopenia becomes apparent, and cannot be attributed to the disease being treated, Plaquenil should be discontinued.

All patients on long-term therapy with this preparation should be questioned and examined periodically, including the testing of knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs discontinue the drug.
**Cardiac Conduction Defects**
Cases of QT interval prolongation, torsades de pointes and sudden cardiac death have been observed with hydroxychloroquine use. Although the majority of cases occurred in the overdose setting, an association with therapeutic use cannot be ruled out. Hydroxychloroquine should be used cautiously in patients with other risk factors for QT prolongation including advanced age, renal or hepatic disease, hypokalaemia or severe hypomagnesaemia, structural heart disease, bradycardia, an underlying genetic predisposition, or in patients using other potential QT prolonging medicines.

**Miscellaneous**
Gastrointestinal disturbances such as nausea, anorexia, abdominal cramps or rarely vomiting, occur in some patients. The symptoms usually stop on reducing the dose or temporarily stopping the drug.

Muscle weakness, vertigo, tinnitus, nerve deafness, headache and nervousness, have been reported less frequently.

In the treatment of rheumatoid arthritis, if objective improvement (such as reduced joint swelling, increased mobility) does not occur within six months, the drug should be discontinued. Safe use of the drug in the treatment of juvenile rheumatoid arthritis has not been established.

Suicidal behaviour has been reported in very rare cases in patients treated with hydroxychloroquine.
Extrapyramidal disorders may occur with hydroxychloroquine.

**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. In humans, there are insufficient data to rule out an increased risk of cancer in patients receiving long term treatment.

**4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION**
It has been suggested that 4-aminoquinolines are pharmacologically incompatible with monoamine oxidase inhibitors.
Concomitant hydroxychloroquine and digoxin therapy may result in increased serum digoxin concentrations. Consequently serum digoxin concentrations should be closely monitored in patients receiving concomitant therapy.
As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.
Hydroxychloroquine prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias, including halofantrine. Also there may be an
increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin.

Increased plasma cyclosporin levels have been reported when cyclosporin and hydroxychloroquine are co-administered.

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.

The activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine.

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.

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

4.6 PREGNANCY AND LACTATION

Pregnancy:

Category D

Only limited preclinical data are available for hydroxychloroquine, therefore chloroquine data are considered due to the similarity of structure and pharmacological properties between the 2 products. In animal studies on chloroquine, embryo-fetal development toxicity was shown at very high, supratherapeutic doses (ranging from 250 to 1500 mg/kg bodyweight). Chloroquine preclinical data show a potential risk of genotoxicity in some test systems.

For hydroxychloroquine, when used on long term therapy with high dosages for autoimmune diseases: studies have not observed a statistically significant increased risk of congenital malformations or poor pregnancy outcomes.

Hydroxychloroquine should be avoided in pregnancy except when, in the judgement of the physician, the individual potential benefits outweigh the potential hazards. The use of this drug in the treatment of malaria or suppression of malaria in high risk situations may be justified if the treating physician considers the risk to the foetus is outweighed by the benefits to the mother and foetus.

Lactation:

Nursing Mothers: Careful consideration should be given to using hydroxychloroquine during lactation, since it has been known to be excreted in small amounts in human breast milk and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinones.
4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be warned about driving and operating machinery since hydroxychloroquine can impair visual accommodation and cause blurring of vision. If the condition is not self-limiting, the dosage may need to be temporarily reduced.

4.8 UNDESIRABLE EFFECTS

Note very common \( \geq 1/10 \ (\geq 10\%) \)

common \( \geq 1/100 \ and \ < 1/10 \ (\geq 1\% \ and \ < 10\%) \)

uncommon \( \geq 1/1000 \ and \ < 1/100 \ (\geq 0.1\% \ and \ < 1.0\%) \)

rare \( \geq 1/10,000 \ and \ < 1/1000 \ (\geq 0.01\% \ and \ < 0.1\%) \)

very rare \( < 1/10,000 \ (< 0.01\%) \)

not known frequency cannot be estimated from available data

Blood and Lymphatic System Disorders

Not known: bone marrow depression, anaemia, aplastic anaemia, leucopenia, thrombocytopenia, agranulocytosis

Immune System Disorders

Not known  urticaria, angioedema, bronchospasm

Metabolism and Nutritional Disorders

Common: anorexia

Not known hypoglycaemia

Hydroxychloroquine may exacerbate porphyria

Psychiatric Disorders

Common affect lability

Uncommon nervousness

Very rare nightmares

Not known psychosis, suicidal behaviour

Nervous System Disorders

Common headache
**Uncommon:** dizziness, nerve deafness

**Very rare:** nystagmus, ataxia

**Not known:** convulsions, extrapyramidal disorders such as dystonia, dyskinesia, tremor

### Eye Disorders

**Common:** blurring of vision

**Uncommon:** corneal changes, retinal changes, retinopathy with changes in pigmentation and visual field defects. In its early form, it appears reversible on discontinuation of Plaquenil. If allowed to develop, there may be a risk of progression even after treatment withdrawal.

Corneal changes including oedema and opacities have occurred from three weeks (infrequently) to some years after the beginning of therapy. They are either symptomless or may cause disturbances such as halos, blurring of vision, or photophobia. They may be transient or are reversible on stopping treatment. Should these types of corneal changes occur with Plaquenil, it should be either stopped or temporarily withdrawn.

Reversible extra-ocular muscle palsies and temporary blurring of vision due to interference with accommodation have also been noted.

Retinal changes such as abnormal macular pigmentation and depigmentation (sometimes described as a "bull's eye"), pallor of the optic disc, optic atrophy and narrowing of the retinal arterioles have been reported.

**Not known:** Cases of maculopathies and macular degeneration have been reported and may be irreversible.

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

Originally, the condition was thought to be progressive and irreversible but more recent evidence suggests that routine ophthalmological examinations may detect retinal changes, especially pigmentation, at an early and reversible stage when there is no apparent visual disturbance.

Much evidence suggests that there is a threshold of dosage above which retinopathy appears. These results seem to correlate more with daily dosage than with a cumulative dose, although the risk increases with increased duration of treatment.

See section 4.4 for information on eye examinations.

Any adverse changes in the ocular findings or the appearance of scotoma, night blindness or other retinal changes require immediate discontinuation of Plaquenil; these patients should not subsequently receive any pharmacologically similar drugs.

### Ear and Labyrinth Disorders

**Uncommon:** vertigo, tinnitus

**Not known:** hearing loss
Cardiac Disorders

Not known: cardiomyopathy which may result in cardiac failure, and in some cases a fatal outcome (see section 4.4)

Chronic toxicity should be considered when conduction disorders (bundle branch block /atrioventricular heart block) as well as biventricular hypertrophy are diagnosed.

Gastrointestinal Disorders

Very common: abdominal pain, nausea
Common: diarrhoea, vomiting

Hepatobiliary Disorders

Uncommon: abnormal liver function tests
Not known: fulminant hepatitis

Skin and Subcutaneous Tissue Disorders

Common: skin rashes, pruritus
Uncommon: pigmentary changes, bleaching of hair, alopecia
Rare: exacerbation or precipitation of porphyria and attacks of psoriasis
Not known: bullous eruptions such as acute generalised exanthematous pustulosis (AGEP), exfoliative dermatitis and erythema multiforme, Stevens-Johnson syndrome, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), toxic epidermal necrolysis, photosensitivity

Musculoskeletal and Connective Tissue Disorders

Uncommon: sensory-motor disorders
Not known: absent or hypoactive deep tendon reflexes, muscle weakness or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups (muscle weakness may be reversible after drug discontinuation, but recovery may take many months). Depression of tendon reflexes and abnormal nerve conduction studies
Very rare: extraocular muscle palsies

Miscellaneous

Very rare: weight loss, lassitude

4.9 OVERDOSE

Symptoms
Overdosage with the 4-aminoquinolines is dangerous. Children are particularly sensitive to these compounds and a number of fatalities have been reported following the accidental ingestion of chloroquine, sometimes in relatively small doses (0.75 or 1 gram in one 3 year old child).

The 4-aminoquinolines are very rapidly and completely absorbed after ingestion and toxic symptoms following overdosage may occur within 30 minutes. Toxic symptoms consist of headache, drowsiness, visual disturbances, hypokalaemia, cardiovascular collapse and convulsions followed by sudden and early respiratory and cardiac arrest. The ECG may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time and QT prolongation, torsade de pointe, ventricular tachycardia and progressive bradycardia leading to ventricular fibrillation and/or cardiac arrest. Immediate medical attention is required, as these effects may appear shortly after overdose.

**Treatment**

Treatment is symptomatic and must be prompt. Emesis is not recommended because of the potential for CNS depression, convulsions and cardiovascular instability. Activated charcoal should be administered. The dose of activated charcoal should be at least five times the estimated amount of hydroxychloroquine ingested.

Consideration should be given to using diazepam parenterally as there have been reports that it may decrease cardiotoxicity.

Respiratory support and management of shock should be instituted as necessary.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMAACODYNAMIC PROPERTIES

Hydroxychloroquine sulfate is designated chemically as 2- \{N-(4-(7-Chloro-4-quinolylamino)pentyl)-N-ethylamino\}ethanol sulfate, and has the following chemical structure:

\[
\text{C}_{18}\text{H}_{26}\text{ClN}_{3}\text{O}, \text{H}_{2}\text{SO}_{4} \quad \text{Molecular Weight: 433.96}
\]

CAS No. 747-36-4 (hydroxychloroquine sulfate), CAS No. 118-42-3 (hydroxychloroquine).
Mechanism of action:

Anti-malarial. Plaquenil also exerts a beneficial effect in mild systemic and discoid lupus erythematosus and rheumatoid arthritis. The precise mechanism of action is not known.

Malaria

Like chloroquine phosphate, Plaquenil is highly active against the erythrocytic forms of P.vivax and P.malariae and most strains of P.falciparum (but not the gametocytes of P.falciparum).

Plaquenil does not prevent relapses in patients with vivax or malariae malaria because it is not effective against exo-erythrocytic forms of the parasite, nor will it prevent vivax or malariae infection when administered as a prophylactic. It is highly effective as a suppressive agent in patients with vivax or malariae malaria, in terminating acute attacks, and significantly lengthening the interval between treatment and relapse. In patients with falciparum malaria it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of P.falciparum.

5.2 PHARMACOKINETIC PROPERTIES

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

5.3 PRECLINICAL SAFETY DATA

There are no preclinical safety data of relevance to the prescriber, which are additional to that already included in other sections of the Data Sheet.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

_Tablet core:_

- Calcium hydrogen phosphate dihydrate
- Maize starch
- Purified water
Magnesium stearate

Film coating:

Hypermellose
Macrogol 400
Titanium dioxide
Polysorbate 80
Carnauba wax
Purified water

6.2 INCOMPATIBILITIES

No incompatibilities are known.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Plaquenil tablets should be stored below 25° C.

6.5 NATURE AND CONTENTS OF CONTAINER

Plaquenil is supplied as 100 tablets in a plastic HDPE bottle with a child resistant closure.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

None.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

sanofi-aventis new zealand limited
Level 8, 56 Cawley Street, Ellerslie,
Auckland New Zealand
Toll Free Number (medical information): 0800 283 684

9 DATE OF FIRST APPROVAL
31 December 1969

10 DATE OF REVISION OF THE TEXT
25 August 2017
### SUMMARY TABLE OF CHANGES

<table>
<thead>
<tr>
<th>Section changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Updated the spelling of ‘Sulphate’ to ‘Sulfate’ as per TPDR</td>
</tr>
<tr>
<td>4.4</td>
<td>Addition of new subheadings as per CCDSv11 (Chronic Cardiac Toxicity; Hypoglycaemia). Renaming of subheading ‘Haematological Reactions’ to ‘Other Monitoring On Long Term Treatments’. Relocation of text from immediately above ‘Skin Reactions’ subheading to immediately above ‘Chronic Cardiac Toxicity’ subheading with deletion of duplicated text. Relocation of text from ‘Miscellaneous’ subsection to newly named ‘Other Monitoring On Long Term Treatments’ subsection. Also added ‘abnormalities such as’ to the first paragraph of this subsection. Addition of new subsection ‘Potential Carcinogenic Risk’ as per CCDSv11.</td>
</tr>
<tr>
<td>4.5</td>
<td>Editorial change to statement regarding Halofantrine interaction.</td>
</tr>
<tr>
<td>4.6</td>
<td>Removal of outdated statements and addition of new information (first 2 paragraphs). The addition of the word ‘individual’ to paragraph 3 in relation to ‘individual’ potential benefits.</td>
</tr>
<tr>
<td>4.8</td>
<td>Headings updated and rearranged in accordance with CCDSv11 and MedDRA SOC. Skin and Subcutaneous Tissue Disorders subsection has had the addition of ‘bullous eruptions such as’ to the ‘Not known’ frequency.</td>
</tr>
<tr>
<td>4.9</td>
<td>Overdosage section has had the reference to Gastric lavage removed as this is no longer an acceptable treatment method.</td>
</tr>
<tr>
<td>5.3</td>
<td>Addition of ‘No preclinical data…’ statement as per DS template guidelines.</td>
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<tr>
<td>10</td>
<td>Date has been amended to 25 August 2017</td>
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</tbody>
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