SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dapsone 50mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg dapsone.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White to off-white, circular, biconvex uncoated tablets debossed with ‘50’ on one side and plain on other side, with dimensions of 5.5 mm diameter and 2.8 mm thick.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dapsone Tablets are indicated for:

- As part of a multi – drug regimen in the treatment of all forms of leprosy.
- Treatment of dermatitis herpetiformis and other dermatoses.
- Prophylaxis of malaria in combination with pyrimethamine.
  Prophylaxis of *Pneumocystis carinii* pneumonia in immunodeficient subjects, especially AIDS patients.

4.2 Posology and method of administration

Posology

Adults and children over 12 years of age:

Multibacillary leprosy (3 drug regimen): 100 mg daily for at least two years.

Paucibacillary leprosy (2 drug regimen): 100 mg daily for at least 6 months.

Malaria prophylaxis: 100 mg weekly with 12.5 mg pyrimethamine.

Dermatitis herpetiformis: initially 50 mg daily, gradually increasing to 300 mg daily if required. Once lesions have begun to subside, the dose should be reduced to a minimum as soon as possible, usually 25 mg – 50 mg daily, which may be continued for a number of years. Maintenance dosage can often be reduced in patients receiving a gluten-free diet.

Pneumocystis carinii pneumonia: in combination with trimethoprim, 50 mg – 100 mg daily; 100 mg twice weekly, or 200 mg once weekly.

Paediatric population

Children aged 6 years to 12 years:

Multibacillary leprosy (3 drug regimen): 50 mg daily for at least two years.

Paucibacillary leprosy (2 drug regimen): 50 mg daily for at least 6 months.

Children aged less than 6 years:

The safety and efficacy of Dapsone in children aged less than six years has not been established.

No data are available.

Elderly population

Dosage should be reduced in the elderly where there is an impairment of hepatic function.

Method of administration

For oral administration. Tablets should be swallowed whole with a glass of water.

4.3 Contraindications

Dapsone Tablets are contraindicated in cases of:

- Hypersensitivity to the dapsone, sulfonamides, sulfones, or to any of the excipients listed in section 6.1.
- Severe anaemia.
- Porphyria.
- Severe glucose-6-phosphate dehydrogenase deficiency.

4.4 Special warnings and precautions for use

Dapsone should be used with caution in patients with cardiac or pulmonary disease.

Performance of regular blood counts during dapsone therapy is recommended. Patients deficient in glucose-6-phosphate dehydrogenase, or methaemoglobin reductase, or with haemoglobin M, are more susceptible to the haemolytic effects of dapsone.

Dapsone should be used with caution in anaemia. Severe anaemia should be treated prior to initiation of dapsone therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Oral typhoid vaccine: should not be taken until at least three days after finishing a course of dapsone, because the dapsone could make this vaccine less effective.

Probenecid: concurrent administration results in a reduction of dapsone excretion, and increase in dapsone plasma concentrations.

Rifampicin / Rifabutin: has been reported to increase the plasma clearance of dapsone.

Saquinavir: should not be used in combination, as this could increase the risk of irregular heartbeat.

Trimethoprim: increased dapsone and trimethoprim concentrations have been reported following concurrent administration in AIDS patients.

4.6 Fertility, pregnancy and lactation

Pregnancy:

It is generally considered that the benefits of dapsone in the treatment of leprosy outweigh any potential risk to the pregnant patient. Some leprologists recommend 5 mg folic acid supplementation daily for leprosy patients receiving dapsone during pregnancy.

Breast-feeding:

Dapsone is excreted into breast milk, and there has been a report of haemolytic anaemia in a breast-fed infant. While there is an opinion that dapsone should not be used in lactating mothers, in general therapy for leprosy is continued in such patients.

Fertility:

There is limited information available on the effect of dapsone on fertility; it may reduce the numbers and / or motility of sperm, thereby rendering impregnation less likely.

4.7 Effects on ability to drive and use machines

Dapsone has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Dapsone should be discontinued, or reduced in dosage, if severe lepra reactions affecting the eyes or nerve trunks occur.

The frequencies of undesirable effects are reported according to the following convention:

Very Common:	≥ 1 / 10 users	**Rare:**	≥ 1 / 10,000; < 1 / 1,000 users
Common:	≥ 1 / 100; < 1 / 10 users	**Very Rare:**	< 1 / 10,000 users
Uncommon:	≥ 1 / 1,000; < 1 / 100 users	**Unknown:**	Cannot be estimated

System Organ Class (SOC)	Frequency	Undesirable Effect
Blood Disorders:	Common	Haemolysis[1)]
		Methaemoglobinaemia[1)]
	Uncommon	Haemolytic anaemia
	Rare	Agranulocytosis[2)]
Cardiac Disorders:	Uncommon	Tachycardia
Gastrointestinal Disorders:	Uncommon	Anorexia
		Nausea
		Vomiting
General Disorders:	Rare	Dapsone Syndrome[3)]
Hepatic Disorders:	Uncommon	Hepatitis
		Jaundice
		Changes in liver function tests
Metabolic Disorders:	Uncommon	Hypoalbuminaemia
Nervous System Disorders:	Uncommon	Headache
		Neuropathy peripheral[4)]
		Peripheral motor neuropathy[4)]
Psychiatric Disorders:	Uncommon	Insomnia
		Psychoses
Skin Disorders:	Uncommon	Photosensitivity
		Pruritis
		Rash
	Rare	Exfoliative dermatitis
		Maculopapular rash
		Toxic epidermal necrolysis
		Stevens – Johnson syndrome
	Very rare	Fixed drug eruptions

1) – these are the most frequently reported adverse effects of dapsone and are dose related; occurring in most subjects administered more than 200 mg daily; doses of up to 100 mg daily do not cause significant haemolysis, but subjects deficient in glucose-6-phosphate dehydrogenase are affected by doses above about 50 mg daily.

2) – this is rare when dapsone is used alone; reports are more common when dapsone has been used with other medicines for malarial prophylaxis.

[3] – this may occur following 3 – 6 weeks of therapy; symptoms include rash (always present), fever and eosinophilia. Id dapsone is not stopped immediately; the syndrome may progress to exfoliative dermatitis, hepatitis, albuminuria, and psychosis. Deaths have been recorded. The majority of patients require steroid therapy for several weeks; this is possibly due to prolonged elimination time of dapsone.

[4] – peripheral neuropathy may occur as part of leprosy reaction states and it is not an indication to discontinue dapsone.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after 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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms:

The typical symptoms of overdose are hypoxia, methaemoglobinaemia, and haemolytic anaemia.

Treatment:

In instances of severe overdosage, gastric lavage should be used to empty the stomach. Administration of oral activated charcoal has been shown to enhance elimination of both dapsone and the monoacetyl metabolite. Methaemoglobinaemia may be treated with slow intravenous injections of methylene blue, 1 mg-2 mg/Kg body weight, which may be repeated after 1 hour if required. In patienst with glucose-6-phosphate dehydrogenase deficiency methylene blue should not be administered since it will be ineffective. Haemolysis may be treated by infusion of concentrated human red blood cells to replace the damaged cells.

Supportive therapy should include oxygen to alleviate hypoxia, and administration of fluids to maintain renal flow and promote the elimination of dapsone.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infectives for systemic use; antimycobacterials; drugs for treatment of lepra.

ATC code: J04BA02

Dapsone is a sulfone with activity against a wide range of bacteria. The mechanism of action is believed to be similar to that of the sulfonamides; inhibition of folic acid synthesis in susceptible organisms. Dapsone is usually considered bacteriostatic against *M. leprae*, although it may also possess weak bactericidal activity. Dapsone is also active against *Plasmodium* and *Pneumocystis carinii* (*Pneumocystis jirovecii*). In common with sulfonamides, antibacterial activity is inhibited by *p*-aminobenzoic acid.

As an antimicrobial agent, dapsone is bacteriostatic in action. It inhibits the synthesis of dihydrofolic acid through by competing with para-aminobenzoic acid for the active site of dihydropteroate synthetase, thus resembling the action of sulfonamides. Sulfones were found to suppress the growth of various pathogenic bacteria such as streptococci, staphylococci, pneumococci, mycobacteria, and other strains. The mechanism of action of topical dapsone in the treatment of acne vulgaris may result from a combination of both antiinflammatory and antimicrobial effects. *In vitro*, dapsone has some antibacterial activity against *Propionibacterium acnes*. Owing to its antimicrobial activities, dapsone is clearly playing a role in the treatment of certain infectious diseases.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration, dapsone is almost completely absorbed from the gastrointestinal tract, with reported bioavailability exceeding 86 %. Peak serum concentrations are reached within 2 h – 8 h. Post ingestion of a single

50 mg – 300 mg dose of dapsone, maximum serum concentrations range from 0.63 mg/L to 4.82 mg/L. Under steady state conditions, the most frequently used dose of 100 mg/day, results in serum concentrations of maximum 3.26 mg/L, and a minimum, at 24 h, of 1.95 mg/L. Steady state concentrations are not achieved until after at least 8 days daily administration.

Distribution:

Dapsone is 50 % – 80 % bound to plasma proteins, whereas the principal metabolite, monoacetyldapsone is almost completely bound to plasma proteins. Dapsone is distributed to almost all organs, and is retained in the skin, muscle, kidneys, and liver, with trace concentrations present in these tissues up to 3 weeks post discontinuation. Dapsone is dirtibuted into sweat, saliva, sputum, tears, and bile. It crosses the blood – brain barrier, and the placenta, and is excreted in breast milk. The half life ranges from 10 h – 80 h.

Biotransformation:

Post absorption, dapsone undergoes enterohepatic recirculation. It is metabolised by the liver, and additionally by activated polymorphonuclear leukocytes and mononuclear cells. In the liver dapsone is primarily metabolised via acetylation by *N*-acetyltransferase to monoacetyldapsone, and through hydroxylation by cytochrome P-450 enzymes, resulting in the generation of dapsone hydroxylamine. Dapsone hydroxylamine may be responsible for dapsone associated methaemoglobinaemia and haemolysis. Acetylation exhibits genetic polymorphism, with both rapid and slow acetylators.

Elimination:

Around 20 % of dapsone is excreted, unchanged, via urine, with 70 % – 80 % of the dose being eliminated as water soluble metabolites following conjugation with glucuronic acid. A small amount of the dose may be excreted in faeces, including some unidentified metabolites.

Linearity/non – linearity:

The drug shows linear pharmacokinetics within the therapeutic range.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, E 460;
Pregelatinised maize starch;
Sodium laurilsulfate, E 487;
Colloidal anhydrous silica, E 551;
Stearic acid, E 570;
Magnesium stearate, E 470b.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Dapsone tablets are packed in white opaque PVC-aluminium blisters.
Packs containing 7, 10, 14, 21, 28, 30, 56, 60, 84, 90, 100 or 112 tablets are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd
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Leicester, LE19 1WP
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0260

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

29/08/2019