SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dapsone 100mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100mg Dapsone

3 PHARMACEUTICAL FORM

White uncoated tablets.

White to off-white, uncoated, circular, biconvex tablets debossed "100" above and “D” below the score on one side and plain on the other side. Tablet size: 7.5 mm

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1) As part of a multi-drug regimen in the treatment of all forms of leprosy.

2) Treatment of dermatitis herpetiformis.

3) Prophylaxis of Pneumocystis jirovecii pneumonia in immunodeficient subjects, especially AIDS patients.

4.2 Posology and method of administration

Posology

Adults and children over 12 years:

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

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

Dermatitis herpetiformis: Initially 50mg daily, gradually increased to 300mg daily if required. Once lesions have begun to subside, the dose should be reduced to a minimum as soon as possible, usually 25-50mg daily, which may be continued for a

number of years. Maintenance dosage can often be reduced in patients receiving a gluten-free diet.

Pneumocystis jirovecii pneumonia: In combination with trimethoprim, 50-100mg daily; 100mg twice weekly or 200mg once weekly.

Paediatric population:

Children 6-12 years:

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

Paucibacillary leprosy (2-drug regimen): 50mg daily for at least six 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:

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

Method of Administration

For oral administration.

4.3 Contraindications

Hypersensitivity to dapsone, sulfonamides, sulfones, or any of the excipients listed in section 6.1.

Severe anaemia; porphyria; severe glucose-6-phosphate dehydrogenase deficiency; severe liver disease.

4.4 Special warnings and precautions for use

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

It is recommended that regular blood counts be performed during treatment with dapsone. 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 before starting Dapsone.

4.5 Interaction with other medicinal products and other forms of interaction

Excretion of dapsone is reduced and plasma concentrations are increased by concurrent administration of probenecid. Rifampicin has been reported to increase the plasma clearance of dapsone.

Increased dapsone and trimethoprim concentrations have been reported following concurrent administration in AIDs patients.

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

Dapsone diffuses into breast milk and there has been a report of haemolytic anaemia in a breast fed infant. While some feel that dapsone should not be used in lactating mothers, in general treatment for leprosy is continued in such patients.

Fertility

There are no data on fertility in humans available.

4.7 Effects on ability to drive and use machines

None known.

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)
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 (cannot be estimated from the available data)

System Organ Class (SOC)	Frequency	Undesirable Effect
Blood disorders	Common	Hemolysis[1] Methemoglobinaemia[1]
	Uncommon	Hemolytic 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 Psychosis
Skin disorders	Uncommon	Rash Photosensitivity Pruritis

	Rare	Maculopapular rash Exfoliative dermatitis Toxic epidermal necrolysis Stevens-Johnson syndrome
	Very rare	Fixed drug eruptions

[1] these are the most frequently reported adverse effects of dapsone and occur in most subjects given more than 200mg daily; doses of up to 100mg daily do not cause significant haemolysis but subjects deficient in glucose-6-phosphate dehydrogenase are affected by doses above approximately 50mg daily.

[2] although agranulocytosis has been reported rarely with dapsone when used alone, reports have been more common when dapsone has been used with other agents in the prophylaxis of malaria.

[3] this may occur after 3-6 weeks therapy; symptoms include rash, which is always present, fever, and eosinophilia. If dapsone is not stopped immediately, the syndrome may progress to exfoliative dermatitis, hepatitis, albuminuria and psychosis. Deaths have been recorded. Most patients require steroid therapy for several weeks, possibly due to the prolonged elimination time of the drug.

[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; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms are hypoxia, methaemoglobinaemia and haemolytic anaemia. In severe overdosage the stomach should be emptied by gastric lavage. Administration of activated charcoal by mouth has been shown to enhance the elimination of dapsone and its monoacetyl metabolite. Methaemoglobinaemia has been treated with slow IV injections of methylene blue 1-2mg/kg bodyweight, repeated after one hour if necessary. Methylene blue should not be administered to patients with glucose-6-phosphate dehydrogenase deficiency since it will not be effective. Haemolysis has been treated by infusion of concentrated human red blood cells to replace the damaged cells.

Supportive therapy includes 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: Drugs for treatment of lepra

Therapeutic classification: JO4B A02

Dapsone is a sulfone active against a wide range of bacteria.

Mechanism of action

Dapsone's mechanism of action is probably similar to that of the sulfonamides which involves inhibition of folic acid synthesis in susceptible organisms. It is usually considered to be bacteriostatic against *M leprae* although it may also possess weak bactericidal activity. It is also active against *Plasmodium* and *Pneumocystis jirovecii*. As with sulfonamides, antibacterial activity is inhibited by *p-aminobenzoic acid.*

In dermatitis herpetiformis there is local accumulation of polymorphonuclear leukocytes (PMNL). The role of these PMNL cells in the development of inflammation, especially by the respiratory burst of highly toxic oxygen compounds is known. These active substances released against the micro-organisms can cause considerable damage in various tissues such as dermatitis herpetiformis on the skin.

Dapsone also inhibits the cytotoxic extremely active myeloperoxidase hydrogen superoxide-halogen compound and the respiratory burst. Further, an inhibition of the Arthus reaction, the reduction of the response of lymphocytes to phytohemagglutinin, inhibition of complement binding by the alternative route of its activation, inhibition of several lysosomal enzyme systems and inhibition of leukotriene B4 with its specific receptors has been described with dapsone. It also interacts with the reactive oxygen species and may have antioxidant action.

Resistance Mechanism

The mechanism of resistance of *Mycobacterium leprae* against dapsone is not known. It is believed that mutations in the *folP1* gene which codes for the Dihydropteroate synthetase, are responsible for the dapsone resistance.

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 distributed 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 pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline (Grade – 102)

Maize starch

Silica colloidal anhydrous

Magnesium stearate

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Dapsone 100mg tablets are available in White opaque PVC-Aluminium foil blister pack

Blister pack sizes: 28 tablets

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Milpharm Limited

Ares Block,

Odyssey Business Park,

West End Road,

Ruislip, HA4 6QD

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16363/0646

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/01/2021

10 DATE OF REVISION OF THE TEXT

23/12/2021