For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

DAPSONE

1. GENERIC NAME

Dapsone Tablets I.P. 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:
Dapsone I.P. 100 mg

List of Excipients

Maize Starch, Magnesium Stearate, Purified Water (evaporates during processing).

3. DOSAGE FORM AND STRENGTH

Uncoated tablets.
For information on strength see *2. Qualitative and Quantitative Composition*.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

As part of a multidrug regimen in the treatment of all forms of leprosy.

4.2 Posology and Method of Administration

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

Adults and children over 12 years

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

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

DAPSONE 100 mg tablets are not recommended for children below 12 years of age.

Elderly

DAPSONE is not recommended in the elderly where there is an impairment of hepatic function.

4.3 Contraindications

Hypersensitivity to dapsone, sulfonamides, sulfones, or any of the excipients listed in Section 2.
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.

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 Drug Interactions

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.

4.6 Use in Special Populations

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 5 mg folic acid daily for leprosy patients receiving dapsone during pregnancy.

Lactation

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.

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

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

* 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.

[1] these are the most frequently reported adverse effects of dapsone and occur in most subjects given 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 approximately 50 mg daily.

[2] 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.

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

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 Mechanism of Action & Pharmacodynamic Properties

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

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 cariniii*. As with sulfonamides, antibacterial activity is inhibited by *p-aminobenzoic acid*.

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.

6. NONCLINICAL PROPERTIES

No pre-clinical data of relevance.

7. DESCRIPTION

Each uncoated tablet contains:
Dapsone I.P.100 mg

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable

8.2 Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Tablets in a HDPE container.

8.4 Storage and Handling Information

Store protected from light at a temperature not exceeding 30°C.

Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or patients' caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contraindications of *DAPSONE.* Patients (and/or patients' caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Manufacturing License number is indicated on the label and packaging.

12. DATE OF REVISION

13-MAR-2024

Version: DAP/PI/IN/2024/01

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