

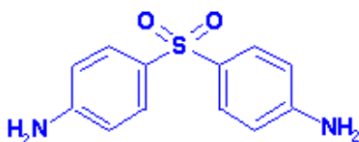
## Australian Product Information

### Dapsone

#### NAME OF THE MEDICINE

dapsone

The chemical name for dapsone is 4,4'-Sulfonylbisbenzenamine



Molecular formula: C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S

CAS number: 80-08-0

Molecular weight: 248.31

#### DESCRIPTION

Dapsone tablets are available in strengths of 25 mg and 100 mg round, white, scored tablets with the following excipients: maize starch, microcrystalline cellulose, magnesium stearate and silicon dioxide.

Dapsone tablets do not contain alcohol, gluten, lactose, parabens, sugar, sulfites or tartrazine.

#### PHARMACOLOGY

##### Pharmacokinetics:

- Dapsone is almost completely absorbed from the gastrointestinal tract with peak plasma concentrations occurring 2 to 8 hours after a dose. Steady-state concentrations are not attained until after at least 8 days of daily administration, doses of 100 mg daily provide trough concentrations of 0.5 micrograms/mL, which are well in excess of the MIC for *M. leprae*. About 50 to 80% of dapsone in the circulation is bound to plasma proteins and nearly 100% of its monoacetylated metabolite is bound.
- Dapsone undergoes enterohepatic recycling. It is widely distributed; it is present in saliva and breast milk and crosses the placenta. The half-life ranges from 10 to 80 hours.
- Dapsone is acetylated to monacetyldapsone, the major metabolite, and to other mono and diacetyl derivatives. Acetylation exhibits genetic polymorphism. Hydroxylation is the other major metabolic pathway resulting in hydroxylamine dapsone, which may be responsible for dapsone-associated methaemoglobinaemia haemolysis.
- Dapsone is mainly excreted in the urine, only 20% of a dose as unchanged drug.

**Microbiology:**

- Dapsone is a sulfone active against a wide range of bacteria, but it is mainly used for its action against *Mycobacterium leprae*. Its 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 carinii*. As with the sulfonamides, antibacterial activity is inhibited by P-aminobenzoic acid.

Secondary (acquired) dapsone resistance of *Mycobacterium leprae* is mainly associated with dapsone being used on its own. Primary dapsone resistance has also been reported with increasing frequency in areas with secondary resistance. Resistance of *M. leprae* to dapsone should be suspected whenever a patient relapses clinically and bacteriologically.

**INDICATIONS**

Dermatitis herpetiformis. Leprosy. Actinomycotic mycetoma.

**CONTRAINDICATIONS**

Hypersensitivity to dapsone and/or its derivatives.

**PRECAUTIONS**

The patient should be warned to respond to the presence of clinical signs such as sore throat, fever, pallor, purpura or jaundice. Deaths associated with the administration of dapsone have been reported from agranulocytosis, aplastic anaemia and other blood dyscrasias. Complete blood counts should be done frequently in patients receiving dapsone. The FDA Dermatology Advisory Committee recommended that, when feasible, counts should be done weekly for the first month, monthly for six months and semi-annually thereafter. If a significant reduction in leucocytes, platelets or haemopoiesis is noted, dapsone should be discontinued and the patient followed intensively. Folic acid antagonists have similar effects and may increase the incidence of haematologic reactions; if co-administered with dapsone the patients should be monitored more frequently. Patients on weekly pyrimethamine and dapsone have developed agranulocytosis during the second and third month of therapy.

Severe anaemia should be treated prior to initiation of therapy and haemoglobin monitored. Haemolysis and methaemoglobin may be poorly tolerated by patients with severe cardiopulmonary disease.

Cutaneous reactions, especially bullous, include exfoliative dermatitis and are probably one of the most serious, though rare, complications of sulfone therapy. They are directly due to drug sensitisation. Such reactions include toxic erythema, erythema multiforme, toxic epidermal necrolysis, morbilliform and scarlatiniform reactions, urticaria and erythema nodosum. If new or toxic dermatologic reactions occur, sulfone therapy must be promptly discontinued and appropriate therapy instituted.

Leprosy reactional states, (abrupt changes in clinical activity occur in leprosy with any effective treatment and are known as reactional states, see Leprosy Reactional States section under ADVERSE EFFECTS) including cutaneous, are not hypersensitivity reactions to dapsone and do not require discontinuation.

Haemolysis and Heinz body formation may be exaggerated in individuals with a glucose-6-phosphate dehydrogenase (G6PD) deficiency, or methaemoglobin reductase deficiency, or haemoglobin M. This reaction is frequently dose-related. Dapsone should be given with caution to these patients or if the patient is exposed to other agents or conditions such as infection or diabetic ketosis capable of producing haemolysis. Drugs or chemicals which have produced significant haemolysis in G6PD or methaemoglobin reductase deficient patients include dapsone, sulfanilamide, nitrite, aniline, phenylhydrazine, naphthalene, niridazole, nitrofurantoin and 8-amino-antimalarials such as primaquine.

Toxic hepatitis and cholestatic jaundice have been reported early in therapy. Hyperbilirubinaemia may occur more often in G6PD deficient patients. When feasible, baseline and subsequent monitoring of liver function is recommended. If abnormal, dapsone should be discontinued until the source of the abnormality is established.

**Use in patients with cardiac, pulmonary, hepatic conditions:**

Dapsone should be used with caution in patients with cardiac, pulmonary, hepatic or renal diseases.

**Use in Pregnancy (Category B2):**

The sulfone drugs are generally contraindicated in pregnancy and therefore the use of dapsone during pregnancy should be avoided unless, in the judgment of the doctor, potential benefit outweighs the risk. Animal reproduction studies have not been conducted with dapsone. Dapsone in high doses has been reported to be carcinogenic in rats and mice, but negative in Salmonella mutagenicity assays. The relevance of this finding to human exposure is unclear. Dapsone is excreted in breast milk in therapeutic amounts. Sulfones may cause haemolytic anaemia in glucose-6-phosphate deficient neonates.

**Use in Lactation:**

Dapsone is excreted in breast milk in substantial amounts. Haemolytic reactions can occur in neonates. (See Blood Disorders section under ADVERSE EFFECTS). Because of the potential for tumourgenicity shown for dapsone in animal studies a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Paediatric Use:**

Children are treated on the same schedule as adults but with correspondingly smaller doses. Dapsone is generally not considered to have an effect on the later growth, development and functional development of the child.

**Use in Porphyria Patients:**

Dapsone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

**Carcinogenicity and Mutagenicity:**

Dapsone has been found carcinogenic (sarcomagenic) for male rats and female mice causing mesenchymal tumours in the spleen and peritoneum, and thyroid carcinoma in female rats. Dapsone is not mutagenic with or without microsomal activation in *S. typhimurium* tester strains 1535, 1537, 1538, 98, or 100.

**INTERACTIONS WITH OTHER MEDICINES****Amprenavir:**

Possible increase in plasma levels of dapsone.

**Didanosine** (buffered formulations):

Dapsone bioavailability reduced

**Rifampicin:**

Rifampicin reduces serum concentrations of dapsone to a level that may compromise efficacy in infections other than leprosy. Increased risk of methaemoglobinaemia from metabolite. Rifampicin concentrations are generally unaffected.

**Clofazimine:**

Dapsone may antagonise the anti-inflammatory activity of clofazimine.

**Probenecid:**

Serum concentrations of dapsone are increased with a consequent increased risk of adverse effects when given with probenecid, probably as a result of reduced renal excretion of dapsone.

**Trimethoprim:**

Increased dapsone and trimethoprim concentrations have also been reported in patients receiving both drugs and such patients may be at increased risk of dapsone toxicity.

**Cimetidine:**

Cimetidine has been reported to increase the area under the curve for dapsone, but to decrease the area under the curve for the metabolite dapsone hydroxylamine. Haemotoxicity is thought to be related to production of this metabolite. (See Blood Disorders section under ADVERSE EFFECTS)

**Pyrimethamine:**

Folic acid antagonists such as pyrimethamine may increase the likelihood of haematologic reactions.

## **ADVERSE EFFECTS**

The following convention has been used for the classification of adverse reactions in terms of frequency: Very Common  $\geq 10\%$ ; common (frequent)  $\geq 1\%$  and  $< 10\%$ ; uncommon  $\geq 0.1\%$  and  $< 1\%$ ; rare  $\geq 0.01\%$  and  $< 0.1\%$ ; very rare  $< 0.01\%$ .

### **Blood Disorders:**

Rare agranulocytosis has occurred rarely following dapsona use in leprosy and skin disease. More cases have been observed when used for malaria prophylaxis.

Very rare aplastic anaemia. Thrombocytosis was reported in a patient with HIV/AIDS receiving dapsona prophylactically.

Dose-related haemolysis is the most common adverse effect and is seen in patients with or without G6PD deficiency. Almost all patients demonstrate the interrelated changes of a loss of 1-2 g of haemoglobin, an increase in the reticulocytes (2-12%), a shortened red cell life span and a rise in methaemoglobin. G6PD deficient patients have greater responses.

### **Liver Disorders:**

Toxic hepatitis and cholestatic jaundice have been reported. Jaundice may also form part of the dapsona reaction (See Hypersensitivity Reactions). Deterioration in liver function tests during dapsona treatment has been noted in a patient with dermatitis herpetiformis and primary sclerosing cholangitis.

### **Nervous System Disorders:**

Peripheral neuropathy, motor loss, muscle weakness and some patients experienced sensory impairment, most recovered within several months of discontinuing dapsona.

### **Hypersensitivity Reactions:**

Dapsona syndrome is a rare hypersensitivity reaction, although it has been suggested that the incidence has increased since the introduction of multidrug therapy for leprosy. It occurs in the first 6 weeks of therapy and symptoms include rash, which is always present, fever, jaundice and eosinophilia.

If dapsona 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.

### **Body As A Whole:**

In addition to the warnings and adverse effects reported above, additional adverse reactions include: nausea, vomiting, abdominal pains, pancreatitis, vertigo, blurred vision, tinnitus, insomnia, fever, headache, psychosis, phototoxicity, pulmonary eosinophilia, tachycardia, albuminuria, nephrotic syndrome, hypoalbuminaemia without proteinuria, renal papillary necrosis,

male infertility, drug-induced lupus erythematosus and an infectious mononucleosis-like syndrome. In general, with the exception of the complications of severe anoxia from overdosage (retinal and optic nerve damage, etc.) these adverse reactions have regressed off drug.

### **Leprosy Reactional States:**

Leprosy patients receiving effective chemotherapy may suffer episodes of acute or chronic inflammation, which are called reactions. Generally, anti-leprosy chemotherapy should be continued unchanged but these reactions must be adequately treated since they may result in crippling deformity. Abrupt changes in clinical activity occur in leprosy with any effective treatment and are known as reactional states. The majority can be classified into two groups.

The "Reversal" reaction (Type 1) may occur in borderline or tuberculoid leprosy patients often soon after chemotherapy is started. The mechanism is presumed to result from a reduction in the antigenic load: the patient is able to mount an enhanced delayed hypersensitivity response to residual infection leading to swelling ("Reversal") of existing skin and nerve lesions. If severe, or if neuritis is present, large doses of steroids should always be used. If severe, the patient should be hospitalised. In general, anti-leprosy treatment is continued and therapy to suppress the reaction is indicated such as analgesics, steroids, or surgical decompression of swollen nerve trunks. Erythema nodosum leprosum (ENL) (lepromatous reaction) (Type 2 reaction) occurs mainly in lepromatous patients and small numbers of borderline patients. Approximately 50% of treated patients show this reaction in the first year. The principal clinical features are fever and tender erythematous skin nodules sometimes associated with malaise, neuritis, orchitis, albuminuria, joint swelling, iritis, epistaxis or depression. Skin lesions can become pustular and/or ulcerate. Histologically there is a vasculitis with an intense polymorphonuclear infiltrate. Elevated circulating immune complexes are considered to be the mechanism of reaction. If severe, patients should be hospitalised. In general, anti-leprosy treatment is continued. Analgesics, steroids, and other agents are used to suppress the reaction.

### **Non-Lepromatous Lepra or "Reversal" Reactions:**

Complications may include severe peripheral neuritis with accompanying cutaneous sensory loss and paralysis and may require surgical decompression. In the management of acute neuritis, corticosteroids should always be used.

### **Lepromatous Lepra or Erythema Nodosum Lepromatous (ENL) Reactions:**

Complications may include neuritis, an increase in muscle weakness, lymphadenitis, iridocyclitis, orchitis and more rarely nephritis and large joint arthritis. In the management of these reactions, corticosteroids, and agents to modify the autoimmune reaction are used.

## **DOSAGE AND ADMINISTRATION**

To be taken with or after food. Tablets should be taken whole and small doses should be made up from 25 mg tablets. Do not split the tablet.

### **Dermatitis herpetiformis:**

**Adults:** The usual maintenance dosage is 50 to 100 mg daily, but as little as 50 mg weekly may be adequate. Dosages of up to 300 mg daily may be considered, but efforts should be made to reduce this to the minimal maintenance dosage as soon as possible.

### **Leprosy:**

**Adults:** The standard dose is 100 mg daily (1 to 2 mg/kg bodyweight).

**Children:** Dosage should be adjusted according to bodyweight.

The modern treatment of leprosy involves the use of multiple drug regimens to avoid the development of resistant strains. The World Health Organization has made the following recommendations for standard adult treatment regimens (with dosage adjustments according to bodyweight).

### **Multibacillary leprosy:**

Rifampicin 600 mg once monthly supervised; dapson 100 mg daily, self-administered; clofazimine 300 mg once monthly, supervised; and 50 mg daily self-administered.

### **Paucibacillary leprosy:**

Rifampicin 600 mg once monthly for 6 months, supervised; dapson 100 mg daily for 6 months, self-administered.

### **Actinomycotic mycetoma:**

**Adults:** Published reports suggest that a dose of 100 mg should be given twice daily and continued for some months after the clinical symptoms have disappeared. Streptomycin at 14 mg/kg daily for the first month and alternate days thereafter (or the equivalent) should always be used in combination with dapson. Streptomycin, sulfamethoxazole and trimethoprim is an alternative therapy.

## **OVERDOSAGE**

There is no specific antidote and therefore treatment should be symptomatic, e.g. intravenous methylene blue 1 to 2 mg/kg bodyweight, intravenous ascorbic acid 0.5 to 1 g and oxygen for the methaemoglobinaemia plus general supportive measures. The repeated administration of activated charcoal has been reported to increase the elimination rate of dapson and its metabolite following overdose.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

**PRESENTATION AND STORAGE CONDITIONS**

Dapsone 25 mg, 100 tablets in a bottle with a child-resistant cap – available as round white scored tablets, debossed '25' above and '102' below the score line and 'JACOBUS' on the reverse. AUST R 104482.

Dapsone 100 mg, 100 tablets in a bottle with a child-resistant cap, available as round white scored tablets, debossed '100' above and '101' below the score line and 'JACOBUS' on the reverse. AUST R 104483.

Store below 25°C. Protect from light.

**NAME AND ADDRESS OF THE SPONSOR**

Link Medical Products Pty Ltd  
5 Apollo Street  
Warriewood, NSW 2102, Australia

**POISONS SCHEDULE OF THE MEDICINE**

Schedule 4 – prescription only medicine.

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS:**

7 January 2005

**DATE OF MOST RECENT AMENDMENT**

14 April 2016