(L)210mm

(W)148.5mm

pharmaniaga®

Dapsone

Tablet

DESCRIPTION
White, round, biconvex tablet with breakline on one side and plain on the other.

COMPOSITION
Each tablet contains 100 mg of Dapsone.

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

Dapsone is a sulfone with activity against 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 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.

PHARMACOKINETICS
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 - 8 hours. Post ingestion of 50mg - 300mg 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 hours, 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 - 80 hours.

Biotransformation - Post absorption, dapsone undergoes enterohepatic recirculation. It is metabolized by the liver, and additionally by activated polymorphonuclear leukocytes and mononuclear cells. In the liver, dapsone is primarily metabolized via acetylation by *N*-acetyl-transferase 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 unidentified metabolites.

Linearity/non-linearity - The drug shows linear pharmacokinetics within the therapeutic range.

INDICATIONS
Dapsone is indicated in all types of leprosy, especially of lepromatous and tuberculoid leprosy. It is also used for dermatitis herpetiformis and other dermatoses. It is also of value in mycetoma and was formerly reported to have a beneficial effect in toxoplasmosis. Dapsone has also been used in combination regimens in the prophylaxis of malaria.

CONTRAINDICATIONS
Hypersensitivity to dapsone, sulfonamides, sulfones, or any of the excipients, severe anaemia, porphyria and severe glucose-6-phosphate dehydrogenase (G6PD) deficiency. Sulfones are contraindicated in patients with advanced amyloidosis of the kidney.

ADVERSE REACTIONS
Most adverse reactions are dose-related and uncommon at dosages up to 100mg daily. Dapsone should be discontinued, or reduced in dosage, if severe lepra reactions affecting the eyes or nerve trunks occur.

System Organ Class	Frequency	Adverse Reactions
Blood Disorder	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 (TEN)
		Stevens – Johnson syndrome (SJS)
	Very rare	Fixed drug eruptions
Other Miscellaneous Reactions	-	Nephrotic syndrome
		Renal papillary necrosis

attn	customer **Pharmaniaga Manufacturing Berhad**	date **19.07.2021**
1 colours **Black**		**Please Chop & Sign For Approval**
size description (L)**210 x** (W)**148.5mm** **Dapsone(PRP 0603.3 160421) – Front**	material finishing **60gm Simili**	
FocusPrint SDN BHD	t: 603-8766 6030 f: 603-8766 6033 (Factory) website: www.focusprint.com.my	
artwork prepared by: cynthia yap	email: graphic@focusprint.info (Graphic Dept)	**date:**

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ARTWORK LOG

Revision no.	Date	Reason for Change
01	16.07.19	- Amend wording.
02	27.07.2020	- New artwork received. Amend Revision date and Description.
03	10.03.2021	- Amend PRP no.
04	16.04.2021	- Amend wording from V8 (16.07.19).
05	26.04.2021	- Amend wording.
06	15.07.2021	- Amend wording and date of revision.
07	16.07.2021	- Amend PRP no.
08	19.07.2021	- Amend wording.

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[1] – these are the most frequently reported adverse effects of dapsone and are dose related.
[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. If 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.

WARNINGS AND PRECAUTIONS
Dapsone should be used with caution in patients with G6PD deficiency, cardiac, pulmonary, hepatic or renal disease. Routine haematologic analyses should be carried out during long-term therapy with sulfones, because of the danger of haemolytic anaemia.

The risk of methaemoglobinemia and the haemolytic effect of sulfones such as dapsone may be exaggerated in G6PD deficient individuals. Dapsone should be used with caution in anaemia. Severe anaemia should be treated prior to initiation of dapsone therapy.

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 Folic Acid 5 mg 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Dapsone has no negligible influence on the ability to drive and use machines.

DRUG INTERACTIONS
i. Excretion of dapsone is reduced and plasma concentrations are increased by concurrent administration of probenecid.
ii. Rifampicin/ rifabutin has been reported to increase the plasma clearance of dapsone.
iii. Increased dapsone and Trimethoprim concentrations have been reported following concurrent administration in AIDS patients.
iv) Oral typhoid vaccine should not be taken until at least three days after finishing a course of dapsone because dapsone could make this vaccine less effective.
v) Saquinavir should not be used in combination, as this could increase the risk of irregular heartbeat.
vi) Administration of dapsone with chloroquine and/or primaquine may lead to an increase of methaemoglobin levels in individuals predisposed to methaemoglobinaemia.

DOSAGE AND ADMINISTRATION
Usual adult and adolescent dose:
Leprosy (Hansen's disease) - Oral, in combination with one or more other antileprosy agents, 50 to 100 mg of dapsone once a day or 1.4 mg per kg of body weight once a day.

Dermatitis herpetiformis suppressant - Oral, initially 50 mg daily. Doses may be increased up to 300 mg daily if symptoms are not completely controlled. The dose should then be reduced to the lowest effective maintenance dose as soon as possible.

Actinomycotic mycetoma - Oral, 100 mg twice a day for several months after clinical symptoms have disappeared.

Dermatosis, subcorneal pustular - Oral, initially 100 mg once a day, increasing the dose by 50 mg every one to two weeks until remission occurs. The dose should then be gradually reduced to the lowest effective maintenance dose.

Granuloma annulare - Oral, 100 mg once a day.

Malaria (prophylaxis) - Oral, 100 mg of dapsone in combination with 12.5 mg of pyrimethamine once every seven days.

Usual adult prescribing limits:
Leprosy (Hansen's disease) - up to 100 mg daily.

Dermatitis herpetiformis suppressant - up to 300 mg daily.

Usual paediatric dose:
Leprosy (Hansen's disease) - Oral, in combination with one or more other antileprosy agents, 1.4 mg of dapsone per kg of body weight once a day.

Dermatitis herpetiformis suppressant - Oral, initially 2 mg per kg of body weight daily. Doses may be increased if symptoms are not completely controlled. The dose should then be reduced to the lowest effective maintenance dose as soon as possible.

OVERDOSAGE
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 patients with G6PD 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.

ROUTE OF ADMINISTRATION
Oral.

STORAGE CONDITIONS
Store below 30°C.
Keep container tightly closed.
Protect from light.

SHELF LIFE
Product should not be used beyond the expiry date imprinted on the product packaging.

PRESENTATION
In blisters of 1000 tablets

Date of revision: 15 July 2021

PRODUCT REGISTRATION HOLDER/ MANUFACTURER:
PHARMANIAGA MANUFACTURING BERHAD (198001006232)
11A, Jalan P/1, Kawasan Perusahaan Bangi,
43650 Bandar Baru Bangi, Selangor Darul Ehsan, Malaysia.

PRP 0603.4 150721

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