PRESCRIBING INFORMATION

INCLUDING PATIENT MEDICATION INFORMATION

Pr RIVA-DAPSONE

Dapsone Tablets USP,

100 mg

Antibacterial Sulfone

Laboratoire Riva Inc.
660 Boul. Industriel
Blainville, Quebec, Canada.
J7C 3V4
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Date of Preparation:
May 24, 2019

Submission Control No: 212058

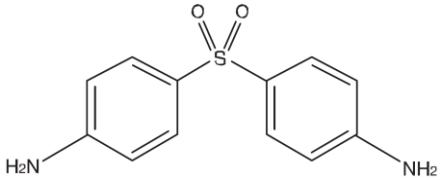
[Pr] RIVA-DAPSONE

SUMMARY PRODUCT INFORMATION:

Route of Administration	Dosage Form / Strength	All non-medicinal ingredients
Oral	Tablet, 100 mg	Colloidal Silicon Dioxide, Corn Starch, Magnesium Stearate, Microcrystalline Cellulose.

Chemical Name and Structure:

Dapsone U.S.P. is chemically, benzenamine, 4,4'-sulfonylbis-4,4'-sulfonyldianiline.



Comparative Bioavailability Studies

A randomized, double blind, single dose, two treatment, two sequence, two period, crossover oral bioequivalence study comparing RIVA-DAPSONE tablets, 100 mg (Laboratoire Riva Inc.) to [Pr]DAPSONE tablets, 100 mg (Jacobus Pharmaceutical Company Inc.) was performed in 30 healthy adult human male subjects under fasting conditions. The rate and extent of absorption of dapsone were measured and compared. The results from 27 subjects who completed the study are summarized in the table below:

Summary Table of the Comparative Bioavailability Data

Dapsone Single dose: 1 x 100 mg From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval (%)**
AUC_{0-72} (hr*µg/mL)	49.09 50.44 (23.39)	49.38 50.80 (23.85)	99.40	97.4 – 101.5
AUC_I (hr*µg/mL)	58.08 61.19 (34.40)	58.26 61.39 (34.44)	99.69	97.2 – 102.2
C_{MAX} (µg/mL)	1.69 1.70 (11.92)	1.76 1.78 (15.95)	96.07	91.5 – 100.9
T_{MAX}§ (hr)	2.25 (0.83 -6.00)	2.50 (0.67 – 6.00)		
$T_{½}$€ (h)	25.44 (33.60)	25.07 (30.38)		

* RIVA-DAPSONE tablets, 100 mg (Laboratoire Riva Inc.).
† [Pr]Dapsone tablets, 100 mg (Jacobus Pharmaceutical Company Inc.) were purchased in Canada.
§ Expressed as the median (range) only.
€ Expressed as arithmetic mean (CV%) only.

INDICATIONS AND CLINICAL USE:

Leprosy, Dermatitis herpetiformis, actinomycotic mycetoma.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of RIVA-DAPSONE and other antibacterial drugs, RIVA-DAPSONE should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS:

Sulfones are contraindicated in patients with advanced amyloidosis of the kidneys.

Do not use RIVA-DAPSONE if you are allergic to sulfones or to any ingredient in this formulation. For a complete listing see the Dosage Forms, Composition and Packaging section of the Prescribing Information.

WARNINGS AND PRECAUTIONS:

RIVA-DAPSONE should be used with caution in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, cardiac, pulmonary, hepatic or renal disease. Routine hematologic analyses should be carried out during long-term therapy with sulfones, because of the danger of hemolytic anemia.

The risk of methemoglobinemia and the hemolytic effect of sulfones such as dapsone may be exaggerated in glucose-6-phosphate dehydrogenase deficient individuals.

Reaction States:

Leprosy patients receiving effective chemotherapy may suffer episodes of acute or chronic inflammation. Generally, anti-leprosy chemotherapy should be continued unchanged but these reactions must be adequately treated since they may result in crippling deformity.

Non Lepromatous Lepra Reactions:

Complications may include severe peripheral neuritis with accompanying cutaneous sensory loss and paralysis. In the management of acute neuritis corticosteroids may be considered.

Lepromatous Lepra 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 clofazimine may be considered.

Pregnancy and Lactation:

The use of RIVA-DAPSONE during pregnancy should be avoided unless, in the judgment of the physician, potential benefit outweighs the risk. 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 hemolytic anemia in glucose-6-phosphate dehydrogenase deficient neonates.

Susceptibility/Resistance :

Development of Drug Resistant Bacteria:

Prescribing RIVA-DAPSONE in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug resistant bacteria.

DRUG INTERACTIONS:

Rifampicin has been reported to increase the plasma clearance of dapsone, and probenecid has been reported to decrease excretion of dapsone.

Administration of dapsone with chloroquine and/or primaquine may lead to an increase of methemoglobin levels in individuals predisposed to methemoglobinemia.

ADVERSE REACTIONS:

Most adverse reactions are dose-related and uncommon at dosages up to 100 mg daily. They include anorexia, nausea, vomiting, headache, dizziness, tachycardia, nervousness, insomnia and skin disorders. Agranulocytosis, peripheral neuritis and psychosis have also been reported. Varying degrees of dose-related hemolysis and methemoglobinemia may occur during treatment at therapeutic doses, but individuals with glucose-6-phosphate-dehydrogenase deficiency may be affected by dosages above 50 mg daily. Rare reactions include the "Dapsone syndrome" and hypoalbuminemia.

The "Dapsone syndrome" are hypersensitivity reactions which develop rarely and tend to occur during the first 6 weeks of therapy. Symptoms may include fever, eosinophilia, mononucleosis, lymphadenopathy, leukopenia, jaundice with hepatitis, and exanthematous skin eruptions which may progress to exfoliative dermatitis, toxic epidermal necrolysis, or Stevens-Johnson syndrome.

Although patients usually improve if dapsone is withdrawn fatalities have occurred. Fixed drug eruptions occur in dark-skinned people. Although agranulocytosis has been reported rarely for dapsone when used alone, reports have been more common when the drug has been used with other agents in the prophylaxis of malaria. Other miscellaneous reactions such as peripheral neuropathy, nephrotic syndrome and renal papillary necrosis have been reported.

DOSAGE AND ADMINISTRATION:

Leprosy:

Adults: The standard dose is 100 mg daily (1-2 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
Dapsone	100 mg	daily, self-administered
Clofazimine	300 mg 50 mg	once-monthly, supervised and daily, self-administered

Paucibacillary Leprosy:

Rifampicin	600 mg	once a month for 6 months, supervised
Dapsone	100 mg	daily for 6 months, self-administered

Further information on treatment regimens is contained in "Chemotherapy of Leprosy for Control Programmes" W.H.O. Technical Report Series 675 (1982)

Dermatitis Herpetiformis:

Adults: The usual maintenance dosage is 50 to 100 mg daily, but as little as 50 mg weekly may be adequate. Dosage 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.

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.

OVERDOSAGE:

In cases of severe overdosage the stomach should be emptied by aspiration and lavage. There is no specific antidote and therefore treatment should be symptomatic e.g. intravenous methylene blue 1-2 mg/kg bodyweight, intravenous ascorbic acid 0.5-1.0 g and oxygen for the methemoglobinemia plus general supportive measures. The repeated administration of activated charcoal has been reported to increase the elimination rate of Dapsone and its metabolite following overdosage.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

STORAGE:

RIVA-DAPSONE tablets should be stored at room temperature and protected from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING:

RIVA-DAPSONE 100 mg: white to off white round tablet, engraved "IT" above the bisect and "53" below the bisect on one side and the other side is plain. Available in bottle of 100 tablets.

Each tablet contains the following non-medicinal ingredients:

Colloidal Silicon Dioxide, Corn Starch, Magnesium Stearate and Microcrystalline Cellulose.

REFERENCES:

1. U.S. P. XXI

2. B.P. 1988

3. B.P.C. 11th Edition

4. W.H.O. Technical Report Series 675 (1982) Chemotherapy of Leprosy for Control Programmes

5. Prescribing Information for DAPSONE (Dapsone Tablets USP, 100 mg) – Jacobus Pharmaceutical Company Inc. Submission Control No. 209694, Date of revision: January 9, 2018.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr] RIVA-DAPSONE

Dapsone Tablets USP, 100 mg

Read this carefully before you start taking **RIVA-DAPSONE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RIVA-DAPSONE**.

What is RIVA-DAPSONE used for?

RIVA-DAPSONE is used to treat

- leprosy
- dermatitis herpetiformis (a skin condition)
- actinomycotic mycetoma (a fungal disease)

This medication is sometimes prescribed for other uses; ask your doctor for more information.

Antibacterial drugs like RIVA-DAPSONE treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, RIVA-DAPSONE should be used exactly as directed. Misuse or overuse of RIVA-DAPSONE could lead to the growth of bacteria that will not be killed by RIVA-DAPSONE (resistance). This means that RIVA-DAPSONE may not work for you in the future. Do not share your medicine.

How does RIVA-DAPSONE work?

- RIVA-DAPSONE works by killing the bacteria or fungi causing your infection.
- When used for the treatment of dermatitis herpetiformis (a skin condition), Dapsone reduces the skin blisters and skin itch.

What are the ingredients in RIVA-DAPSONE?

Medicinal ingredient: Dapsone
Non-medicinal ingredients: Colloidal Silicon Dioxide, Corn Starch, Magnesium Stearate, Microcrystalline Cellulose.

RIVA-DAPSONE comes in the following dosage forms:

Tablet 100 mg

Do not use RIVA-DAPSONE if:

- you are allergic to RIVA-DAPSONE, to sulfones, or to any ingredient in this formulation. (See What are the ingredients in RIVA-DAPSONE)
- you have high amyloid levels or advanced amyloidosis of the kidneys.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RIVA-DAPSONE. Talk about any health conditions or problems you may have, including if you have:

- heart problems
- lung disease
- liver disease
- kidney problems
- anemia
- lack of the enzyme glucose-6-phosphate dehydrogenase in the body, so that red blood cells don't work properly.

RIVA-DAPSONE may cause blood cell problems such as:

- Hemolytic anemia - red blood cells are destroyed so that they do not do their job carrying oxygen in the body
- Methemoglobinemia – where a high amount of methemoglobin is made in the blood, and this prevents oxygen release into body tissues
- Lack of the enzyme glucose-6-phosphate dehydrogenase can worsen the above blood cell problems.

Your doctor will do routine blood work during RIVA-DAPSONE treatment to watch for blood problems and changes in liver function.

Other warnings you should know about:

Don't use RIVA-DAPSONE while pregnant unless advised by your doctor. If you become pregnant while taking RIVA-DAPSONE, tell your doctor immediately.

RIVA-DAPSONE is excreted in breast milk. Your doctor will decide with you if you should continue breastfeeding or stop taking RIVA-DAPSONE.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RIVA-DAPSONE:

- rifampicin
- probenecid
- chloroquine
- primaquine

These medicines may be affected by RIVA-DAPSONE, or may affect how well it works. You may need to take different amounts of your medicine, or you may need to take different medicines. Your healthcare professional will advise you.

How to take RIVA-DAPSONE:

Take RIVA-DAPSONE at the same time each day. The tablet should be swallowed with a full glass of water, with or after food.

RIVA-DAPSONE should be taken exactly as directed, for as long as your healthcare professional tells you to. Do not stop taking RIVA-DAPSONE even if you begin to feel better, unless advised by your healthcare professional.

Usual dose:

Leprosy:

When used for the treatment of leprosy, RIVA-DAPSONE is usually taken with one or more other drugs, to prevent the development of resistance.

The usual dose of RIVA-DAPSONE in adults is 100 mg daily. RIVA-DAPSONE dosing in children is based on the child's body weight.

Dermatitis Herpetiformis:

The usual adult dose is 50 mg to 100 mg RIVA-DAPSONE daily, but a dose as little as RIVA-DAPSONE 50 mg once a week may be adequate.

Actinomycotic Mycetoma:

The usual adult dose is 100 mg RIVA-DAPSONE taken twice a day.

Overdose:

If you think you have taken too much **RIVA-DAPSONE**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately. Do this even if there are no signs of discomfort or poisoning, as symptoms may not develop right away.

Missed Dose:

If you missed a dose of this medication, take it as soon as you remember. This will help to keep a constant amount of medication in your blood. But, if it is almost time for your next dose, skip the missed dose, and continue with your next scheduled dose. Do not take two doses at the same time.

What are possible side effects from using RIVA-DAPSONE?

These are not all the possible side effects you may feel when taking **RIVA-DAPSONE**. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

RIVA-DAPSONE may cause:

- loss of appetite
- nausea

- vomiting
- headache
- dizziness
- nervousness
- difficulty sleeping

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON Anemia symptoms (i.e.: hemolysis, methemoglobinemia) - rapid heart rate - shortness of breath - unusual tiredness or weakness - jaundice, or yellowing of the skin and eyes - dark coloured urine - bluish colouring of the skin		✓	
UNCOMMON Low white blood cell symptoms - persistent fever - chills - increased infections (e.g. sore throat, mouth sores, swollen lymph glands) - weakness - bleeding gums		✓	
Mood or other mental changes		✓	
Numbness, tingling, pain, burning or weakness in hands and feet		✓	
<u>RARE</u> Hypersensitivity reaction - fever - flu-like symptoms - rash			✓
Skin reactions - severe skin rash - itching, redness, scaling or peeling of skin - painful blisters			✓
Kidney problems - back pain - swollen, puffy skin especially in the face, arms, legs (feet and ankles) and belly area - change in appearance of urine - painful and frequent urination		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for more information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

RIVA-DAPSONE tablets should be stored at room temperature and protected from light.

Keep out of reach and sight of children.

If you want more information about RIVA-DAPSONE:

- Talk to your healthcare professional
- Find the full prescribing information that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website www.labriva.com, or by calling 1-800-363-7988.

This leaflet was prepared by:

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