PRODUCT INFORMATION

DESERIL®
Methysergide 1mg (as maleate) Tablets

NAME OF THE MEDICINE
Methysergide

1-Methyl-d-lysergic acid-(1-hydroxybut-2-yl)amide
MW = 469.5
CAS number: 361-37-5

DESCRIPTION
Excipients: Gelatin, maleic acid, stearic acid, talc-purified, starch-maize, lactose, , sucrose, acacia, carnauba wax, silica-colloidal anhydrous, titanium dioxide, fine black ink 2202C Markem (ARTG 2110).

PHARMACOLOGY
Deseril is effective in the prevention of migraine chiefly on account of two properties:
• It’s marked serotonin antagonism (inhibition of pain-facilitating action and of permeability-increasing effect of serotonin).
• It’s potentiating action on vasoconstrictor stimuli.

INDICATIONS
Prophylactic therapy of recurrent attacks of migraine, migraine variants, cluster headaches (histaminic cephalalgia) and other vascular headaches.

It is particularly indicated for patients suffering from one or more vascular headaches per week or headaches so severe that preventive therapy is indicated. It is not indicated in the treatment of the acute attack.

CONTRAINDICATIONS
• Known hypersensitivity to methysergide or any other components of the formulation.
• Peripheral vascular disorders, progressive arteriosclerosis, severe and/or inadequately controlled hypertension, coronary heart disease, valvular heart disease, phlebitis or cellulitis of the lower extremities, pulmonary heart disease, collagen disease, impaired renal or hepatic function, disease of the urinary tract, cachectic or septic conditions, history of drug-induced fibrotic disorders (e.g. retroperitoneal fibrosis), pulmonary fibrosis.
• Temporal arteritis, hemiplegic or basilar migraine.
• Concomitant treatment with CYP3A4 inhibitors, including antifungals (ketoconazole, itraconazole), HIV-protease inhibitors or reverse transcriptase inhibitors (ritonavir, nelfinavir, indinavir, delavirdine) and macrolide antibiotics (erythromycin, clarithromycin [see “PRECAUTIONS”]
• Concomitant treatment with vasoconstrictive agents (including ergot alkaloids, sumatriptan and other 5HT1-receptor agonists)[see PRECAUTIONS – Interactions with other drugs]
• Pregnancy, lactation

Use in pregnancy (Category C):
Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

Ergotamine and ergot derivatives induce uterine contraction and may therefore cause premature parturition or hypertonic labour. Products containing ergotamine or ergot derivatives should therefore be avoided as far as possible during pregnancy.

PRECAUTIONS

CYP3A4 inhibitors
There have been rare reports of serious adverse events in connection with the co-administration of ergot alkaloids and potent CYP3A4 inhibitors, such as protease inhibitors and macrolide antibiotics, resulting in vasospasm that led to cerebral ischaemia and/or ischaemia of the extremities. Examples of some of the more potent CYP3A4 inhibitors include the antifungals ketoconazole and itraconazole, the protease inhibitors ritonavir, nelfinavir and indinavir, and the macrolide antibiotics erythromycin and clarithromycin. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine and clotrimazole. The use of CYP3A4 inhibitors with Deseril is contraindicated [see CONTRAINDICATIONS]. These lists are not exhaustive and the prescriber should consider the effects on CYP3A4 of other agents being considered for concomitant use with Deseril.

Fibrotic complications
There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged use of ergot alkaloids. Rarely, prolonged use of ergot alkaloids has also been associated with cardiac valvular fibrosis (see ADVERSE EFFECTS”).
Continuous administration of Deseril should not exceed six months. Deseril should be withdrawn for 3 to 4 weeks at the latest after 6 months of treatment. The dosage should be reduced gradually during the last 2-3 weeks of each course to avoid rebound headache.

At the first signs of impaired peripheral circulation, prompt withdrawal of the drug is recommended.

**INTERACTIONS WITH OTHER DRUGS**

CYP3A4 inhibitors (e.g. macrolide antibiotics and protease inhibitors):

Pharmacokinetic interactions have been reported in patients treated orally with ergot alkaloids (e.g. increased levels of ergotamine) and macrolide antibiotics, principally troleandomycin, presumably due to inhibition of CYP3A4 metabolism of the alkaloids by troleandomycin. Ergot alkaloids have also been shown to be inhibitors of CYP3A4 catalysed reactions and rare reports of ergotism have been obtained from patients treated with ergot alkaloids and macrolide antibiotics (e.g. troleandomycin, clarithromycin, erythromycin) and patients treated with ergot alkaloids and protease inhibitors (e.g. ritonavir), presumably due to inhibition of CYP3A4 metabolism of ergotamine (see CONTRAINDICATIONS and PRECAUTIONS - CYP3A4 inhibitors). No pharmacokinetic interactions involving other CYP450 isoenzymes are known.

**Other vasoconstrictors:**

Methysergide should not be administered with other vasoconstrictors. Use with sympathomimetics (pressor agents) may cause extreme elevation of blood pressure. The beta-blocker propranolol has been reported to potentiate the vasoconstrictive action of ergot alkaloids by blocking the vasodilating property of epinephrine. Nicotine (e.g. smoking) may provoke vasoconstriction in some patients, predisposing to a greater ischaemic response to ergot therapy. Concurrent use of methysergide with other ergot alkaloids, sumatriptan and other 5-HT₁ receptor agonists must also be avoided since this may result in enhanced vasoconstriction [see CONTRAINDICATIONS].

**Effects on ability to drive or operate machinery**

Patients experiencing dizziness or other central nervous system disturbances should not drive or operate machinery.

**Use in children**

Deseril is not recommended for use in children.

**ADVERSE EFFECTS**

Nausea and vomiting may occur at doses within the therapeutic range. These side effects can often be minimised by taking the preparation with food. Insomnia, vertigo, transient psychic alterations of a mild nature, skin reactions, oedema, vasoconstriction of large and small arteries
may occur. Depending on the vessel involved, this complication may present as chest pain, abdominal pain, or cold, numb, painful extremities with or without paraesthesias and diminished or absent pulse. There were isolated reports of myocardial infarction particularly in patients not adhering to the contraindications of coronary heart disease or the use of other vasoconstrictive drugs.

With long-term uninterrupted administration of Deseril, retroperitoneal fibrosis has been reported. This side effect occurred, however, very rarely after an administration period shorter than six months. This disorder usually produces obstruction of the urinary tract with symptoms such as general malaise, backache, girdle or flank pain, dysuria, oliguria, increased blood nitrogen, vascular insufficiency of the lower limbs. A related condition, pleuro-pulmonary fibrosis, has also been reported in a small number of patients. Presenting symptoms include chest pain, dyspnoea or pleural friction rub and pleural effusion. There have also been rare reports of fibrotic changes of the pericardium and cardiac valves (see PRECAUTIONS – Fibrotic complications).

Cardiac murmurs or vascular bruits have been reported. Medication must cease as soon as any of these symptoms occurs. Withdrawal of the drug results, in most cases, in a regression of the signs and symptoms.

Treatment of arterial spasm:
Arterial spasm arising as an idiosyncrasy should be treated by cessation of the drug together with administration of vasodilators - e.g. sodium nitroprusside, or alpha-adrenoreceptor blockers such as phenoxybenzamine or phentolamine. Anticoagulants (heparin and phenindione) should also be given.

**DOSAGE AND ADMINISTRATION**
1 or 2 mg two or three times daily with meals is the recommended dose. Treatment should begin with a low starting dose (1 mg), increasing progressively up to the optimum.

Since vascular headache is a paroxysmal but basically chronic disorder, treatment must extend over an adequate period of time in order to obtain maximum benefit. While some patients have responded rather quickly, most investigators agree that a 3-week trial period should be instituted to determine the true efficacy of Deseril. Moreover, the periodic nature of the disorder will have to be taken into account in determining when and for how long therapy should be maintained.

**OVERDOSAGE**
Symptoms of acute poisoning include nausea, vomiting, abdominal pain, diarrhoea, thirst, coldness of the skin, pruritus, rapid and weak pulse, numbness and tingling of the extremities, cyanosis, peripheral vasoconstriction with diminished pulses, mydriasis, headache, agitation, hyperactivity, confusion.

Treatment is symptomatic. Administration of activated charcoal is advised. Oxygen and assisted respiration if necessary. Arterial spasm should be treated as indicated above. Nausea and
vomiting may be relieved by atropine. Anticoagulants (heparin and phenindione) should be given. Diazepam may be required for sedation.

PRESENTATION AND STORAGE CONDITIONS
Round, whitish sugar-coated tablets printed in black on one side “DSL”; containing 1 mg methysergide (present as 1.33 mg methysergide hydrogen maleate), 50's.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR
Link Medical Products Pty Ltd.
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Warriewood NSW 2102
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POISON SCHEDULE OF THE MEDICINE
Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)
19 November 2002

DATE OF MOST RECENT AMENDMENT
8 October 2012

Version 02