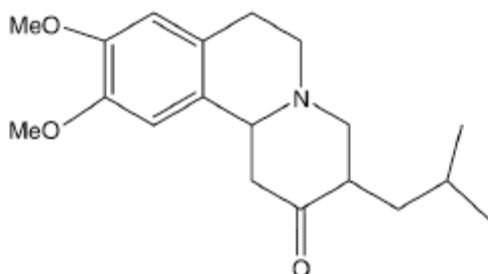


PRODUCT INFORMATION

Tetrabenazine Tablets

NAME OF THE MEDICINE



Tetrabenazine

CAS Registry Number: 58 46 8

DESCRIPTION

The chemical name of tetrabenazine is 1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo-[a]quinolizin-2-one. Tetrabenazine is white to slightly yellow crystalline powder. Tetrabenazine is soluble in hot water, but practically insoluble in acetone. UV max (alcohol): 230, 284 nm (ϵ 7780, 3820).

Tetrabenazine Tablets contain tetrabenazine, lactose, starch, talc, magnesium stearate and iron oxide yellow.

PHARMACOLOGY

Pharmacodynamics

Tetrabenazine has a central amine depleting effect. This effect resembles that of reserpine, but Tetrabenazine is shorter acting, i.e. its effect lasts 24 hours and it has a more specific central action than reserpine.

Pharmacokinetics

Tetrabenazine has a low and erratic bioavailability. It appears to be extensively metabolised by first-pass metabolism. The major metabolite, hydroxytetrabenazine, is formed by reduction. Little unchanged tetrabenazine can be detected in the urine. Since hydroxybenazine is reported to be as active as tetrabenazine in depleting brain amines, it

is likely that this is the major therapeutic agent. It is excreted in the urine mainly in the form of metabolites.

INDICATIONS

May be useful for the control of chorea, hemiballismus, tardive and buccolingual dyskinesias and certain dystonic syndromes.

CONTRAINDICATIONS

Tetrabenazine should not be given closer than one day before or in combination with levodopa or reserpine as it blocks the action of these drugs, particularly the central action.

Tetrabenazine should not be administered to persons with a known sensitivity to tetrabenazine or to any of the excipients.

Tetrabenazine should not be given to patients with Parkinsonism or depression, as it may worsen these conditions. It should not be administered within two weeks of treatment with a monoamine oxidase inhibitor (MAOI).

Tetrabenazine is contraindicated during breast-feeding.

PRECAUTIONS

As for other CNS active drugs, the effect of combination of tetrabenazine and other central depressants including alcohol should be considered. Tetrabenazine may potentiate the action of antihypertensive drugs.

Depression

Tetrabenazine may cause depression or worsen pre-existing depression. Cases of suicidal ideation and behaviour have been reported in patients taking the product. Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation.

If depression or suicidal ideation occurs it should be controlled by reducing the dose and/or initiating antidepressant therapy. If depression or suicidal ideation is profound, or persists, discontinuation of tetrabenazine and initiation of antidepressant therapy should be considered.

MAOI antidepressants should not be used until at least two weeks have elapsed since the last tetrabenazine dose, to avoid restlessness, disorientation and confusion, as well as a potentially serious drug interaction resulting in hypertensive crisis.

Parkinsonism

Tetrabenazine can induce Parkinsonism and exacerbate pre-existing symptoms of Parkinson's disease. The tetrabenazine dose should be adjusted as clinically indicated to minimise this side effect.

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome is a rare complication of tetrabenazine therapy. Neuroleptic Malignant Syndrome most often occurs early in treatment or in response to changes in dose. The main symptoms of this condition are mental changes, rigidity, hyperthermia, autonomic dysfunction (sweating and fluctuations in blood pressure) and elevated creatinine phosphokinase levels. If Neuroleptic Malignant Syndrome is suspected tetrabenazine should be withdrawn immediately and appropriate treatment initiated.

QTc

Tetrabenazine causes a small increase (about 8 msec) in the corrected QT interval. Tetrabenazine should be used with caution with other drugs known to prolong QTc and in patients with congenital long QT syndromes and a history of cardiac arrhythmias (See Interactions with other medicines).

Dysphagia and choking

Dysphagia and choking attacks with a possibly consequent bronchopneumonia appear to be the only acutely dangerous adverse effects of tetrabenazine reported so far. If these occur, therapy should be discontinued.

Effects on ability to drive and use machines

As drowsiness may occur in up to 20% of patients, caution should be used when driving or operating machines until competence to do so under treatment has been established. It might be possible to reduce the drowsiness by careful dosage adjustment, especially initially.

Lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malsorption, should not take tetrabenazine tablets as they contain lactose.

Renal

The use of tetrabenazine in patients with renal insufficiency has not been studied.

Effects on fertility

Mammary gland hypertrophy was observed in 4 to 6 month old rats at dose levels of 10 and 20 mg/kg. The effect of tetrabenazine on prolactin levels is not known. There are no data available on the potential of tetrabenazine to affect fertility.

Use in pregnancy - Category B2

There is inadequate evidence of safety of the drug in human pregnancy, and the potential risk to humans is unknown. Because of the lack of data, tetrabenazine should not be used during pregnancy. In the developmental toxicity tests there was no evidence of *in utero* mortality, growth retardation or teratogenicity in either rats or rabbits. In the perinatal and postnatal study in rats, neonatal deaths were observed. However based on the observation of maternal care in the dams and the pattern of pup deaths, the effects noted in this study are attributable to inadequate maternal care at or just after birth rather than to a direct effect on any developmental or reproductive parameter.

Use in lactation

Tetrabenazine is contraindicated during breast-feeding.

Paediatric use

No adequately controlled clinical studies have been performed in children.

Use in the elderly

No specific studies have been performed in the elderly.

Carcinogenicity

No carcinogenicity studies have been performed with tetrabenazine.

Genotoxicity

No mutagenicity studies have been performed with tetrabenazine.

Interactions with other medicines

Interaction may occur when the following medications are administered with tetrabenazine (see PRECAUTIONS and CONTRAINDICATIONS):

- Reserpine and Levodopa:
Inhibit the action of these drugs and thereby attenuate their effects
- MAOIs:
Possible serious interactions resulting in hypertensive crisis. At least 14 days should elapse between the discontinuation of a MAOI and initiation of treatment with Tetrabenazine.
- Tricyclic antidepressants:
Have been reported to antagonise the locomotor activity induced by Tetrabenazine in animals.
- CNS stimulants and depressants:
Possible additive sedative effects should be considered when used in conjunction with CNS depressants (including alcohol, neuroleptics, hypnotics and opioids).
- Neuroleptic agents:
Potential for significant dopamine depletion when administering with neuroleptic agents e.g. haloperidol, chlorpromazine and metoclopramide. Patients should be monitored clinically for the development of Parkinsonism. Neuroleptic malignant syndrome has been observed in isolated cases.

- Antihypertensives:
May increase risk of orthostatic hypotension.
- Beta-blockers:
May increase risk of orthostatic hypotension.
- CYP2D6 inhibitors:
In vitro and *in vivo* studies indicate that tetrabenazine metabolites α -DTBZ and β -DTBZ are substrates for CYP2D6. Caution should be used when adding a CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine, duloxetine, terbinafine, amiodarone, or sertraline) to a patient already receiving a stable dose of tetrabenazine and a reduction in the dose of tetrabenazine should be considered.
- Antipsychotics, antibiotics and Class IA and III antiarrhythmic medications:
Tetrabenazine causes a small increase (about 8 msec) in the corrected QT interval.

Effects on laboratory tests

There are no special requirements to monitor effects on laboratory tests.

ADVERSE EFFECTS

Side effects include drowsiness, depression (which has on occasion been reported to be associated with suicidal ideation and behaviour) and Parkinsonism.

The most commonly reported side effects are as follows:

Body System	Reaction (frequency)
<i>Central and peripheral nervous system disorders:</i>	Drowsiness (20%) Parkinsonism (2 to 12%) at higher doses (may include balancing problems, tremor or excess salivation)
<i>Psychiatric disorders:</i>	Depression (6 to 10%) Agitation (2.7%) Anxiety (2 to 9%) Insomnia (2 to 9%) Confusion (1%)
<i>Gastrointestinal system disorders:</i>	Dysphagia and choking attacks (4%) with possibly consequent bronchopneumonia (See PRECAUTIONS)
<i>Respiratory disorders:</i>	Bronchopneumonia (see <i>Gastrointestinal system disorders</i>)

Other adverse reactions, which have been reported, are:

Body System	Reaction (frequency)
<i>Central and peripheral nervous system disorders:</i>	Ataxia Akathisia Dizziness Dyskinetic seizures Dystonia Memory impairment Neuroleptic malignant syndrome
<i>Gastrointestinal system disorders:</i>	Nausea Anorexia Dryness of the mouth Sialorrhoea Constipation Diarrhoea Vomiting Epigastric pain Dysphagia
<i>Psychiatric disorders:</i>	Disorientation Feelings of unreality Restlessness Nervousness Sleep disorders
<i>General disorders:</i>	Lassitude Hypothermia Weight gain Weakness Fatigue
<i>Cardiovascular disorders:</i>	Postural hypotension (1%) Hypertensive crisis
<i>Heart rate and rhythm disorders:</i>	Bradycardia
<i>Reproduction disorders:</i>	Lactation Irregular menstrual cycle
<i>Skin and subcutaneous tissue disorders:</i>	Sweating
<i>Blood and lymphatic systems disorders:</i>	Leucopenia
<i>Eye disorders</i>	Oculogyric crisis Photophobia

Neuroleptic malignant syndrome (NMS) associated with the use of tetrabenazine has been reported rarely. This may occur soon after initiation of therapy, following an increase in dosage or after prolonged treatment. The main symptoms are mental changes, rigidity, hyperthermia, autonomic dysfunction and elevated creatinine phosphokinase levels. If NMS is suspected tetrabenazine should be withdrawn and appropriate supportive therapy instituted; treatment with dantrolene and bromocriptine may be effective.

DOSAGE AND ADMINISTRATION

Dosage given below is a guide only. For each patient, the dose of tetrabenazine should be titrated to determine the most appropriate dose. Treatment should be reassessed periodically in the context of the patient's underlying condition.

Adults An initial dosage in adults of 25 mg twice a day is recommended. This can be increased by 25 mg a day every 3 or 4 days until the desired therapeutic effect is achieved, or until 200 mg/day is given, or unwanted side effects intervene.

Children In children, 12.5 mg twice a day has been used as an initial dose with increments of 12.5 mg every 3 to 4 days until the desired therapeutic effect is obtained, or an upper limit of 3 mg/kg/day is reached, or unwanted side effects intervene.

Note. Only very limited information on use in children is available.

Dosage may need to be reduced in patients with impaired renal or hepatic function or in elderly patients.

It is reported that if no improvement is found after 7 to 10 days at the maximum dose then it is unlikely that a higher dose or a longer duration of therapy will benefit the patient.

OVERDOSAGE

Signs and symptoms of overdosage may include nausea, vomiting, diarrhoea, confusion, hallucinations, sedation, drowsiness, sweating, hypotension and hypothermia.

Management should be supportive. There is no information available on the effect of pharmacological antagonists or of dialysis. For advice on the management of overdosage, please contact the Poisons Information Centre (telephone 13 11 26).

PRESENTATION

Tetrabenazine are yellowish-buff tablets with “CL” over “25” on one side and a single scoreline on the other.

Each tablet contains 25 mg tetrabenazine. Bottles of 112 tablets are available.

STORAGE CONDITIONS

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Orphan Australia Pty. Ltd.
48 Kangan Drive
Berwick
Victoria 3806
Australia

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

Date of TGA approval: 4 May 1999

Date of latest amendment: 30 November 2009