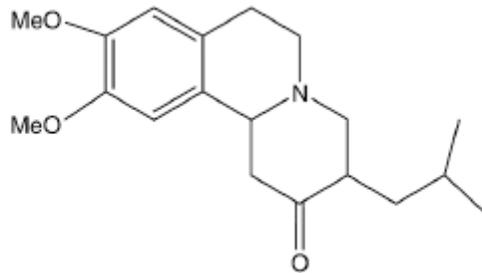


PRODUCT INFORMATION

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 is a synthetic derivative of benzylquinolizine that causes depletion of dopamine and other monoamines in the central nervous system.

Studies conducted *in vitro* have shown that tetrabenazine is an inhibitor of monoamine transportation into pre-synaptic neuronal vesicles, by inhibition of VMAT2 (vesicular monoamine transporter 2), which is principally located in the central nervous system. Dihydro-tetrabenazine, the principal metabolite of tetrabenazine, has a similar affinity and more significant selectivity for VMAT2, and both compounds are believed to contribute to the pharmacological effect.

At a synaptic level tetrabenazine creates a reversible depletion of monamines in the presynaptic vesicles. Animal studies have shown that tetrabenazine causes preferential depletion of dopamine from nerve terminals in the CNS but neurotransmitter depletion by a single dose of tetrabenazine is reversible and lasts only a few hours. This pharmacological effect explains the therapeutic benefit of tetrabenazine in patients' suffering from hyperkinetic movement disorders.

Pharmacokinetics

Based on metabolite levels, tetrabenazine is quickly and mostly absorbed after oral administration. Its absorption is not affected by the taking of food.

After administration of single doses from 12.5 to 50mg of tetrabenazine, for the metabolites alpha and beta dihydrotetrabenazine, the maximum plasma concentration and the area under the curve increased approximately in proportion to the dose, indicating a linear kinetic.

Clinical testing has shown that a single oral dose of tetrabenazine undergoes extensive (>75%) absorption from the gastro-intestinal tract. The metabolism of tetrabenazine is complex, initially proceeding via the formation of alpha and beta dihydrotetrabenazine. The majority of the observed metabolites appear to be formed from these dihydrotetrabenazines as a result of O-dealkylation, hydroxylation and conjugation.

No significant build-up has been observed after daily administration. The elimination half-life of dihydrotetrabenazine is approximately 5 to 6 hours.

Tetrabenazine is mostly eliminated in metabolised form in urine.

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. In slow metabolisers this increase may be greater (30msec). 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

There are no data available on the potential of tetrabenazine to affect fertility.

Use in pregnancy - Category B3

There is inadequate evidence of safety of the drug in human pregnancy, and the potential risk to humans is unknown. Tetrabenazine crosses the placenta and, 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 at oral doses up to 5 and 27 times the clinical dose based on body surface area. When tetrabenazine was administered orally to female rats from the beginning of organogenesis to weaning, an increase in stillbirths and postnatal mortality was observed from 15 mg/kg/day, while delayed development was seen at 30 mg/kg/day. The no-effect dose for neonatal effects (5 mg/kg/day) was approximately equivalent to the clinical dose based on body surface area. The relative contributions of *in utero* and neonatal exposure and postnatal maternal neglect to these effects are unclear.

Use in lactation

Tetrabenazine is excreted in milk. Oral administration to rats from early gestation to weaning was associated with increased stillbirths, hypothermia and neonatal mortality in pups (15 mg/kg/day, twice the clinical dose based on body surface area), and delayed pup development (30 mg/kg/day, 5 fold the clinical dose). The relative contributions of *in utero* and neonatal exposure and postnatal maternal neglect to these effects are unclear. 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

A 6 month study in transgenic p53(+/-) heterozygous mice and a long term study in male rats at oral doses up to 30 mg/kg/day and 6 mg/kg twice daily, respectively, did not provide any evidence of carcinogenic potential. These doses correspond to exposures approximately 3 to 4 times the clinical exposure, based on plasma AUC or dose based on body surface area. Mammary gland hyperplasia was observed in female rats that received twice daily oral doses of 7.5 mg/kg or greater for 6 months associated with exposures (plasma AUC) similar to the clinical exposure. As the effect of tetrabenazine on prolactin levels is not known, the relevance of this finding is uncertain.

Genotoxicity

Tetrabenazine and its major metabolites, α - and β -dihydrotetrabenazine, were negative in the *in vitro* bacterial reverse mutation assay. Tetrabenazine was clastogenic in the *in vitro* chromosome aberration assay in Chinese hamster ovary cells in the presence of metabolic activation, while α - and β -dihydrotetrabenazine were clastogenic in Chinese hamster lung cells in the presence and absence of metabolic activation. *In vivo* micronucleus tests in rats and mice with tetrabenazine were negative. The genotoxic potential of tetrabenazine is considered to be low.

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 and its metabolites, α - and β -dihydrotetrabenazine and are substrates for CYP2D6. β -HTBZ was also an inhibitor of CYP2D6 at clinically relevant concentrations. 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 (<0.01%)
<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 and STORAGE CONDITIONS

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.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

iNova Pharmaceuticals (Aust) Pty Ltd
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12 Help Street
Chatswood, NSW 2067
Australia

POISON SCHEDULE OF THE MEDICINE

S4

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER
OF THERAPEUTIC GOODS** 23rd August 1991

DATE OF MOST RECENT AMENDMENT 22nd October 2013