

Data Sheet

Motetis

Tetrabenazine tablets 25mg

Presentation

Yellow, round, flat tablet with a score line on one side.

Uses

Actions

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 a selective inhibitor of monoamine transportation into pre-synaptic neuronal vesicles, by reversible inhibition of the VMAT2 (vesicular monoamine transporter 2), which is principally located in the central nervous system. Studies have shown that dihydrotetrabenazine, the principal metabolite of tetrabenazine, has a similar affinity and more significant selectivity for VMAT2.

At a synaptic level tetrabenazine creates a reversible depletion of monoamines in the presynaptic vesicles. Within the CNS tetrabenazine causes preferential depletion of dopamine from nerve terminals but neurotransmitter depletion by a single dose of tetrabenazine is reversible and lasts only a few hours. This feature differentiates the drug from reserpine, a drug that causes long lasting monoamine depletion. This pharmacological effect explains the therapeutic benefit of tetrabenazine in patients suffering from hyperkinetic movement disorders.

Pharmacokinetics

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 50 mg of tetrabenazine, the maximum plasma concentration and the area under the curve increased 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 five hours.

Tetrabenazine is mostly eliminated in metabolised form in urine (less than 2% of tetrabenazine is excreted in unchanged form).

Indications

Movement disorders associated with organic central nervous system conditions, e.g. Huntington's chorea, hemiballismus and senile chorea.

Tetrabenazine is also indicated for the treatment of moderate to severe tardive dyskinesia, which is disabling and/or socially embarrassing. The condition should be persistent despite withdrawal of antipsychotic therapy, or in cases where withdrawal of antipsychotic medication is not a realistic option; also where the condition persists despite reduction in dosage of antipsychotic medication or switching to atypical antipsychotic medication.

Dosage and Administration

The tablets are for oral administration.

Organic Central Nervous System Movement Disorders

Adults

Dosage and administration are variable and only a guide is given. An initial starting dose of 25 mg three times a day is recommended. This can be increased by 25 mg a day every three or four days until 200 mg a day is being given or the limit of tolerance, as dictated by unwanted effects, is reached, whichever is the lower dose.

If there is no improvement at the maximum dose in seven days, it is unlikely that the compound will be of benefit to the patient, either by increasing the dose or by extending the duration of treatment.

Tardive Dyskinesia

Recommended starting dose of 12.5 mg a day subsequently titrated according to response. Medication should be discontinued if there is no clear benefit or if the side-effects cannot be tolerated.

The elderly

No specific studies have been performed in the elderly, but tetrabenazine has been administered to elderly patients in standard dosage without apparent ill effect. Parkinson-like adverse reactions are quite common in these patients and could be dose-limiting.

Children

No adequate controlled studies have been performed in children. The treatment is not recommended in children.

Hepatic insufficiency

In patients with mild and moderate hepatic impairment half the initial dose and a slower up-titration of the dose is recommended. Patients with severe hepatic impairment have not been studied, therefore additional caution is advised in these patients.

Renal insufficiency

No studies have been performed in patients with renal impairment. Caution is advised in the treatment of these patients. It is recommended that, if tetrabenazine is administered to patients with poor renal function, the upward titration of tetrabenazine should be slow and a lower daily dose may be required.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Tetrabenazine can block the action of reserpine. Thus these substances should not be taken concomitantly.
- Use of monoamine oxidase inhibitors
- Presence of a hypokinetic-rigid-syndrome (Parkinsonism)
- Depression
- Breast feeding
- Pheochromocytoma
- Pro-lactin-dependent tumours, e.g. pituitary or breast cancer

Warnings and Precautions

Preclinical safety data

In repeated dose toxicity studies orally administered tetrabenazine is generally well tolerated across all animal species tested. Most effects observed are related to the pharmacological parameters of the drug and reflect central monoamine depletion. These signs typically include hypoactivity, lethargy, squinted eyes, or eyes closed. They last up to several hours after dosing and in some species at high doses interfere with normal food intake with consequent decreased or suppressed body weight gain. Across all animal species tested dose-dependent sedation is the dose limiting effect and the principal adverse effect following oral administration of tetrabenazine.

The standard battery of genotoxicity studies was conducted with tetrabenazine, and no mutagenic effects were found in the bacterial reverse mutation assay. For the *in vitro* mammalian chromosome aberration test (CHO cells), tetrabenazine was cytotoxic and clastogenic at toxic levels. The positive response was noted only in the presence of S9 mix at tetrabenazine concentrations that were toxic to the cells. However, in the *in vivo* mammalian erythrocyte micronucleus test (rats), tetrabenazine was not clastogenic at the maximum tolerated dose (100 mg/kg/day).

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 inadequate maternal care observed 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.

No carcinogenicity studies have been conducted on tetrabenazine.

Tardive Dyskinesia:

The condition should be persistent despite withdrawal of antipsychotic therapy, or in cases where withdrawal of antipsychotic medication is not a realistic option; also where the condition persists despite reduction in dosage of antipsychotic medication or switching to atypical antipsychotic medication.

Depression:

Tetrabenazine may cause depression or worsen pre-existing depression. If depression occurs it may be controlled by reducing the dose of tetrabenazine and/or initiating antidepressant therapy. If depression 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 a potentially serious drug interaction.

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malsorption should not take this medicine.

Pregnancy and Lactation (category B2)

There is inadequate evidence of safety of the drug in human pregnancy and no evidence from animal work, but it has been in wide use for many years without apparent ill consequence. Tetrabenazine should be avoided in breast-feeding mothers.

Effects on Ability to Drive and Use Machines

Patients should be advised that tetrabenazine may cause drowsiness and therefore may modify their performance at skilled tasks (driving ability, operation of machinery, etc.) to a varying degree, depending on dose and individual susceptibility.

Cardiac Effects

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

Adverse Effects

Adverse effects are usually mild with little hypotensive action and few digestive disorders. The main unwanted effect reported to date has been drowsiness, which occurs with higher doses. If depression occurs, it can be controlled by reducing the dose or by giving antidepressant drugs such as the monoamine oxidase inhibitors. However, tetrabenazine should not be given immediately after a course of any of the monoamine oxidase inhibitors as such treatment may lead to a state of restlessness, disorientation and confusion. In man, a Parkinsonian-like syndrome has been reported on rare occasions, usually in doses above 200 mg per day, but this disappears on reducing the dose.

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 clinical features usually include hyperthermia, severe extrapyramidal symptoms including muscular rigidity, autonomic dysfunction and altered levels of consciousness. Skeletal muscle damage may occur. If NMS is suspected tetrabenazine should be withdrawn and appropriate supportive therapy instituted; treatment with dantrolene and bromocriptine may be effective.

Other potential adverse effects are listed below. Effects are generally reversible once the treatment is stopped.

Body System	Reaction
Blood and lymphatic systems disorders	Leucopenia (<1/10,000)
Psychiatric disorders	Depression (>1/10) Agitation (<1/10 and >1/100) Confusion (<1/10 and >1/100) Anxiety (<1/10 and >1/100) Insomnia (<1/10 and >1/100) Disorientation Nervousness Restlessness Sleep disorders
Nervous system disorders	Drowsiness (>1/10) Parkinsonism (>1/10) (may include Balance impaired, Trembling, Drooling) Ataxia Akathisia Dystonia Memory impairment Dizziness Neuroleptic malignant syndrome (<1/10,000)
Eye disorders	Oculogyric crisis (<1/10,000) Photophobia (<1/10,000)
Cardiac Disorders	Bradycardia

Vascular Disorders:	Postural hypotension
Gastrointestinal system disorders:	Dysphagia Nausea Vomiting Epigastric pain Diarrhoea Constipation Dry mouth
Skin and subcutaneous tissue disorders:	Sweating
Reproductive system and breast disorders:	Menstrual irregularity
General disorders and administration site conditions:	Fatigue Weakness Hypothermia

Interactions

Levodopa should be administered with caution in the presence of tetrabenazine.

Tetrabenazine should not be administered in the presence of MAOIs because of the risk of possible severe adverse effects.

Tetrabenazine should not be used concomitantly with reserpine.

The possibility of additive sedative effects should be considered when tetrabenazine is used in conjunction with CNS depressants (including alcohol, neuroleptics, hypnotics and opioids).

There is a potential for significant dopamine depletion when administering tetrabenazine concomitantly with neuroleptic agents (e.g. haloperidol, chlorpromazine, metoclopramide, etc.) and patients should be monitored clinically for the development of Parkinsonism. Neuroleptic malignant syndrome has been observed in isolated cases.

The concurrent use of tetrabenazine with anti-hypertensive drugs and beta-blockers may increase the risk of orthostatic hypotension.

Inhibitors of CYP2D6 (e.g. fluoxetine, paroxetine, terbinafine, moclobemide and quinidine) may result in increased plasma concentrations of the active metabolite dihydrotetrabenazine, and they should only be combined with caution. A reduction of the tetrabenazine dose may be necessary.

Tetrabenazine should be used with caution with drugs known to prolong QTc including antipsychotic medications (e.g. chlorpromazine, thioridazine), antibiotics (e.g. gatifloxacin, moxifloxacin) and Class IA and III antiarrhythmic medications (e.g. quinidine, procainamide, amiodarone, sotalol).

Overdosage

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

Pharmaceutical Precautions

Store below 25 °C, protect from light and moisture. Shelf life is 36 months.

Medicine Classification

Prescription Medicine

Package Quantities

White HDPE bottle, pack size 112 tablets.

Further Information:

Tablets contain the following excipients: Pregelatinised Maize Starch, Lactose Monohydrate, Talc, Magnesium Stearate, Iron Oxide yellow (E172).

Name and Address

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Date of Preparation

12 July 2011