4.1 Therapeutic Indications

As per locally approved indications.

4.2 Posology and Method of Administration

The tablets are for oral administration.

Adults

As per locally approved indications.

The Elderly

No specific studies have been performed in the elderly.

Children

No adequately controlled clinical studies have been performed in children. Limited clinical experience suggests that treatment should be started at approximately half the adult daily dose and titrated slowly and carefully according to tolerance and individual response.

As per local approval.
Other information

Hepatic insufficiency

It is recommended that if Tetrabenazine is administered to patients with liver impairment the upward titration of Tetrabenazine should be slow and a lower daily dose may be required.

As per local approval.

Renal insufficiency

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

As per local approval.

4.3 Contra-indications

Hypersensitivity to the active substance (tetrabenazine) or to any of the excipients.

Tetrabenazine is contraindicated pregnancy and during breast-feeding.

Tetrabenazine is contraindicated in patients with poorly controlled clinical depression. Tetrabenazine should not be administered within two weeks of treatment with a monoamine oxidase inhibitor (MAOI) (see 4.4, 4.5 and 4.8).

Use in patients in conjunction with reserpine.

In patients with parkinsonism and hypokinetic-rigid syndrome (parkinsonism).

4.4 Special Warnings and Precautions for Use

The dose of tetrabenazine should be titrated to determine the most appropriate dose for each patient. Treatment should be reassessed periodically in the context of the patient’s underlying condition.

Tardive Dyskinesia (where the product is licensed for this indication)

Tetrabenazine treatment may be considered should this condition persist despite reduction or withdrawal of antipsychotic therapy, or switching to atypical antipsychotic medication, or in cases where withdrawal of antipsychotic medication is not a realistic option.

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 may be controlled by reducing the dose of tetrabenazine 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 a potentially serious drug interaction (see 4.3, 4.5 and 4.8)

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 8msec) 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 section 4.5).

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

4.5 Interaction with Other Medicaments and other forms of Interaction

Tetrabenazine inhibits the action of levodopa and thereby attenuates its effect.

Tetrabenazine should not be administered in the presence of MAOIs because of the risk of possible serious interactions resulting in hypertensive crisis (see Section 4.3 Contraindications & 4.8 Undesirable Effects). At least 14 days should elapse between the discontinuation of a
MAOI and initiation of treatment with Tetrabenazine.

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.

*In vitro* and *in vivo* studies indicate that the 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.

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 antiarrythmic medications (e.g. quinidine, procainamide, amiodarone, sotalol).

### 4.6 Pregnancy and Lactation

There are no adequate data from the use of Tetrabenazine in pregnant women. Studies in animals have shown reproductive toxicity (see 5.3). The potential risk for humans is unknown. Because of the lack of data, tetrabenazine should not be used during pregnancy.

It is unknown whether Tetrabenazine is excreted in human milk. A risk to the suckling child cannot be excluded. Tetrabenazine is contra-indicated during breast-feeding (see section 4.3).

### 4.7 Effects on Ability to Drive and Use Machines

Tetrabenazine may cause drowsiness and therefore may have a minor to moderate influence on the ability to drive and use machines.

### 4.8 Undesirable Effects

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

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

The incidence of adverse effects is provided where known, however for some effects the incidence cannot be accurately estimated from the available data.

<table>
<thead>
<tr>
<th>System/organ class</th>
<th>Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very common (&gt; 1/10)</td>
</tr>
<tr>
<td>Blood &amp; lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depression</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Drowsiness, Parkinsonism (may include balancing problems), tremor or excess salivation</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
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<tr>
<td>Vascular disorders</td>
<td></td>
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<tr>
<td>Gastro-intestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Skin &amp; subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
</tbody>
</table>

Neuroleptic Malignant Syndrome (NMS) has been reported in patients treated with Tetrabenazine. This may occur soon after initiation of therapy, following changes 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 immediately and appropriate supportive therapy instituted (see Section 4.4 Special warnings and precautions for use).

To avoid the risk of a potentially serious interaction resulting in hypertensive crisis at least 14 days should elapse between the discontinuation of a MAOI and initiation of treatment with Tetrabenazine, as well as between the discontinuation of Tetrabenazine and the initiation of treatment with a MAOI.

4.9 Overdose

Symptoms associated with overdoses of tetrabenazine may include: nausea, vomiting, diarrhoea, sweating, hypotension, confusion, hallucinations, hypothermia and sedation.

Treatment with Tetrabenazine should be stopped and symptomatic treatment initiated.

5. Pharmacological Properties

Pharmacotherapeutic group: Other nervous system drugs, ATC Code: NO7XX

5.1 Pharmacodynamic Properties

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 monamine 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 monamines 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 is patients' suffering from hyper-kinetic movement disorders.

5.2 Pharmacokinetic Properties

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).

5.3 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.