SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Tetrabenazine 25 mg Tablets
Xenazine® 25

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg tetrabenazine.

Excipient: Each tablet also contains 64 mg of lactose monohydrate.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Yellowish-buff, circular, bevel-edged tablets with ‘CL25’ on one face and a single scoreline on the other. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Xenazine 25 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.

4.2 Posology and Method of 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.

**Children**

No specific dosage recommendations are made for the administration of tetrabenazine to children, although it has been used without ill effect.

### 4.3 Contraindications

Hypersensitivity to the active substance (tetrabenazine) or to any of the excipients. Tetrabenazine is contraindicated during breast-feeding. Tetrabenazine is contraindicated in patients with poorly controlled clinical depression. Tetrabenazine should not be administered within two weeks of treatment together with a monoamine oxidase inhibitor (MAOI) (see Sections 4.4, 4.5 and 4.8). 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.

In vitro and in vivo studies indicate that the tetrabenazine metabolites α-HTBZ and β-HTBZ are substrates for CYP2D6 (see section 5.2). Therefore dosing requirements may be influenced by a patient’s CYP2D6 metaboliser status and concomitant medications which are strong CYP2D6 inhibitors (see section 4.5).

Treatment should be reassessed periodically in the context of the patient’s underlying condition and their concomitant medications (see section 4.5).

**Tardive Dyskinesia:**

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 Sections 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 (up to 8 msec) 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 (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 severe adverse effects serious interactions resulting in hypertensive crisis (see Sections 4.3 Contraindications and 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 antiarrhythmic medications (e.g., quinidine, procainamide, amiodarone, sotalol).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well controlled studies for the use of tetrabenazine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Tetrabenazine is not recommended during pregnancy and in women of childbearing potential not using contraception. The effect of tetrabenazine on labour and delivery in humans is unknown.

Lactation
It is unknown whether tetrabenazine or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Tetrabenazine is contraindicated during breast-feeding (see section 4.3).

Fertility
In animal studies with tetrabenazine there was no evidence of effect on pregnancy or in utero survival. Female cycle lengths were increased and a delay in fertility was seen (see section 5.3).

4.7 Effects on Ability to Drive and Use Machines

Patients should be advised that Xenazine 25 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.

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 categories</th>
<th>Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥1/10)</td>
<td>Common (&lt;1/10 but ≥1/100,)</td>
</tr>
<tr>
<td>Blood &amp; lymphatic system disorders</td>
<td>Leukopaenia</td>
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<td>-----------------------------------</td>
<td>-------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th>Depression</th>
<th>Agitation; Anxiety; Insomnia; Confusion.</th>
<th>Insomnia</th>
<th>Disorientation; Nervousness; Restlessness; Sleep disorders.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Drowsiness; Parkinsonism (may include balancing problems); Tremor or Excess salivation.</th>
<th>Neuroleptic Malignant Syndrome</th>
<th>Ataxia; Akathisia; Dystonia; Memory loss; Dizziness.</th>
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<tr>
<th>Eye disorders</th>
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<th>Oculogyric crisis; Photophobia</th>
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<th>Cardiac disorders</th>
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<th>Bradycardia</th>
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<tr>
<th>Vascular disorders</th>
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<th>Postural hypotension; Hypertensive crisis.</th>
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<tr>
<th>Gastro-intestinal disorders</th>
<th></th>
<th>Problems with swallowing; Nausea; Vomiting; Epigastric pain; Diarrhoea; Constipation; Dry mouth.</th>
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<tr>
<th>Skin &amp; subcutaneous tissue disorders</th>
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<th>Transpiration</th>
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<tr>
<th>Reproductive system and breast disorders</th>
<th></th>
<th>Irregular menstrual cycle</th>
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</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th></th>
<th>Fatigue; Weakness; Hypothermia.</th>
</tr>
</thead>
</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: acute dystonia, oculogyric crisis, nausea, vomiting, diarrhoea, sweating, hypotension, hypothermia, confusion, hallucinations, sedation, rubor and tremor.

Treatment should consist of those general measures employed in the management of overdosage with any CNS-active drug. General supportive and symptomatic measures are recommended. Cardiac rhythm and vital signs should be monitored. In managing overdosage, the possibility of multiple drug involvement should always be considered. The physician should consider contacting a poison control center on the treatment of any overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacoherapeutic group: Other nervous system drugs, ATC Code: NO7XX06

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

The precise mechanism by which tetrabenazine exerts its effects is unknown, but is believed to be related to its effect as a reversible depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals.

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 dihydrotetabenazine, the principal metabolite of tetrabenazine, has a similar affinity and more significant selectivity for VMAT2.

At a synaptic level tetrabenazine and α-dihydrotetabenazine creates a reversible depletion of monamines in the presynaptic terminals. Within the CNS tetrabenazine and α-dihydrotetabenazine 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.

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 most effects observed are related to the pharmacodynamic action of tetrabenazine and reflect central monoamine depletion. Dose dependent sedation was the principal dose limiting adverse effects of tetrabenazine. Common symptoms were hypoactivity, lethargy, strabismus, tremor, and convulsions. Histopathological changes consistent with elevated prolactin in female rats included mammary gland hyperplasia and changes in reproductive tissues.

Tetrabenazine and its metabolites accumulate in melanin-containing tissues in partially pigmented rats. The clinical relevance of this finding is unknown.

Tetrabenazine and its metabolites α-HTBZ and β-HTBZ were not mutagenic in the in vitro bacterial reverse mutation assay but were clastogenic in the in vitro chromosome aberration assay. Tetrabenazine was not genotoxic in vivo inmale mice and rats but produced equivocal results in female rats.

Tetrabenazine did not cause an increase in any tumour type when administrated for 26 weeks in the transgenic p53 heterozygous mouse model at doses up to 30 mg/kg/day. In a limited study in male rats tetrabenazine was noncarcinogenic when administered for 94 weeks at doses up to 12 mg/kg/day.

In a fertility and early embryonic development study at systemic exposures below those observed clinically there was no evidence of effect on pregnancy or in utero survival in rats. Length of the estrous cycle was increased and a delay in fertility was seen in female rats. Reproduction was unaffected in male rats.

In embryo-fetal developmental toxicity studies there was no evidence of embryotoxicity or teratogenicity in either rats or rabbits. In a perinatal and postnatal study in rats, neonatal deaths and delayed pup maturation were observed at systemic exposures below those observed clinically. These effects could either be indirect effects due to inadequate maternal care or a direct effect of tetrabenazine on the pups.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Maize starch
Lactose Monohydrate
Talc
Magnesium Stearate
Iron Oxide Yellow E172

6.2 Incompatibilities
Not applicable.

6.3 Shelf Life
5 years

6.4 Special Precautions for Storage
Do not store above 30°C.

6.5 Nature and Contents of Container
White HDPE bottle with a white HDPE cap. Pack size of 112 tablets.

6.6 Instructions for use, handling and disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER
Lundbeck UK LLP
Building K1
Timbold Drive
Kents Hill
Milton Keynes
MK7 6BZ
United Kingdom

8. MARKETING AUTHORISATION NUMBER
PL 39386/0001

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23 October 1995 / 23 October 2005

10. DATE OF REVISION OF THE TEXT
October 2015