# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. TRADE NAME OF THE MEDICINAL PRODUCT

**Xenazine® 25 mg**

## 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.
Moderate to severe tardive dyskinesia, which is disabling and/or socially embarrassing. The condition should be persistent despite a switch to atypical antipsychotic medication and/or reduction in dosage of antipsychotic medication, when withdrawal of antipsychotic medication is not a realistic option.

### 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. 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.

Patients with renal impairment
No studies have been performed in patients with renal impairment. Caution is advised in the treatment of these patients.

## 4.3 Contraindications

Tetrabenazine is contraindicated in patients:

- With Hypersensitivity to the active substance (tetrabenazine) or to any of the excipients listed in section 6.1.
- Who are actively suicidal.
- during breast-feeding.
- with poorly controlled clinical depression
- Taking a monoamine oxidase inhibitor (MAOI) (see sections 4.4, 4.5 and 4.8)
- With Impaired hepatic function.,
- With parkinsonism and hypokinetic-rigid syndrome (parkinsonism).

## 4.4 Special Warnings and Precautions for Use

In the treatment of chorea the dose of tetrabenazine should be titrated to determine the most appropriate dose for each patient. When first prescribed, tetrabenazine therapy should be titrated slowly over several weeks to allow the identification of a dose that both reduces chorea and is well tolerated. If the adverse effect does not resolve or decrease, consideration should be given to discontinuing tetrabenazine.

Once a stable dose has been achieved, treatment should be reassessed periodically in the context of the patient's underlying condition.

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:
Pre-synaptic dopamine depletion could theoretically lead to supersensitivity to

dopamine. Tetrabenazine is a central monoamine depleting agent which can cause extrapyramidal symptoms and theoretically cause tardive dyskinesia in humans.

There have been cases of tardive dyskinesia with tetrabenazine reported in the literature and in post-marketing; therefore, physicians should be aware of the possible risk. If signs and symptoms of tardive dyskinesia appear in a patient treated with tetrabenazine, drug discontinuation should be considered.

Depression/ Suicidality:
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.

Patients should be closely monitored for the emergence of such adverse events, and patients and their caregivers should be informed of the risks and instructed to report any concerns to their doctor immediately.

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).

Anger and aggression
There is a potential risk of anger and aggressive behavior occurring or worsening in patients taking tetrabenazine with a history of depression or other psychiatric illnesses.

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.

Dysphagia
Dysphagia is a component of Huntington's disease. However, drugs that reduce dopaminergic transmission have been associated with esophageal dysmotility and dysphagia. Dysphagia may be associated with aspiration pheumonia. In clinical trials, some of the cases of dysphagia were associated with aspiration pneumonia. Whether these events were related to treatment is unknown.

Neuroleptic Malignant Syndrome:
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant

Syndrome (NMS) has been reported in association with tetrabenazine and other drugs that reduce dopaminergic transmission. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure.

The management of NMS should include (1) immediate discontinuation of tetrabenazine and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available.

There is no general agreement about specific pharmacological treatment regimens for NMS.

If the patient requires treatment with tetrabenazine after recovery from NMS, the potential reintroduction of therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported

QTc Prolongation:
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 arrythmias (see Section 4.5).

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

Cardiac disease
Tetrabenazine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease.

Akathisia, restlessness, and agitation
Patients taking tetrabenazine should be monitored for the presence of akathisia. Patients taking tetrabenazine should also be monitored for signs and symptoms of restlessness and agitation, as these may be indicators

of developing akathisia. If a patient develops akathisia, the tetrabenazine dose should be reduced. However, some patients may require discontinuation of therapy.

Orthostatic hypotension
Tetrabenazine can induce postural dizziness. Patients who are vulnerable to hypotension should be closely monitored in the initial stages of therapy

Hyperprolactinemia
Tetrabenazine elevates serum prolactin concentrations in humans. Following administration of 25 mg to healthy volunteers, peak plasma prolactin levels increased 4 to 5-fold. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if tetrabenazine is being considered for a patient with previously detected breast cancer. Although amenorrhea, galactorrhea, gynecomastia and impotence can be caused by elevated serum concentrations, the clinical significance of elevated serum prolactin concentrations for most patients is unknown.

Chronic increase in serum prolactin levels (although not evaluated in the tetrabenazine development program) has been associated with low levels of estrogen and increased risk of osteoporosis. If there is a clinical suspicion of symptomatic hyperprolactinemia, appropriate laboratory testing should be done and consideration should be given to discontinuation of tetrabenazine.

Binding to melanin-containing tissues
Since tetrabenazine or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time. This raises the possibility that tetrabenazine may cause toxicity in these tissues after extended use. The clinical relevance of tetrabenazine's binding to melanin-containing tissues is unknown.
Although there are no specific recommendations for periodic ophthalmic monitoring, prescribers should be aware of the possibility of ophthalmologic effects after long term exposure.

Laboratory tests
No clinically significant changes in laboratory parameters were reported in clinical trials with tetrabenazine. In controlled clinical trials, tetrabenazine caused a small mean increase in ALT and AST laboratory values as compared to placebo.

Paediatric Population
The safety and efficacy of tetrabenazine in children have not been established.

Use in the Elderly
The pharmacokinetics of tetrabenazine and its primary metabolites have not been formally studied in geriatric subjects.

## 4.5 Interaction with Other Medicaments and Other Forms of Interaction

In vitro-studies indicate that tetrabenazine may be an inhibitor of CYP2D6 and therefore may cause increased plasma concentrations of medicinal products metabolised via CYP2D6, e.g. metoprolol, amitriptyline, imipramine, haloperidol, and risperidone.

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

Monoamine Oxidase Inhibitors

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

Interaction with CNS Depressants

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

Concomitant Use of Neuroleptic Drugs

Adverse reactions associated with tetrabenazine, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists.

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.

Antihypertensive Drugs and Beta-Blockers

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

Patients Taking CYP2D6 Inhibitors

In vitro and in vivo studies indicate that the tetrabenazine metabolites α-HTBZ and β-HTBZ are substrates for CYP2D6. The effect of CYP2D6 inhibition on the pharmacokinetics of tetrabenazine and its metabolites was studied in 25 healthy subjects following a single 50 mg dose of tetrabenazine given after 10 days of administration of the strong CYP2D6 inhibitor paroxetine 20 mg daily. There was approximately 30% increase in Cmax and an approximately 3-fold increase in AUC for α-HTBZ in subjects given paroxetine prior to tetrabenazine compared to tetrabenazine given alone. For β-HTBZ, Cmax and AUC were increased 2.4- and 9-fold, respectively, in subjects given paroxetine prior to tetrabenazine given alone. The elimination half-life of α-HTBZ and β-HTBZ was approximately 14 hours when tetrabenazine was given with paroxetine. Caution should be used when adding a strong CYP2D6 inhibitor (such as fluoxetine, paroxetine or quinidine) to a patient already receiving a stable dose of tetrabenazine and a reduction in the dose of tetrabenazine should be considered. The effect of moderate or weak CYP2D6 inhibitors such as duloxetine, terbinafine, amiodarone, or sertraline has not been evaluated.

Other Cytochrome P450 inhibitors: Based on in vitro studies, a clinically significant interaction between tetrabenazine and other P450 inhibitors (other than CYP2D6 inhibitors) is not likely.

Medicines known to Prolong QTc
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).

Digoxin
Digoxin is a substrate for P-glycoprotein. A study in healthy volunteers showed that tetrabenazine (25 mg twice daily for 3 days) did not affect the bioavailability of digoxin, suggesting that at this dose, tetrabenazine does not affect P- glycoprotein in the intestinal tract. In vitro studies also do not suggest that tetrabenazine or its metabolites are P-glycoprotein inhibitors.

Paediatric Population
Interaction studies have only been performed in adults.

## 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 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.

## 4.8 Undesirable Effects

| *System/organ categories* | **Reactions** | | | | | |
|---|---|---|---|---|---|---|
| | Very common (>1/10) | Common (<1/10 but ≥1/100) | Uncommon (<1/100 but (≥1/1,000) | Rare (<1/1,000 but (≥1/10,000) | Very rare (<1/10,000) | Unknown |
| **Blood & lymphatic system disorders** | | | | | Leukopaenia, Neutropenia | |
| **Immune system disorders** | | | | | Hypersensitivity | |
| **Metabolism and nutrition disorders** | | Decreased appetite | | | Dehydration | |
| **Psychiatric disorders** | Depression, Anxiety, Restlessness, Confusion | Irritability, Obsessive-compulsive disorder, Agitation; | | | Aggression, Anger, Suicidal ideation, Suicide attempt, Nervousness, Sleep disorder | |
| **Nervous system disorders** | Sedation/ Somnolence/ Drowsiness, Extrapyramidal event, Insomnia, Akathisia | Parkinsonism (may include balancing problems), Gait imbalance/ balance difficulty, Bradykinesia, Dystonia, Lethargy, Dizziness, Dysarthria, Headache | | | Neuroleptic Malignant Syndrome, Ataxia, Tremor, Excess salivation | Memory loss |
| **Eye disorders** | Blepharospasm | | | | Oculogyric crisis, Photophobia | |
| **Cardiac disorders** | | | | | Palpitations | |
| **Vascular disorders** | | | | | Hypertension | Postural hypotension, Hypertensive crisis. |
| **Respiratory, thoracic and mediastinal disorders** | Upper respiratory tract infection | Pneumonia, Dyspnoea, Bronchitis | | | Cough, Pneumonia aspiration | |
| **Gastro-intestinal disorders** | Nausea | Diarrhoea, Vomiting, Constipation | | Dysphagia | Dry mouth | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Heptaobiliary disorders** | | | | | | Increased ALT, Increased AST |
| **Skin & subcutaneous tissue disorders** | | | | | Hyperhidrosis, Rash, Pruritus Urticaria | |
| **Renal and urinary disorders** | | Dysuria | | | Urinary tract infection | |
| **Reproductive system and breast disorders** | | | | | Irregular menstrual cycle/amenorrhea/ menstrual disorders | |
| **General disorders and administration site conditions** | Fatigue | Ecchymosis | | | Malaise, Pyrexia, Drug interaction | Weakness |
| **Investigations** | | | | | Weight decreased | |
| **Injury, poisoning and procedural complications** | Fall | Laceration, Inflicted injury | | Drug administration error | Overdose | |

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/
and emailed to the Registration Holder's Patient Safety Unit at:
drugsafety@neopharmgroup.com

### 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

Pharmacotherapeutic 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 and in vivo 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 α-dihydrotetrabenazine, one of the principal metabolite of tetrabenazine, has a similar affinity and more significant selectivity for VMAT2.

At a synaptic level tetrabenazine and α-dihydrotetrabenazine creates a reversible depletion of monamines in the presynaptic terminals. Within the CNS tetrabenazine and α-dihydrotetrabenazine causes preferential depletion of dopamine from nerve terminals. 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 phamacodynamic 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 in male 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**

The expiry date of the product is indicated on the packaging materials

**6.4 Special Precautions for Storage**

Do not store above 30°C.
Use within 3 months after first opening.

**6.5 Nature and Contents of Container**

White HDPE bottle with a white HDPE cap. Pack size of 112 tablets.

**6.6 Special precautions for disposal**

No special requirements.

**7. Manufacturer**

Recipharm Fontaine, Fontaine-Les Dijon, France for
Valeant Pharmaceuticals, Dublin, Ireland

**8. Marketing Authorization Holder:**

NEOPHARM LTD ,
Hashiloach 6, Pob 7063, Petach Tiqva 4917001, Israel

**9. Marketing Authorization Number:**

132-07-31010

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