SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<Product name> 25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg tetrabenazine.
Excipient(s) with known effect: each tablet also contains 64 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Yellowish, cylindrical, bevel-edged tablets of 7 mm in diameter with 'CL25' on one side and score-line on the other. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Huntington's chorea in adults.

4.2 Posology and method of administration

Posology

Adults
Dosage and administration are variable and only a guide is given. The therapy should be supervised by a doctor experienced in treating hyperkinetic disorders.

The initial dose is 12.5 mg once a day for the first week. For the second week the dose is 12.5 mg twice a day and for the third week 12.5 mg three times a day. The daily dose should be increased with increments of 12.5 mg in daily dose with the interval of one week.

Individual optimal doses range usually between 25-100mg/day divided into two or three doses. Maximum daily dose is 100 mg. Doses above 50 mg per day should be given in a three times a day regimen. Maximum recommended single dose is 37.5 mg.

If adverse events such as akathisia, parkinsonism, depression, insomnia, anxiety or sedation occur, titration should be stopped and the dose should be reduced. If the adverse event does not resolve, consideration should be given to withdrawing tetrabenazine treatment or initiating other specific treatment (e.g., antidepressants).

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.

Elderly

No formal studies have been performed in the elderly and pharmacokinetic data is inconclusive. Tetrabenazine has been administered to elderly patients in standard dosage without apparent ill effect, however, Parkinson-like adverse reactions are quite common in these patients and could be dose-limiting.

Paediatric population
There is no relevant use of tetrabenazine in the paediatric population in the treatment of Huntington's disease.

Patients with hepatic impairment
Tetrabenazine is contraindicated in patients with hepatic impairment (Child-Pugh score ≥5, or class A-C) (see sections 4.3, 4.4 and 5.2).

Patients with renal impairment
No studies have been performed in patients with renal impairment. In patients with moderate (CrCL ≥30 to <50 mL/min), or severe renal impairment (CrCL <30 mL/min) a more cautious titration approach is appropriate to ensure a balance between reduction in chorea and possible adverse effects (see section 4.4).

CYP2D6 polymorphism
Patients requiring doses above 50 mg per day should be considered for genotyping of the CYP2D6 to determine if the patient is a poor metabolizer if clinically indicated (see section 4.5).
Poor metabolisers
The maximum recommended daily dose for patients who are identified as CYP2D6 poor metabolizers, should not exceed 50 mg and the maximum recommended single dose 25 mg.
Extensive and Intermediate metabolisers
Patients who are identified as CYP2D6 extensive or intermediate metabolizers may need a dose of tetrabenazine above 50 mg per day to reduce chorea. The dose should be titrated up slowly with one week interval before each increment of the daily dose by 12.5 mg. The maximum recommended daily dose is 100 mg and the maximum recommended single dose is 37.5 mg.

Method of administration
The tablets are for oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients who are actively suicidal (see sections 4.4 and 4.8).
- Patients with untreated or inadequately treated depression (see sections 4.4 and 4.8).
- Breast-feeding.
- Patients taking or who have taken within 14 days a monoamine oxidase inhibitor (MAOI) (see sections 4.5 and 4.8).
- Patients with hepatic impairment (Child-Pugh class A, B and-C, score ≥5) (see sections 4.2, 4.4 and 5.2).
- Patients taking reserpine within 20 days (see sections 4.5 and 5.1).
- Patients with parkinsonism and hypokinetic-rigid syndrome.

4.4 Special warnings and precautions for use

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 (see section 4.2). 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.

Depression/Suicidality
Tetrabenazine may cause depression or worsen pre-existing depression. Cases of suicidal ideation and behaviour have been reported in patients taking the medicinal product. Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation (see also section 4.3). Tetrabenazine is contraindicated in patients who are actively suicidal or who have inadequately treated depression (see sections 4.3, 4.8).
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 suicidal ideation is profound, or persists, discontinuation of tetrabenazine and initiation of antidepressant therapy should be considered.

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

Parkinsonism
Tetrabenazine is contraindicated in patients with parkinsonism (see section 4.3). Tetrabenazine can induce parkinsonism and exacerbate pre-existing symptoms of Parkinson's disease. Tetrabenazine dose should be adjusted as clinically indicated to minimize this side effect.

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

Neuroleptic Malignant Syndrome
Neuroleptic Malignant Syndrome (NMS) has been reported very rarely in patients treated with tetrabenazine. This may occur soon after initiation of therapy, following changes in dosage or after prolonged treatment. Clinical manifestations on NMS include 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. If NMS is suspected tetrabenazine should be withdrawn immediately and appropriate supportive therapy instituted.
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 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 or with a history of cardiac arrhythmias (see section 4.5 and 5.1) or if conditions causing electrolyte disturbances such as hypokalemia emerges.

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 and also 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. Some patients may require discontinuation of therapy.

Sedation and somnolence
Sedation is the most common dose-limiting adverse effect of tetrabenazine. Patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery, until they are on a maintenance dose of tetrabenazine and know how the drug affects them.

Orthostatic hypotension
Tetrabenazine may induce postural hypotension at therapeutic doses. This should be considered in patients who may be vulnerable to hypotension or its effects. Monitoring of vital signs on standing should be considered in patients who are vulnerable to hypotension.

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 (see section 5.1).

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 pneumonia. In a 12-week, double-blind, placebo-controlled study in patients with chorea associated with Huntington's disease, dysphagia was observed in 4% of tetrabenazine-treated patients and 3% of placebo-treated patients. In 48-week and 80-week open-label studies, dysphagia was observed in 10% and 8% of tetrabenazine-treated patients, respectively. Some of the cases of dysphagia were associated with aspiration pneumonia. Whether these events were related to treatment is unknown.

Hepatic impairment
The single dose safety and pharmacokinetics of tetrabenazine has not been fully evaluated in patients with hepatic impairment (Child-Pugh class A-C, score ≥ 5) and there is no data on repeated doses of tetrabenazine in patients with hepatic impairment. In subjects with hepatic impairment (Child-Pugh score 5-9) the rate of conversion of tetrabenazine to its primary metabolites, α- and β-HTBZ, were reduced, and exposure and half-life to α- and β-HTBZ increased. (see sections 4.2, 4.3 and 5.2).

Renal impairment

No formal studies have been performed in patients with renal impairment. However, it is known that there is a decrease in renal function with increasing age, which may lead to decreased clearance of tetrabenazine, α-HTBZ and β-HTBZ. Based upon a cross study population PK analysis, clearance was reduced for tetrabenazine, α-HTBZ and β-HTBZ with increasing age. This was considered a significant statistical relationship between age and clearance.

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

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). At least 14 days should elapse between the discontinuation of a MAOI and initiation of treatment with tetrabenazine.

Reserpine
Concomitant use of tetrabenazine and reserpine is contraindicated (see section 4.3). Reserpine binds irreversibly to VMAT2 and the duration of its effect is several days. Caution should therefore be used when switching a patient from reserpine to tetrabenazine. The physician should wait for chorea to re-emerge before administering tetrabenazine to avoid overdosage and major depletion of serotonin and norepinephrine in the CNS. Since the effects of reserpine can be prolonged, clinical judgment and caution should be used regarding time to discontinuation before starting tetrabenazine.

CYP2D6 inhibitors
In vitro and *in vivo* studies indicate that the tetrabenazine metabolites α-HTBZ and β-HTBZ are substrates for CYP2D6. Caution should be used when adding a strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine, bupropion) to a patient already receiving a stable dose of tetrabenazine (see section 4.2), a reduction in the dose of tetrabenazine should be considered. The effect of moderate or weak CYP2D6 inhibitors is not known. In a clinical interaction study with a strong CYP2D6 inhibitor paroxetine, the AUC increased by 3,4-fold and 9,6-fold for α-HTBZ and β-HTBZ, respectively. If strong CYP2D6 inhibitors are used concomitantly the dose of tetrabenazine should be not more than 25-50 mg daily.

Other cytochrome P450 inhibitors
Based on *in vitro* studies, a clinically significant interaction between tetrabenazine or β-HTBZ, and other P450 inhibitors or inducers is not anticipated. The active metabolite α-HTBZ is also metabolised by CYP1A2 and by CYP3A4 *in vitro*; *in vivo* studies have not been conducted with inhibitors of these enzymes. Caution should be used when adding a strong inhibitor of CYP1A2 (such as ciprofloxacin, fluvoxamine) or CYP3A4 (such as ketoconazole, ritonavir) to a patient on a stable dose of tetrabenazine. A reduction in dose may be needed if the patient is CYP2D6 poor metaboliser or concomitantly taking CYP2D6 inhibitor.

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

Concomitant use of antipsychotic drugs
Adverse reactions, such as QTc prolongation, NMS and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists and tetrabenazine. There is a potential for significant dopamine depletion when administering tetrabenazine concomitantly with antipsychotic agents (e.g. haloperidol, chlorpromazine) or dopamine receptor antagonists like metoclopramide 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.

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

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), (see section 4.4 and 5.1).
P-glycoprotein (P-gp)
A study in healthy volunteers showed that tetrabenazine (25 mg twice daily for 3 days) did not affect P-gp in the intestinal tract. Tetrabenazine did not interact with pharmacokinetics of digoxin, which is a substrate for P-gp. *In vitro* studies also do not suggest that tetrabenazine or its metabolites are P-gp inducers or inhibitors.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from 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. Because of the lack of data, 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 contra-indicated during breast-feeding (see section 4.3).

Fertility
No human data on the effect of tetrabenazine on fertility are available. In rats disrupted estrous cyclicity was seen (see section 5.3). Tetrabenazine may impact the ability of a woman to become pregnant.

4.7 Effects on ability to drive and use machines

Tetrabenazine has moderate to major influence on the ability to drive and use machines. Patients should be advised that tetrabenazine may cause somnolence 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 (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of the safety profile

In clinical studies tetrabenazine was administered to 773 unique subjects and patients. The conditions and duration of exposure to tetrabenazine varied greatly, and included single and multiple dose clinical pharmacology studies in healthy volunteers (n=259) and open-label (n=529) and double-blind studies (n=84) in patients.

In a randomized, 12-week, placebo-controlled clinical trial of Huntington's disease subjects, adverse reactions were more common in the tetrabenazine group than in the placebo group. Forty-nine of 54 (91%) patients who received XENAZINE experienced one or more adverse reaction at any time during the study. The most commonly reported adverse reactions (over 10%, and at least 5% greater than placebo) were sedation/somnolence (31% vs. 3% on placebo), fatigue (22% vs. 13% on placebo), insomnia (22% vs. 0% on placebo), depression (19% vs. 0% on placebo), akathisia (19% vs. 0% on placebo), and nausea (13% vs. 7% on placebo).

Dose escalation was discontinued or dosage of study drug was reduced because of one or more adverse reaction in 28 of 54 (52%) patients randomized to tetrabenazine. These adverse reactions consisted of sedation (15%), akathisia (7%), parkinsonism (4%), depression (3%), anxiety (2%), fatigue (1%) and diarrhoea (1%). Some patients had more than one adverse reaction and are, therefore, counted more than once. Depression, fatigue, insomnia, sedation/somnolence, parkinsonism and akathisia may be dose-dependent and may resolve or lessen with dosage adjustment or specific treatment. If the adverse effect does not resolve or decrease, discontinuing of tetrabenazine should be considered. In clinical trials the most common reasons of discontinuation of tetrabenazine therapy were depression, sedation/somnolence, and parkinsonism/akathisia.

Tabulated list of adverse reactions

The following undesirable effects are ranked according to system organ class and to their frequency:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Side 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.

System organ class	**Undesirable effect**					
	very common	common	uncommon	rare	very rare	not known
Infections and infestations					pneumonia	
Blood and lymphatic system disorders					leukopaenia	
Psychiatric disorders	depression	agitation, anxiety, insomnia, confusion			aggression, anger, suicidal ideations	disorientation, nervousness, restlessness, sleep disorders
Metabolism and nutrition					decreased appetite, dehydration	

disorders						
Nervous system disorders	akathisia, somnolence, parkinsonism, tremor, excess salivation				neuroleptic malignant syndrome	ataxia, dystonia, memory loss, dizziness
Eye disorders					oculogyric crisis, photophobia	
Cardiac disorders						bradycardia
Vascular disorders						postural hypotension, hypertensive crisis
Gastrointestinal disorders						problems with swallowing, nausea, vomiting, epigastric pain, diarrhoea, constipation, dry mouth
Skin and subcutaneous tissue disorders					rash, pruritus, urticaria	hyperhidrosis
Reproductive system and breast disorders						irregular menstrual cycle
General disorders and administration site conditions						fatigue, weakness, hypothermia
Investigations					weight decreased	hyperprolactinemia, elevated ALT, elevated AST
Injury, poisoning and procedural complications					fall	

Description of selected adverse reactions

Extrapyramidal Symptoms (EPS)

Akathisia (including hyperkinesia, restlessness) were reported in 10 patients (19%) receiving tetrabenazine (n=54) in double blind placebo controlled randomised trial. Extrapyramidal events (parkinsonism, including problems with gait and balance and bradykinesia; dystonia) were reported in 8 patients (15%) tetrabenazine patients in the same study. Any extrapyramidal event was reported in 18 patients (33%) while none of the subjects in placebo arm (n=30) had any (see section 4.4).

Neuroleptic Malignant Syndrome (NMS)
Neuroleptic malignant syndrome (NMS), a life threatening condition which has been very rarely reported in patients treated with tetrabenazine. This may occur any time during treatment. Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, excessive sweating and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria, rhabdomyolysis and acute renal failure. If NMS is suspected tetrabenazine should be withdrawn immediately and appropriate supportive therapy instituted (see section 4.4).

Depression and suicidality
In a 12-week, double-blind placebo-controlled study in patients with Huntington's chorea, 10 of 54 patients (19%) treated with tetrabenazine were reported to have an adverse event of depression or worsening depression compared to none of the 30 placebo-treated patients. In two open-label studies (in one study, 29 patients received tetrabenazine for up to 48 weeks; in the second study, 75 patients received tetrabenazine for up to 80 weeks), the rate of depression/worsening depression was 35%. In all of the Huntington's chorea studies of tetrabenazine (n=187), one patient committed suicide, one attempted suicide, and six had suicidal ideation. However, the risk of suicide in patients with Huntington's chorea is increased regardless of depression indices. The precise risk of suicidal ideation/suicidality associated to tetrabenazine cannot be estimated (see sections 4.3, 4.4 and 5.1).

Somnolence
Somnolence is the most common dose-limiting adverse effect of tetrabenazine. In a 12-week, double-blind, placebo-controlled trial in patients with Huntington's chorea, somnolence was observed in 17/54 (31%) tetrabenazine-treated patients and in 1 (3%) placebo-treated patient. Somnolence was the reason upward titration of tetrabenazine was stopped and/or the dose of tetrabenazine was decreased in 15/54 (28%) patients. In all but one case, decreasing the dose of tetrabenazine resulted in decreased sedation. In 48-week and 80-week open-label studies, somnolence was observed in 17% and 57% of tetrabenazine treated patients, respectively. In some patients, somnolence occurred at doses that were lower than recommended doses (see section 4.4).

Laboratory tests
Following administration of 25 mg tetrabenazine to healthy volunteers, peak plasma prolactin levels increased 4- to 5-fold. Prolactin plasma level alterations were not monitored in tetrabenazine clinical development program.
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 alanine aminotransferase (ALT) and aspartate aminotransferase (AST), levels as compared to placebo.

Paediatric population

Tetrabenazine is not intended for use paediatric population, no safety data from children and adolescents is available.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms associated with overdoses of tetrabenazine may include: acute dystonia, oculogyric crisis, nausea, vomiting, diarrhoea, sweating, hypothermia, hypotension, 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 use of active charcoal may provide benefit if administered shortly after overdose.

The effect of haemodialysis on tetrabenazine, α-HTBZ and β-HTBZ has not been evaluated. Tetrabenazine is subject of rapid and extensive first pass metabolism in the liver. The large volume of distribution and moderate (~60% protein binding) for these tetrabenazine and its main metabolites may not provide adequate reduction in plasma concentrations in case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC Code: N07XX06
Tetrabenazine is a synthetic derivative of benzylquinolizine.

Mechanism of action
Studies conducted *in vitro* have shown that tetrabenazine reversibly inhibits the human vesicular monoamine transporter type 2 (VMAT2) (Ki ≈ 100 nM), resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. VMAT2 is principally located on the outer membrane of synaptic vesicles in the central nervous system. Studies have shown that α-HTBZ (dihydrotetrabenazine), the principal active metabolite of tetrabenazine, has a similar affinity and more significant selectivity for VMAT2. Due to a very rapid metabolism of tetrabenazine, majority of pharmacological action is probably α-HTBZ mediated. By contrast, β-HTBZ does not bind to VMAT2.

At a synaptic level tetrabenazine creates a reversible depletion of monamines in the presynaptic vesicles. Tetrabenazine preferentially depletes dopamine and affects other monoamines, noradrenaline and serotonin, to a lesser extent. 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.

Tetrabenazine exhibits weak *in vitro* binding affinity at the dopamine D2 receptor (Ki = 2100 nM).

Pharmacodynamic effects
The effect of a single 25 or 50 mg dose of tetrabenazine on the QT interval was studied in a randomized, double-blind, placebo controlled crossover study in healthy male and female subjects with moxifloxacin as a positive control. At 50 mg, tetrabenazine caused an approximately 8 msec mean increase in QTc (90% CI: 5.0, 10.4 msec). Additional data suggest that inhibition of CYP2D6 in healthy subjects given a single 50 mg dose of tetrabenazine does not further increase the effect on the QTc interval. Effects at higher exposures to either tetrabenazine or its metabolites have not been evaluated (see section 4.4 and 4.5).

Tetrabenazine or its metabolites bind to melanin-containing tissues, and could accumulate in these tissues over time (see sections 4.4 and 5.3).
Clinical efficacy and safety
The efficacy of tetrabenazine as a treatment for the chorea of Huntington's disease (HD) was established primarily in a randomized, double-blind, placebo-controlled multi-centre trial (#103.004) conducted in 84 (54 patients randomised to tetrabenazine, 30 to placebo) ambulatory patients with a diagnosis of HD. The diagnosis of HD was based on family history, neurological exam, and genetic testing. Treatment duration was 12 weeks, including a 7-week dose titration period and a 5-week

maintenance period followed by a 1-week washout. The dose of tetrabenazine was started at 12.5 mg per day and titrated upward at weekly intervals in 12.5 mg increments until satisfactory control of chorea was achieved, until intolerable side effects occurred, or until a maximal dose of 100 mg per day was reached.

The primary efficacy endpoint was the Total Chorea Score, an item of the Unified Huntington's Disease Rating Scale (UHDRS). On this scale, chorea is rated from 0 to 4 (with 0 representing no chorea) for 7 different parts of the body. An inclusion criterion was that a subject has a Total Chorea Score (TCS) $\geq$ 10 (median 14 points). TCS for subjects in the drug group declined by an estimated 5.0 units during maintenance therapy (average of Week 9 and Week 12 scores versus baseline), compared to an estimated 1.5 units in the placebo group. The treatment effect of 3.5 units was statistically significant. At the Week 13 follow-up in Study 1 (1 week after discontinuation of the study medication), the TCS of subjects receiving tetrabenazine returned to baseline. During the trial one subject in tetrabenazine arm committed a suicide. The emergence or exacerbation of depression was recorded in 8 of 54 tetrabenazine treated patients, none in placebo treated (see section 4.8).

A placebo controlled withdrawal study (#103.005) was performed in 30 patients who had been treated with open-label tetrabenazine for at least 2 months. After discontinuation of tetrabenazine treatment the signs of chorea returned in a day or two. Although the study failed due to protocol violations and the comparison did not reach statistical significance (p=0.1), the estimate of the treatment effect was similar to that seen in Study 1 (about 3.5 units). No drug related adverse effects or symptoms related to rebound or withdrawal syndrome were recorded.

Paediatric population

PDCO/EMA has granted a waiver for medicinal products intended to treat Huntington's disease in all subsets of the paediatric population, on the grounds that the condition does not normally occur in the paediatric populations. Therefore studies in children are not relevant.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of tetrabenazine, the extent of absorption is at least 75%. After single oral doses ranging from 12.5 to 50 mg, plasma concentrations of tetrabenazine are generally below the limit of detection because of the rapid and extensive first-pass hepatic metabolism of tetrabenazine by carbonyl reductase to the active metabolite α-dihydrotetrabenazine (α-HTBZ) and inactive metabolite β-dihydrotetrabenazine (β-HTBZ). Peak plasma concentrations (Cmax) of α-HTBZ and β-HTBZ are reached within 1 to 1½ hours post-dosing.

The effects of food on the bioavailability of tetrabenazine were studied in subjects administered a single dose with and without food. Food had no effect on mean plasma concentrations, Cmax, or the area under the concentration time course (AUC) of α-HTBZ or β-HTBZ. Tetrabenazine can, therefore, be administered without regard to meals.

Distribution

After administration of single doses from 12.5 to 50 mg of tetrabenazine, the maximum plasma concentration and the area under the curve of the HTBZ metabolites increased in proportion to the dose, indicating a linear kinetic. Tetrabenazine concentrations are usually not detectable. Results of PET-scan studies in humans show that radioactivity is rapidly distributed to the brain following intravenous injection of ^{11}C-labeled tetrabenazine or α-HTBZ, with the highest binding in the striatum and lowest binding in the cortex.

Animal studies suggest extensive distribution to tissues. The *in vitro* protein binding of tetrabenazine, α-HTBZ, and β-HTBZ was examined in human plasma for concentrations ranging from 50 to 200 ng/mL. Tetrabenazine binding ranged from 82% to 85%, α-HTBZ binding ranged from 60% to 68%, and β-HTBZ binding ranged from 59% to 63%. The metabolites α-HTBZ and β-HTBZ are mainly bound to albumin. Clinical population PK modelling indicates that α-HTBZ, and β-HTBZ are widely

distributed within patients.

Biotransformation
After oral administration in humans, at least 19 metabolites of tetrabenazine have been identified. α-HTBZ, β-HTBZ and 9-desmethyl-β-HTBZ, are the major circulating metabolites, and they are, subsequently, metabolized to sulfate or glucuronide conjugates. α-HTBZ and β-HTBZ are formed by carbonyl reductase mainly in the liver. α-HTBZ is O-dealkylated by CYP450 enzymes, principally CYP2D6, with some contribution of CYP1A2 to form 9-desmethyl-α-HTBZ. *In vitro* α-HTBZ is also metabolised by CYP3A4 to hydroxyl metabolite(s), however, it is uncertain whether this pathway is clinically significant *in vivo*. β-HTBZ is O-dealkylated principally by CYP2D6 to form 9-desmethyl-β-HTBZ.

The results of *in vitro* studies do not suggest that tetrabenazine, α-HTBZ, or β-HTBZ are likely to result in clinically significant inhibition of CYP2D6, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A. *In vitro* studies suggest that neither tetrabenazine nor its α- or β-HTBZ metabolites are likely to result in clinically significant induction of CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, or CYP2C19.

Neither tetrabenazine nor its α- or β-HTBZ metabolites is likely to be a substrate or inhibitor of P-glycoprotein at clinically relevant concentrations *in vivo*. Potential interactions with other transporters has not been evaluated.

In humans, β-HTBZ is further metabolised to 9-desmethyl-β-HTBZ and is a major human circulating metabolite. Receptor binding studies indicate that it does not interact with VMAT receptors but may have the potential for interaction at select dopamine, sigma and α-adrenergic receptors. No *in vitro* metabolism studies have been conducted to evaluate the potential of the 9-desmethyl-β-HTBZ metabolite to interact with other drugs.

Elimination
After oral administration, tetrabenazine is extensively metabolized in the liver, and the metabolites are primarily renally eliminated. α-HTBZ, β-HTBZ and 9-desmethyl-β-HTBZ have half-lives of 7 hours, 5 hours and 12 hours respectively. In a mass balance study in 6 healthy volunteers, approximately 75% of the dose was excreted in the urine and faecal recovery accounted for approximately 7-16% of the dose. Unchanged tetrabenazine has not been found in human urine. Urinary excretion of α-HTBZ or β-HTBZ accounted for less than 10% of the administered dose. Circulating metabolites, including sulfate and glucuronide conjugates of HTBZ metabolites as well as products of oxidative metabolism, account for the majority of metabolites in the urine.

Patients with hepatic impairment
The impact of hepatic impairment on the PK characteristics of tetrabenazine and its main metabolites has been evaluated with a single dose of 25 mg tetrabenazine in 6 healthy subjects age matched with 6 hepatic impaired subjects with Child-Pugh scores 5 to 9. Tetrabenazine is minimally detected in plasma of normal hepatic function patients while in hepatic impairment patients it is detectable in plasma with a mean t½ of 17.5 hours. Tetrabenazine's main metabolites, α- and β-HTBZ, Cmax were reduced on average by < 10% in subjects with hepatic impairment, reach a median Tmax of 1.75 hour while AUCs for α- and β-HTBZ increased approximately by 35%. Mean elimination t½ for α- and β-HTBZ in hepatic impaired patients prolonged to approximately 10 hours and 8,5 hours, respectively. In subjects with liver impairment, the apparent rate of conversion of tetrabenazine to α- and β-HTBZ was reduced, and total systemic exposure and elimination half-life to α- and β-HTBZ increased (significantly for Child-Pugh score 9) possibly due to reduced first pass and systemic metabolism of tetrabenazine combined with reduced clearance of the primary metabolites. There are no data on repeated doses of tetrabenazine in patients with hepatic impairment (Child-Pugh class A to C, score ≥5) (see sections 4.2, 4.3 and 4.4). The safety and efficacy of increased exposure to tetrabenazine and its metabolites are unknown and the safe use in patients with hepatic impairment can’t be ensured. Tetrabenazine is contraindicated in subjects with liver impairment.

5.3 Preclinical safety data

In repeat-dose toxicicy studies, the effects observed with orally administered tetrabenazine were related to depletion of central stores of monoamines, such as serotonin and noradrenaline. The activity is mainly limited to the brain. It is thought that the effect of tetrabenazine on brain amines explains its clinical effects in man. Common symptoms were hypoactivity, lethargy, strabismus, or closed eyes. Primarily pharmacological effects such as sedation were observed and considered dose limiting.

The genotoxicity of tetrabenazine has been studied with bacterial reverse gene mutation test and in mammalian cells *in vitro* and *in vivo*. *In vitro*, tetrabenazine in cytotoxic concentrations did not induce point mutations to the DNA but induced chromosomal aberrations in tested mammalian cells (Chinese hamster ovary and lung cells). *In vivo*, tetrabenazine was not genotoxic in the bone marrow micronucleus test when analysed in male rats and mice.

According to *in vivo* studies in rats and mice, tetrabenazine was not carcinogenic or oncogenic.

Tetrabenazine did not affect fertility in the *in vivo* studies conducted in rats. 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. Tetrabenazine did not affect fertility in male rats. Tetrabenazine was not embryotixic or teratogenic in the rats and rabbits. In peri/postnatal study in rats, increased neonatal mortality was observed. These effects from the peri/postnatal study are anticipated to be indirect effects due to inadequate maternal care but a direct effect of tetrabenazine on the pups cannot be ruled out.

Tetrabenazine or its metabolites bind to melanin-containing tissues (i.e., eye, skin, fur) in pigmented rats. After a single oral dose of radiolabeled tetrabenazine, radioactivity was still detected in eye and fur at 21 days post dosing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose monohydrate
Maize starch
Talc
Magnesium stearate
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

Shelf life after first opening: 3 months

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Tablets in white HDPE bottle with a white child-resistant polypropylene cap.
Pack size: 112 tablets

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

PharmaSwiss Česká republika s.r.o.
Jankovcova 1569/2c
170 00 Prague
Czech Republic

8. MARKETING AUTHORISATION NUMBER

< To be completed nationally >

9. DATE OF FIRST AUTHORISATION

< To be completed nationally >

10. DATE OF REVISION OF THE TEXT

< To be completed nationally >