SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tetrabenazine 25 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg tetrabenazine.

Excipient with known effect:

Each tablet contains 85.300 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Yellow, circular, flat faced bevelled edge uncoated tablet debossed with “179” on one side and scored on the other side. The tablet has a diameter of 7 mm and a thickness of 2.3 mm to 2.7 mm).

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tetrabenazine is indicated for hyperkinetic motor disorders with Huntington’s chorea.

4.2 Posology and method of administration

Posology

Adults
Huntington's chorea
Dosage and administration are individual in each patient and therefore only a guide is given.
An initial starting dose of 12.5 mg/day one to three times a day is recommended. This can be increased every three or four days by 12.5 mg until the optimal effect is observed or up to the occurrence of intolerance effects (sedation, Parkinsonism, depression).

The maximum daily dose is 200 mg a day.

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 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.

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

Hepatic impairment
Tetrabenazine is contraindicated in patients with hepatic impairment, Child Pugh 5 to 9 (see also sections 4.3 and 5.2).

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

Method of administration
The tablets are for oral administration. The therapy should be supervised by a doctor experienced in treating hyperkinetic disorders.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Tetrabenazine can block the action of reserpine. Thus these substances should not be taken concomitantly.

Use of monoamine oxidase inhibitors- tetrabenazine should not be administered within two weeks after treatment with MAOIs
Presence of a hypokinetic-rigid-syndrome (Parkinsonism)
Untreated or inadequately treated depression. Patients who are actively suicidal.
Breast feeding
Pheochromocytoma
Pro-lactin-dependent tumours, e.g. pituitary or breast cancer
Patients with liver failure, with a Child-Pugh scale of 5 to 9
Concomitant use with reserpine (see section 4.5)

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). 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 and their concomitant medications (see section 4.5).

It is known that dose dependent adverse events such as sedation, depression and the occurrence of a hypokinetic-rigid-syndrome (Parkinsonism) are possible. In such a case, the dose should be reduced and discontinuation of tetrabenazine be considered if events do not resolve.

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 (see also section 4.3).

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.

MAOI antidepressants are contraindicated and should be stopped 14 days before the treatment with tetrabenazine starts, and should not be used until at least 14 days have elapsed after the treatment with tetrabenazine has ended, to avoid a potentially serious drug interaction (see 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.

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

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a rare complication of tetrabenazine therapy.

Neuroleptic malignant syndrome most often occurs early in treatment or in response to changes in dose or after prolonged treatment, and has also been described after abrupt withdrawal.

The main symptoms of this condition are mental changes, rigidity, hyperthermia, autonomic dysfunction (sweating and irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac arrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure.

If NMS is suspected tetrabenazine should be withdrawn immediately and appropriate treatment initiated.

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

Tetrabenazine causes a small increase (up to 8msec) in the corrected QT interval.

Tetrabenazine should be used with caution in combination with other drugs known to prolong QTc and in patients with congenital long QT syndromes and a history of cardiac arrhythmias (see section 4.5).

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; however, 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.

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

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Tetrabenazine should not be used concomitantly with MAO inhibitors. 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.

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

Concomitant use with tricyclic antidepressants, alcohol, opioids, beta blocking agents, antihypertensive drugs, hypnotics and neuroleptics is not recommended.

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.
Concomitant use of tetrabenazine with antihypertensive drugs and beta-blockers may increase the risk of orthostatic hypotension.

Digoxin
Digoxin is a substrate for P-glycoprotein. A study in healthy volunteers showed that tetrabenazine (25 mg twice daily for 3days) 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.

No interaction studies with tetrabenazine have been performed in vivo, and metabolising enzymes are partly unknown. In vitro studies indicate that tetrabenazine may be a CYP2D6 inhibitor and therefore cause increased plasma concentrations of medicinal products metabolised by CYP2D6.

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

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).

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).

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 should not be used during pregnancy unless no other treatment is available. The effect of tetrabenazine on labour and delivery in humans is unknown.

Breastfeeding

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). Breast feeding must be stopped, if treatment with tetrabenazine is necessary.

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

The following undesirable effects are ranked according to system organ class and to their frequency:

Very common (≥1/10)
Common (≥1/100 and <1/10)
Uncommon (≥1/1000 and <1/100)
Rare (≥1/10,000 and <1/1000)
Very rare (<1/10,000)
Not known (it is not possible to estimate the incidence from available data).

System/Organ categories	Frequency	Event
Infections and infestations	Very rare	Pneumonia
Blood & lymphatic system disorders	Very rare	Leukopaenia
Psychiatric disorders	Very common	Depression
	Common	Anxiety, insomnia, confusion, agitation
	Very rare	Anger, aggression,

System/Organ categories	Frequency	Event
		suicidal ideation, suicide attempt
	Not known	Disorientation, nervousness, restlessness, sleep disorders
Metabolism and nutrition disorders	Common	Decreased appetite
	Very rare	Dehydration
	Not known	Increased appetite
Nervous system disorders	Very common	Drowsiness (with higher dosages), Parkinson-like syndrome (with higher dosages), tremor, excessive salivation
	Uncommon	Altered levels of consciousness
	Rare	Neuroleptic malignant syndrome (see section 4.4)
	Not known	Ataxia, akathisia, dystonia, dizziness, amnesia
Eye disorders	Very rare	Oculogyric crisis, photophobia
Cardiac disorders	Not known	Bradycardia
Vascular disorders	Common	Postural hypotension
	Not known	Hypertensive crisis
Gastro-intestinal disorders	Common	Dysphagia, nausea, vomiting, diarrhoea, constipation, epigastric pain, dry mouth
Skin and subcutaneous tissue disorders	Very rare	Rash, pruritus, urticaria
	Not Known	Hyperhidrosis
Musculoskeletal and connective tissue disorders	Uncommon	Severe extrapyramidal symptoms including muscular rigidity, autonomic dysfunction
	Very rare	Skeletal muscle damage
Reproductive system and breast disorders	Not known	Irregular menstrual cycle
General disorders and administration site conditions	Uncommon	Hyperthermia
	Not known	Fatigue, weakness, hypothermia

System/Organ categories	Frequency	Event
Investigations	Very rare	Weight loss
	Not known	Weight increase
Injury, poisoning and procedural complications	Very rare	Falls

Rarely, a neuroleptic malignant syndrome (NMS) has been described in association with tetrabenazine treatment (see section 4.4). This may occur soon after initiation of therapy, following changes in dosage or after prolonged treatment. The main symptoms are altered mental status, muscle rigidity, hyperthermia, autonomic dysfunction, elevated levels of creatinine phosphokinase. If NMS is suspected, treatment with tetrabenazine should be discontinued immediately and appropriate supportive treatment instituted (see section 4.4).

To avoid the risk of potentially serious interactions that may occur in the form of hypertensive crisis, at least 14 days should elapse between discontinuation of treatment with an MAOI and initiation of treatment with tetrabenazine, as well as between discontinuation of treatment with tetrabenazine and initiation of treatment with the MAOI.

Cardiac abnormalities including QT prolongation and ventricular arrhythmias (including ventricular tachycardia and ventricular fibrillation) leading to cardiac arrest or sudden unexplained death have been reported during treatment with neuroleptics.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms of overdosage may include acute dystonia, oculogyric crisis, nausea, vomiting, diarrhoea, sweating, hypotension, confusion, hallucinations, hypothermia, 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 centre on the treatment of any overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

The central effects of tetrabenazine closely resemble those of reserpine, but it differs from the latter in having less peripheral activity and being much shorter acting.

Mechanism of action

Animal studies have shown that tetrabenazine disturbs the metabolism of biogenic amines, for instance that of serotonin and noradrenaline, and that this activity is limited to the brain. The supposition is that this effect of tetrabenazine on amines in the brain explains the clinical effects in the brain.

Tetrabenazine inhibits the re-uptake of monoamines in the neuroterminal of the presynaptic neurons of the central nervous system. This results in a depletion of monoamines, including dopamine. Dopamine depletion results in hypokinesis leading to a reduction in chorea severity.

Tetrabenazine inhibits the re-uptake of monoamines in synaptic nerve terminals by a reversible and short-term binding to the vesicular monoamine transporter (VMAT). VMAT2 transports monoamines especially in peripheral and central neurons, while VMAT1 regulates the transport in peripheral chromaffine tissues. Tetrabenazine has a higher affinity for VMAT2 than for VMAT1. Thus, tetrabenazine has a short, hardly peripheral effect.

5.2 Pharmacokinetic properties

Tetrabenazine has a low and erratic bioavailability. It appears to be extensively metabolised by firstpass metabolism. The major metabolite, hydroxytetrabenazine, is formed by reduction. Little unchanged tetrabenazine can be detected in the urine. Since hydroxytetrabenazine is reported to be as active as tetrabenazine in depleting brain amines, it is likely that this is the major therapeutic agent.

Special populations

Hepatic impairment

Mild and moderate hepatic impairment increases the exposure and prolongs the half-lives of tetrabenazine and hydroxytetrabenazine (4 patients with Child Pugh score 5-6 and 1 patient with Child Pugh score 9.) Severe hepatic impairment has not been studied.

5.3 Preclinical safety data

In repeated dose toxicity studies, the effects observed with orally administered tetrabenazine were related to depletion of central stores of monoamines. Common symptoms were hypoactivity, lethargy, strabismus, or closed eyes. Primarily pharmacological effects such as sedation were observed and considered dose limiting.

The genotoxic potential of tetrabenazine has been studied using a series of conventional tests. In vitro, tetrabenazine was negative for point mutations and positive for chromosomal aberrations in Chinese hamster ovary cells, at cytotoxic concentrations only. Tetrabenazine was not genotoxic in an in vivo chromosomal aberration test.

Tetrabenazine did not reveal any carcinogenic potential when administered for 26 weeks in the transgenic p53 heterozygous mouse model at doses up to 30 mg/kg/day

and 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

Lactose, anhydrous
Maize starch
Sodium starch glycolate
Talc
Silica, colloidal anhydrous
Magnesium stearate
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Tetrabenazine is packed in a white round high-density polyethylene (HDPE) tablet container with a child resistant, tamper-evident polypropylene (PP) screw cap with mounted desiccant, containing 112 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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2132 JH Hoofddorp
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PL 31750/0064

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