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 effects:
Each tablet contains 60.8 mg lactose (see section 4.4)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet Yellow, round, with a break line on one-side and `TE25` engraved on the reverse side.
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

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

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 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 occurence 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 population
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
The safety and efficacy in children have not yet been established. 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

- 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

- Impaired hepatic function
- 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

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).

Parkinsonism
Tetrabenazine can induce parkinsonism and exacerbate pre-existing symptoms of Parkinson's disease. In such a case, the dose should be reduced and discontinuation of tetrabenazine be considered if event does not resolve.

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.

Neuroleptic Malignant Syndrome
A neuroleptic malignant syndrome has been described under the use of tetrabenazine and after abrupt withdrawal. Neuroleptic malignant syndrome is a rare complication of tetrabenazine therapy. Neuroleptic Malignant Syndrome most often occurs early in treatment, in response to changes in dose or after prolonged treatment. 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 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 arrhythmias (see section 4.5).

Depression/Suicidality
Tetrabenazine may cause depression or worsen pre-existing depression. Cases of suicidal ideation and behaviour have been reported in patients taking this 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 or suicidal ideation is profound, or persists, discontinuation of tetrabenazine and initiation of antidepressant therapy should be considered.
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.

MAO-inhibitors

When using tetrabenazine MAO-inhibitors are contraindicated (see section 4.3) and should be stopped 14 days before the treatment with tetrabenazine starts.

Akathisia, Restlessness and Agitation
Patients taking tetrabenazine should be monitored for the presence of extrapyramidal symptoms and 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.

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, maximum 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, galactorrhoea, 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 hyperprolactinaemia, 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Tetrabenazine should not be used concomitantly with reserpine, MAO inhibitors.

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.

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.

In vitro and in vivo studies indicate that the tetrabenazine metabolites α-DTBZ and β-DTBZ are substrates for CYP2D6. Inhibitors of CYP2D6 (e.g. fluoxetine, paroxetine, terbinafine, moclobemide and quinidine) may result in increased plasma concentrations ofα-HTBZ and β-HTBZ,why they should only be combined with caution. A reduction of the tetrabenazine dose may be necessary.

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
Animal studies are insufficient with respect to effects on pregnancy, embryofetal development, birth, or development post partum (see section 5.3). There are no or limited amount of data from the use of tetrabenazine in pregnant women and the potential risk for humans is unknown. Tetrabenazine should not be used during pregnancy unless no other treatment is available.

Breat-Feeding
Tetrabenazine is contraindicated during breast-feeding (see section 4.3). Breast feeding must be discontinued, 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 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.

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 to < 1/10)
Uncommon (≥1/1.000 to < 1/100)
Rare (≥ 1/10.000 to < 1/1.000)
Very rare (<1/10.000)

Psychiatric disorders
Very common: depression,
Common: anxiety, insomnia, confusion

Nervous system disorders
Very common: somnolence (with higher dosages), Parkinson-like syndrome (with higher dosages)
Uncommon: altered levels of consciousness
Rare: Neuroleptic Malignant Syndrome (NMS) (see section 4.4)

Vascular disorders
Common: Hypotension

Gastrointestinal disorders
Common: dysphagia, nausea, vomiting, diarrhoea, constipation

Musculoskeletal and connective tissue disorders
Uncommon: severe extrapyramidal symptoms including muscular rigidity, autonomic dysfunction
Very rare: Skeletal muscle damage

General disorders and administration site conditions
Uncommon: hypothermia

For the following side-effects, it is not possible to estimate the incidence from available data:

Psychiatric disorders: disorientation, nervousness
Nervous system disorders: ataxia, akathisia, dystonia, dizziness, amnesia
Cardiac disorders: bradycardia
Vascular disorders: orthostatic hypotension
Gastro-intestinal disorders: epigastric pain, dry mouth

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

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

Signs and symptoms of overdosage may include somnolence, sweating, hypotension and hypothermia. Treatment is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other nervous system drugs, ATC code: N07XX06

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.

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

Absorption/Distribution
Tetrabenazine is quickly and completely absorbed after oral administration. Its absorption is not affected by the food intake.

Clinical testing has shown that a single dose of tetrabenazine undergoes extensive absorption (≥75%) from the gastrointestinal tract.

Plasma levels of tetrabenazine decline rapidly, with a half-life of 1.9 hours.

Biotransformation
Tetrabenazine has a low and erratic bioavailability (4.9% to 6%). It appears to be extensively metabolised by first-pass metabolism. Major metabolites, alpha-dihydrotetrabenazine (**α**-HTBZ) and β-dihydrotetrabenazine (β-HTBZ), are formed by reduction.
Primary metabolites **α**-HTBZ and β-HTBZ are mainly metabolised by cytochrome P450 2D6 liver enzyme. CYP2D6 inhibitors may increase the plasma concentration of these metabolites.

Elimination
Tetrabenazine is mostly eliminated in metabolised form in urine (only 2.1% of tetrabenazine is excreted unchanged in the urine.

Linearity/non-linearity
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.

5.3 Preclinical safety data

In repeat-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; however, carcinogenicity studies have not been performed.

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.

Tetrabenazine was not embryotoxic or teratogenic in the rabbit; however, the observed systemic exposure was lower than that observed clinically. The potential embryotoxic and teratogenic effects were also insufficiently studied in the rat. In a peri/postnatal study in the rat, increased neonatal mortality was observed, the cause of which is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised maize starch
Lactose monohydrate
Talc
Ferric oxide yellow E172
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep the container in the outer carton in order to protect from light.
Do not store above 25°C.

6.5 Nature and contents of container

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

No special requirements

7 MARKETING AUTHORISATION HOLDER

Aop Orphan Pharmaceuticals GmbH
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Döbling
Vienna
1190
Austria

8 MARKETING AUTHORISATION NUMBER

PA0934/004/001

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Date of last renewal: 22nd November 2012

10 DATE OF REVISION OF THE TEXT

February 2024