SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tetrabenazine Aristo 25 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg tetrabenazine.

Excipients with known effect
Each tablet contains 63.4 mg lactose (as monohydrate).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Round, pale yellow tablets with a score line on one side and with an approximately diameter of 7.00 mm ± 0.2 mm.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tetrabenazine Aristo is indicated in:

- hyperkinetic movement disorders in Huntington's chorea
- moderate to severe tardive dyskinesia, which has not responded to other therapeutic measures

This medicine must only be used on prescription by a neurologist or paediatric neurologist who is familiar with the treatment of hyperkinetic disorders, or in neurological departments and similar units.

4.2 Posology and method of administration

Posology

Hyperkinetic movement disorders in Huntington's chorea
Dosing and administration times are variable and must be individually adjusted according to the severity of the disease and response to treatment. The dose recommendation can therefore only serve as a guideline. In general, however, the maximum daily dose of tetrabenazine should not be exceeded.

An initial dose of 25 mg three times a day is recommended. This dose can be increased by 25 mg per day every three or four days until either satisfactory efficacy is achieved or until undesirable side effects occur (tolerance limit). The dosage recommendation can therefore serve only as a guide. In general, however, the maximum daily dose of 200 mg tetrabenazine should not be exceeded. Once a stable maintenance dose has been achieved, treatment should be reviewed at regular intervals against the background of the underlying disease and medicinal products used concomitantly (see section 4.5).

If no improvement is seen after seven days of taking the maximum dose, this medicinal product is unlikely to benefit the patient, even if the dose is further increased or the duration of treatment prolonged. Withdrawal of treatment with tetrabenazine should be considered.

Discontinuation of treatment with tetrabenazine
Discontinuation of tetrabenazine is associated with the return of chorea (without significant worsening compared to baseline). Other adverse reactions to sudden treatment withdrawal are possible but unlikely and generally mild.

Tardive dyskinesia
The recommended initial dose is 12.5 mg per day and is then increased depending on the patient's response.
This medicinal product should be discontinued if there is no clear improvement in the clinical picture or if the adverse reactions cannot be tolerated.

The maximum daily dose of 200 mg tetrabenazine should not be exceeded.

Resumption of treatment
Following treatment interruption of greater than 5 days or a treatment interruption occurring due to a change in the patient's medical condition or medicinal products used concomitantly, tetrabenazine therapy should be retitrated when resumed. The dose should be initiated at 12.5 mg twice a day, wait 7 days then titrate up by 12.5 mg per day.

If adverse events such as akathisia, restlessness, parkinsonism, depression, insomnia, anxiety, or intolerable sedation occur, titration should be stopped and the dose should be reduced.
Special populations

Elderly patients
No specific studies have yet been performed with patients of advancing age (> 65 years). However, Tetrabenazine Aristo 25 mg has already been administered to elderly patients at the recommended adult dose and did not cause any discernible adverse effects.

Paediatric Population
No adequately controlled clinical studies have been performed in children. A dosage recommendation cannot be given. Limited clinical experience suggests that treatment be started at approximately half the daily dose for an adult and then to slowly and carefully adjust the dose, depending on tolerance and individual reaction

Hepatic insufficiency, renal insufficiency
In patients with impaired liver or kidney function, dose titration should be done slowly, lower daily doses may be required.

Patients taking CYP2D6 inhibitors
The appropriate tetrabenazine dosage should be determined for each patient by titration. Studies (*in vitro* and *in vivo*) have shown that the tetrabenazine metabolites α-HTBZ and ß-HTBZ are substrates for CYP2D6 (see section 5.2). The dose required for a patient may therefore be influenced by his/her CYP2D6 metaboliser status, as well as by co-administered medicinal substances regarded to be potent CYP2D6 inhibitors (see section 4.5).

Method of administration
Tetrabenazine Aristo is for oral use.
The tablets should be taken with sufficient liquid (water or other non-alcoholic beverages) and should not be chewed.

4.3 Contraindications

Tetrabenazine Aristo should not be used in case of:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- acute risk of suicide;
- untreated or insufficiently treated depression;
- existing prolactin-dependent tumours, such as prolactin-dependent pituitary tumours or breast cancer;
- in the presence of a phaeochromocytoma (tumour of the adrenal medulla);
- during breastfeeding (see section 4.6);
- intake of monoamine oxidase inhibitors (MAOIs), concomitantly or less than 14 days previously (see sections 4.5 and 4.8);
- impaired hepatic function (Child-Pugh score 5 to 9);
- concomitant intake of reserpine (see section 4.5);
- patients with Parkinson's syndrome and hypokinetic-rigid syndrome.

Tetrabenazine Aristo must not be administered together with a monoamine oxidase inhibitor (MAO inhibitor).

4.4 Special warnings and precautions for use

The appropriate dosage of tetrabenazine should be administered for each patient by titration.

Studies (*in vitro* and *in vivo*) have shown that the tetrabenazine metabolites alpha-HTBZ and beta-HTBZ are substrates for CYP2D6 (see section 5.2). The dose required for a patient may therefore be influenced by the patient`s CYP2D6 metaboliser status and by the concomitant use of medicinal substances considered to be strong CYP2D6 inhibitors (see section 4.5).

When first prescribed, the dose of tetrabenazine should be titrated up slowly over several weeks to find a dose that both reduces chorea symptoms and is well tolerated. If side effects do not subside or become less severe, discontinuation of treatment with tetrabenazine should be considered.

Once a stable defined daily dose is achieved, treatment should be reviewed at regular intervals in the light of the underlying disease and concomitant medication (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 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 occurs, it may be controlled by reducing the dose of tetrabenazine and/or initiating antidepressant therapy.

If severe or persistent 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.

To avoid the risk of a potentially serious interaction, it must be ensured that at least 14 days elapse between the discontinuation of tetrabenazine and the start of treatment with a MAO inhibitor, as well as between the discontinuation of the MAO inhibitor and the start of treatment with tetrabenazine.

Anger and aggression
In patients with depression or a history of other psychiatric illnesses taking tetrabenazine, there is a potential risk for the emergence or exacerbation of anger and aggressive behaviour.

Parkinson's symptoms
Tetrabenazine can induce Parkinson's symptoms and exacerbate pre-existing symptoms of Parkinson's disease. The tetrabenazine dose must be adjusted according to clinical need, in order to minimise this adverse reaction.

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

Tardive dyskinesia
Tetrabenazine treatment may be considered if symptoms persist despite discontinuation of antipsychotic therapy or in cases where discontinuation of antipsychotic medication is not a suitable option. This also applies if the symptoms persist despite reducing the dosage of antipsychotic medication or switching to atypical antipsychotic medication.

However, tetrabenazine is a central transmitter-depleting active substance 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, discontinuation of the medicinal product should be considered.

Neuroleptic malignant syndrome (NMS)
In patients treated with tetrabenazine, onset of neuroleptic malignant syndrome has been reported in individual cases. It may occur shortly after the start of treatment, after dose modifications or after long-term treatment. The clinical presentation of NMS includes hyperpyrexia, muscle stiffness, altered mental state and evidence of autonomic instability (irregular pulse or fluctuating blood pressure, tachycardia, diaphoresis and cardiac arrhythmias). Other symptoms are elevated creatinine phosphokinase levels, myoglobinuria, rhabdomyolysis and acute renal failure.

If neuroleptic malignant syndrome is suspected, tetrabenazine must be discontinued immediately and appropriate therapy initiated.

If the patient continues to require treatment with tetrabenazine after recovery from neuroleptic malignant syndrome, possible resumption of treatment with tetrabenazine should be carefully reviewed. The patient should be carefully monitored, as relapse of neuroleptic malignant syndrome has been reported.

QTc prolongation
Tetrabenazine leads to a slight prolongation (approx. 8 msec) of the frequency-corrected QT interval. Caution should be exercised with concomitant intake of other medicines that can prolong the QTc, as well as in patients with congenital long QT syndrome and patients with a history of cardiac arrhythmias (see section 4.5).

Cardiac disease
Tetrabenazine has not been studied in patients with a history of myocardial infarction or unstable cardiac disease.

Akathisia, restlessness and agitation
Patients treated with tetrabenazine should be monitored for the presence of akathisia, as well as signs of restless and agitation, as these may be indicators of developing akathisia. If a patient develops akathisia, the tetrabenazine dose should be reduced. In some patients, discontinuation of therapy may be required.

Sedation and somnolence
Sedation is the most common dose-limiting adverse reaction with tetrabenazine. Patients should be cautioned prior to performing activities that require mental alertness, e.g. driving or using hazardous machinery, for as long as the tetrabenazine maintenance dose has not yet been reached and they are not yet able to gauge the effect of the medicinal product.

Orthostatic hypotension
Tetrabenazine may cause orthostatic dysregulation at therapeutic doses and may include symptoms such as positional dizziness and syncope. This should be considered in patients who are prone to low blood pressure or its effects. Monitoring of orthostatic vital signs while getting up should be considered in patients who are susceptible to hypotension.

Hyperprolactinaemia
Tetrabenazine elevates serum prolactin levels in humans. Following administration of 25 mg to healthy subjects, peak plasma prolactin levels increased by 4- to 5-fold. Tissue culture tests indicate that the growth of cells in approximately one-third of

human breast tumours can be stimulated *in vitro* by prolactin. This is a potentially important factor if tetrabenazine is to be used in patients with previously diagnosed breast cancer.
Although amenorrhea, galactorrhoea, gynecomastia and impotence can be caused by elevated serum prolactin concentrations, the clinical relevance of elevated serum prolactin concentrations for most patients is unknown.
Chronically elevated serum prolactin concentrations (although not investigated during the tetrabenazine development programme) have been associated with low oestrogen levels and an increased risk of osteoporosis. If there is a clinical suspicion of symptomatic hyperprolactinaemia, appropriate laboratory testing should be performed and discontinuation of tetrabenazine treatment should be considered.

Binding to melanin-containing tissues
As tetrabenazine and its metabolites bind to melanin-containing tissues, it may accumulate at these sites over time. This implicates the possibility that tetrabenazine may cause damage in these tissues in long-term use. The clinical relevance of tetrabenazine binding to melanin-containing tissues is unknown. Although there are no specific recommendations for regular eye tests, prescribing physicians should be aware of the possibility of ophthalmologic effects after long-term exposure.

Tetrabenazine Aristo contains lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Tetrabenazine Aristo.

Laboratory tests
In clinical studies with tetrabenazine, no clinically significant changes in laboratory parameters were reported. In controlled clinical studies, tetrabenazine caused a minor increase in alanine-aminotransferase (ALT) and aspartate-aminotransferase (AST) laboratory values compared to placebo.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed *in vivo*. Not all of the metabolising enzymes for tetrabenazine are known. *In vivo* studies indicate that tetrabenazine may be an inhibitor of CYP2D6 and may therefore cause elevated plasma concentrations of medicinal substances that are metabolised via CYP2D6 (e.g. metoprolol, amitriptyline, imipramine, haloperidol and risperidone).

CYP2D6 inhibitors
In vitro and *in vivo* studies suggest that the dihydrotetrabenazine metabolites α-HTBZ and β-HTBZ are substrates for CYP2D6. In patients already stabilised on tetrabenazine, adjuvant administration of CYP2D6 inhibitors (such as fluoxetine, paroxetine, quinidine, duloxetine, terbinafine, amiodarone or sertraline) should proceed with caution and a dose reduction of tetrabenazine should be considered. The effect of moderate to weak CYP2D6 inhibitors, e.g. duloxetine, terbinafine, amiodarone or sertraline, has not been investigated.

Other cytochrome P450 inhibitors:
On the basis of *in vitro* studies, clinically significant interactions between tetrabenazine and other P450 inhibitors (other than CYP2D6 inhibitors) are unlikely.

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

Monoamine oxidase inhibitors
Tetrabenazine must not be administered in patients concomitantly taking MAO inhibitors, due to the risk of possible severe interactions resulting in hypertensive crisis (see section 4.3). At least 14 days should elapse between discontinuation of tetrabenazine and initiation of treatment with a MAO inhibitor, as well as between discontinuation of a MAO inhibitor and initiation of treatment with tetrabenazine.

Concomitant use with neuroleptics
Adverse reactions associated with tetrabenazine use, such as QTc prolongation, neuroleptic malignant syndrome (NMS) and extrapyramidal disorders, can be potentiated by concomitant intake of dopamine antagonists (see section 4.4). Should tetrabenazine be administered together with neuroleptics (e.g. haloperidol, chlorpromazine, metoclopramide, etc.), significant dopamine depletion cannot be excluded. In these cases, patients must be clinically monitored for the development of Parkinson's disease. In individual cases, neuroleptic malignant syndrome has been observed.

Antihypertensives and beta-blockers
Concomitant use of tetrabenazine with antihypertensives and beta-blockers may increase the risk of orthostatic hypotension (see section 4.4).

Interactions with CNS depressants
The possibility of additive sedative effects should be considered, when tetrabenazine is co-administered with CNS depressants (including alcohol, neuroleptics, hypnotics and opioids). See section 4.4.

Medicinal products with known QTc prolongation
Tetrabenazine should be used with caution when medicines that prolong the QTc are co-administered, especially antipsychotics (e.g. chlorpromazine, thioridazine), antibiotics (e.g. gatifloxacin, moxifloxacin) and class IA and class III antiarrhythmics (e.g. quinidine, procainamide, amiodarone, sotalol). See section 4.4.

Reserpine
Concomitant intake of tetrabenazine and reserpine is contraindicated (see section 4.3). Reserpine irreversibly binds to vesicular monoamine transporter 2 (VMAT2) and the duration of its effect is several days. Switching a patient from reserpine to tetrabenazine should therefore proceed with caution. The physician should wait for the re-emergence of chorea symptoms before starting treatment with tetrabenazine, in order to avoid overdose and severe serotonin and noradrenaline depletion in the CNS. As the effects of reserpine can persist for some time after discontinuation of the medicinal product, the wash-out period after discontinuation of reserpine should be determined with caution and on the basis of the clinical evaluation.

Digoxin
Digoxin is a substrate of P-glycoprotein. In a study in healthy subjects, tetrabenazine (25 mg twice daily for 3 days) was shown to have no effect on the bioavailability of digoxin, suggesting that tetrabenazine at this dose has no effect on intestinal P-glycoprotein. Furthermore, *in vitro* studies showed no evidence that tetrabenazine or its metabolites are inhibitors of P-glycoprotein.

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 effects of tetrabenazine on labour and delivery are unknown.

Breast-feeding
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 breastfeeding (see section 4.3).

Fertility
In animal studies with tetrabenazine, no effect on pregnancy or intrauterine survival could be demonstrated. Female cycles were prolonged and a delayed fertility phase was observed (see section 5.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tetrabenazine can lead to drowsiness and may therefore influence the ability to drive and use machines.

4.8 Undesirable effects

The most common dose-dependent adverse reactions include drowsiness, depression (which in some cases was associated with suicidal thoughts and behaviour) and Parkinson's symptoms.

Other potential adverse reactions are listed in the table below. The effects are generally reversible when treatment is discontinued.

The frequency of adverse reactions is reported whenever known, but the frequency for some effects cannot be estimated from the available data.

The assessment of side effects is based on the following frequencies:
Very common (≥1/10)
Common (≥1/100, <1/10)
Uncommon (≥1/1.000, <1/100)
Rare (≥1/10.000, <1/1,000)
Very rare (<1/10.000)
Not known (frequency cannot be estimated based on available data)

System organ class/ Frequency	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**

Infections and infestations					Pneumonia	
Blood and lymphatic system disorders					Leukopenia, Neutropenia	
Immune system disorders					Hypersensitivity	
Metabolism and nutrition disorders		Decreased appetite			Dehydration	Increased appetite
Psychiatric disorders	Depression, anxiety, restlessness, confusion	Irritability, obsessive-compulsive disorder, agitation			Aggression, anger, suicidal thoughts, suicide attempt, nervousness, sleep disorder	Disorientation, nervousness, restlessness, sleep disorders
Nervous system disorders	Sedation/ somnolence/ drowsiness, extrapyramidal event, insomnia, akathisia	Parkinsonism (may include balancing problems), gait imbalance/ balance difficulty, bradykinesia, dystonia, lethargy, dizziness, dysarthria,			Neuroleptic malignant syndrome, ataxia, tremor, excess salivation	Memory loss
Eye disorders	Blepharospasm				Oculogyric crisis, photophobia	
Cardiac disorders					Palpitations	Bradycardia
Vascular disorders					Hypertension	Orthostatic hypotension, hypertensive
Respiratory, thoracic and mediastinal	Upper respiratory tract infection	Pneumonia, dyspnoea, bronchitis			Cough, pneumonia aspiration	

Gastrointestinal disorders	Nausea	Diarrhoea, vomiting, constipation		Dysphagia	Dry mouth	Epigastralgia
Hepatobiliary disorders						Increased ALT, increased AST
Skin and 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, hypothermia
Investigations					Weight loss	Weight increase
Injury, poisoning and procedural complications	Fall	Laceration, inflicted injury		Drug administration error	Overdose	

Prolonged use may lead to an increase in the plasma prolactin level, which will decrease after discontinuation of treatment. As a result, galactorrhoea, absence of menstruation or cycle disorders, gynaecomastia, breast pain, breast enlargement, prolactinomas, orgasmic disorders and impotence may occur.

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

Symptoms associated with overdoses of tetrabenazine may include: acute dystonia, oculogyric crisis, nausea, vomiting, diarrhoea, sweating, hypotension, states of confusion, hallucinations, hypothermia, sedation, rubor and tremor.

Treatment should include general measures that are also used for other CNS-active drugs. General supportive and symptomatic measures are recommended. Cardiac rhythm and vital functions should be monitored. When treating an overdose, 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 PARTICULARS

5.1 Pharmacodynamic properties

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

Mechanism of action
Tetrabenazine is a synthetic derivative of benzylquinolizine, which leads to depletion of the stores of dopamine and other monoamines in the central nervous system. Tetrabenazine differs from reserpine in that it exerts a more specific effect on the central nervous system, has a less potent effect on the peripheral nervous system and has a shorter duration of action.

Pharmacodynamic effects
Studies conducted *in vitro* have demonstrated that tetrabenazine is a selective inhibitor of monoamine transport into presynaptic neuronal vesicles, as it reversibly inhibits the VMAT2. VMAT2 mainly occurs in the central nervous system.

Studies have demonstrated that dihydrotetrabenazine, the main metabolite of tetrabenazine, has a similar affinity and more significant selectivity for VMAT2, compared to the parent substance.

Dihydrotetrabenazine crosses the blood-brain barrier and thus suggests a similar activity profile as tetrabenazine.

Clinical efficacy and safety
At the synaptic level, tetrabenazine causes reversible depletion of monoamines in the presynaptic vesicles with subsequent reduction of impulse transmission. This pharmacological effect explains the therapeutic benefit of tetrabenazine in patients suffering from hyperkinetic movement disorders.

5.2 Pharmacokinetic properties

Absorption

Tetrabenazine is rapidly and mostly absorbed after oral administration. According to results from a clinical study conducted with 25 patients, its absorption is not impaired by food intake. Tetrabenazine is not bound to plasma proteins.

After administration of single doses of 12.5 to 50 mg tetrabenazine, the peak plasma concentration and area under the plasma concentration-time curve increased in proportion to the dose, indicating linear pharmacokinetics.

A further study with healthy volunteers showed extensive (> 75 %) absorption of tetrabenazine from the gastrointestinal tract after administration of a single oral dose.

Biotransformation
The metabolism of tetrabenazine is complex. Initially, alpha and beta-dihydrotetrabenazine are formed, from which the majority of the observed metabolites appear to be formed by subsequent O-dealkylation, hydroxylation and conjugation.

Elimination
No significant accumulation could be observed after daily administration. The elimination half-life of dihydrotetrabenazine is approximately five hours. Tetrabenazine is mainly eliminated in metabolised form via the urine (less than 2 % tetrabenazine is excreted unchanged).

In vitro studies showed no evidence of any clinically relevant influence on human cytochrome P450 liver enzymes. It is therefore unlikely that interactions between tetrabenazine and active substances metabolised by cytochrome P450 enzymes will occur.

The hepatic enzyme CYP2D6 is involved in the degradation of dihydrotetrabenazine. Inhibitors of CYP2D6 could thus prolong the residence time of these metabolites in blood plasma.

5.3 Preclinical safety data

In repeated-dose toxicity studies, orally administered tetrabenazine was generally well tolerated across all tested animal species. Most of the effects observed are associated with the pharmacological parameters of the medicinal product and reflect the depletion of central monoamine stores. These symptoms normally include hypoactivity, lethargy, strabismus or closed eyes. They persist for several hours post ingestion and affect normal food intake in some species at high doses, leading to decreased or suppressed body weight gain. In all tested animal species, dose-dependent sedation is shown to be a dose-limiting effect and the most important adverse reaction after oral administration of tetrabenazine.

The standard tests for genotoxicity were performed with tetrabenazine. No mutagenic effects were established in the conventional bacterial mutagenicity assay. In the chromosomal aberration test in mammalian cells *in vitro* (CHO cells), tetrabenazine was clastogenic at cytotoxic concentrations. These effects, however, were observed only in the presence of S9 mix and only at tetrabenazine concentrations that were toxic to cells. However, tetrabenazine was not clastogenic at the maximum tolerated dose (100 mg/kg/day) in the erythrocyte micronucleus test in mammalian cells *in vivo* (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 non-carcinogenic when administered for 94 weeks at doses up to 12 mg/kg/day.

In studies on rats and rabbits treated with tetrabenazine during organogenesis, neither embryotoxic nor teratogenic effects occurred within the maternotoxic dose range. In a pre/postnatal study on rats, neonatal mortality was increased. However, based on the inadequate maternal care observed in the dams and the pattern of pup deaths, the effects observed in this study are rather attributable to inadequate maternal care during or immediately after birth, than to a direct effect of tetrabenazine on the progeny.

Studies on possible effects on fertility and early embryonic development have not been conducted.
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.

No carcinogenicity studies have been performed on tetrabenazine.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Talc
Magnesium stearate (Ph. Eur.)
Yellow iron oxide (E172)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 Shelf life

5 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30 ºC.
Store in the original package in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

White HDPE bottle with PP child resistant closure.

Pack size: 112 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MARKETING AUTHORISATION HOLDER

Aristo Pharma GmbH
Wallenroder Straße 8-10
13435 Berlin
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 40546/0050

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/04/2019

10 DATE OF REVISION OF THE TEXT

03/01/2025