New Zealand Data Sheet

1. PRODUCT NAME

Motetis 25 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Motetis 25 mg tablets contains 25 mg of tetrabenazine.

Excipient(s) with known effect

Contains lactose monohydrate. For the full list of excipients, *see Section 6.1.*

3. PHARMACEUTICAL FORM

Yellow, round, flat tablet with a score line on one side. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Movement disorders associated with organic central nervous system conditions, such as Huntington's chorea, hemiballismus and senile chorea. Tetrabenazine is also indicated for the treatment of moderate to severe tardive dyskinesia, which is disabling and/or socially embarrassing. The condition should be persistent despite withdrawal of antipsychotic therapy, or in cases where withdrawal of antipsychotic medication is not a realistic option; also, where the condition persists despite reduction in dosage of antipsychotic medication or switching to atypical antipsychotic medication.

4.2. Dose and method of administration

Dose

Proper dosing of tetrabenazine involves careful titration of therapy to determine an individualised dose for each patient. When first prescribed, tetrabenazine therapy should be titrated slowly over several weeks to allow the identification of a dose for chronic use that reduces chorea and is well tolerated.

Movement disorders

Dosage and administration are variable and only a guide is given. An initial starting dose of 25 mg three times a day is recommended. This can be increased by 25 mg a day every three (3) or four (4) days until 200 mg per day is being given or the limit of tolerance, as dictated by unwanted effects, is reached, whichever is the lower dose. If there is no improvement at the maximum dose

in seven (7) days, it is unlikely that the compound will be of benefit to the patient, either by increasing the dose or by extending the duration of treatment.

Tardive Dyskinesia

Recommended starting dose of 12.5 mg a day subsequently titrated according to response. Medication should be discontinued if there is no clear benefit or if the side-effects cannot be tolerated.

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.

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 concomitant medications, tetrabenazine therapy should be retitrated when resumed. For short-term treatment interruption of less than 5 days, treatment can be resumed at the previous maintenance dose without titration. 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 population

No specific studies have been performed in the elderly.

Renal impairment

The use of tetrabenazine in patients with renal insufficiency has not been studied.

Hepatic impairment

A study in hepatically impaired subjects has shown that there is a markedly decreased metabolism of tetrabenazine to its metabolites with a higher mean Cmax in hepatically impaired subjects in comparison with healthy subjects. The elimination half-life of tetrabenazine and its metabolites in subjects with hepatic impairment was also prolonged.

Increased exposure to other circulating metabolites and the contribution of tetrabenazine or those metabolites to safety and efficacy are unknown. Therefore, tetrabenazine is contraindicated in patients with hepatic impairment, Child Pugh 5 to 9, *see Section 5.2*.

Paediatric population

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

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*
- Tetrabenazine can block the action of reserpine. Thus, these substances should not be taken concomitantly, *see Section 4.5*
- Taking or have taken within 14 days a monoamine oxidase inhibitor (MAOI), *see Sections 4.4, 4.5 and 4.8.*
- Untreated or inadequately treated depression. Patients who are actively suicidal.
- Presence of a hypokinetic-rigid-syndrome (Parkinsonism)
- Breast feeding
- Pheochromocytoma
- Pro-lactin-dependent tumours e.g. pituitary breast cancer
- With impaired hepatic function, Child-Pugh 5 to 9

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.*

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 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.

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 illness.

Parkinsonism

Tetrabenazine can induce parkinsonism and exacerbate pre-existing symptoms of Parkinson's Disease. The tetrabenazine dose should be adjusted as clinically indicated to minimise this side effect.

Dysphagia

Dysphagia is a component of Huntington's disease. However, drugs that reduce dopaminergic transmission have been associated with oesophageal 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

Pre- synaptic dopamine depletion could theoretically lead to super sensitivity to dopamine. Tetrabenazine is a central monoamine depleting agent which has can cause extrapyramidal symptoms and theoretically cause tardive dyskinesia in humans.

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

Neuroleptic malignant syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in patients treated with tetrabenazine and other drugs that reduce dopaminergic transmission. This may occur soon after initiation of therapy, following changes in dosage or after prolonged treatment. Clinical manifestations of 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.

Cardiac effects

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 (about 8 msec) 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 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. 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, and symptoms may include postural dizziness and syncope. 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, 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 oestrogen 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.

Drug-disease interactions

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

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.

Elderly

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

Paediatric population

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

4.5. Interaction with other medicines and other forms of interaction

No interaction studies have been performed in vivo. The metabolising enzymes of tetrabenazine are partly unknown.

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

Patients taking CYP2D6 inhibitors

In vitro and in vivo studies indicate that the tetrabenazine metabolites α-HTBZ and β-HTBZ are substrates for CYP2D6. The effect of CYP2D6 inhibition on the pharmacokinetics of tetrabenazine and its metabolites was studied in 25 healthy subjects following a single 50 mg dose of tetrabenazine given after 10 days of administration of the strong CYP2D6 inhibitor paroxetine 20 mg daily. There was approximately 30% increase in Cmax and an approximately 3-fold increase in AUC for α-HTBZ in subjects given paroxetine prior to tetrabenazine compared to tetrabenazine given alone. For β-HTBZ, C max and AUC were increased 2.4- and 9-fold, respectively, in subjects given paroxetine prior to tetrabenazine given alone. The elimination half-life of α-HTBZ and β-HTBZ was approximately 14 hours when tetrabenazine was given with

paroxetine. Caution should be used when adding a strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, or quinidine) to a patient already receiving a stable dose of tetrabenazine and a reduction in the dose of tetrabenazine should be considered. The effect of moderate or weak CYP2D6 inhibitors such as duloxetine, terbinafine, amiodarone, or sertraline has not been evaluated.

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

Levodopa

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

Monoamine oxidase inhibitors (MAOIs)

Tetrabenazine should not be administered in the presence of MAOIs because of the risk of possible serious interactions resulting in hypertensive crisis, see Section 4.3. At least 14 days should elapse between the discontinuation of MAOI and initiation of treatment with tetrabenazine.

Concomitant use of neuroleptic drugs

Adverse reactions associated with tetrabenazine, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists. There is a potential for significant dopamine depletion when administering tetrabenazine concomitantly with neuroleptic agents (e.g. haloperidol, chlorpromazine, metoclopramide, etc.) and patients should be monitored clinically for the development of parkinsonism.

Antihypertensive drugs and beta-blockers

The concurrent use of tetrabenazine with antihypertensive 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, neuroleptics, 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 antiarrhythmic medications (e.g., quinidine, procainamide, amiodarone, sotalol).

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.

Digoxin

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

Paediatric Population

Interaction studies have only been performed in adults.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well controlled studies for the use of tetrabenazine in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Tetrabenazine is not recommended during pregnancy and in women of childbearing potential not using contraception.

The effect of tetrabenazine on labour and delivery in humans is unknown.

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 contra-indicated during breast-feeding, *see Section 4.3.*

Fertility

See section 5.3 for evidence found in animal studies.

4.7. Effects on ability to drive and use machines

Tetrabenazine may cause drowsiness and therefore may impair the ability to drive and use machines

4.8. Undesirable effects

The following undesirable effects are ranked according to System Organ Class and to their frequencies. Frequencies are defined as 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).

System Organ Class	Reaction
Blood and lymphatic systems disorders	Very rare: Leukopenia, Neutropenia
Immune system disorders	Very rare: hypersensitivity
Metabolism and nutrition disorders	Common: decreased appetite Very rare: dehydration Not known: increased appetite
Psychiatric disorders	Very common: depression, anxiety, restlessness, confusion. Common: irritability, obsessive compulsive disorder, agitation. Very rare: Aggression, anger, suicidal ideation, suicide attempt, nervousness, sleep disorder. Not known: disorientation
Nervous system disorders	Very common: sedation, somnolence, drowsiness, extrapyramidal event, insomnia, akathisia. Common: Parkinsonism (may include balancing problems), gait imbalance/ balance difficulty, bradykinesia, dystonia, lethargy, dizziness, dysarthria, headache. Very rare: neuroleptic malignant syndrome, ataxia, tremor, excess salivation. Not known: memory loss.
Eye disorders	Very common: blepharospasm Common: oculogyric crisis, photophobia
Cardiac disorders	Very rare: palpitations. Not known: bradycardia
Vascular disorders	Very rare: hypertension Not known: Postural hypotension, hypertensive crisis.
Respiratory, thoracic and mediastinal disorders	Very common: upper respiratory tract infection. Common: pneumonia, dyspnoea, bronchitis. Very rare: cough, aspiration pneumonia.
Gastrointestinal system disorders	Very common: nausea Common: diarrhoea, vomiting, constipation. Rare: dysphagia Very rare: dry mouth Not known: epigastric pain
Hepatobiliary disorders	Not known: increased ALT, increased AST
Skin and subcutaneous tissue disorders	Very rare: hyperhidrosis, rash, pruritus, urticaria
Renal and urinary disorders	Common: dysuria Very rare: urinary tract infection
Reproductive system and breast disorders	Very rare: irregular menstrual cycle/ amenorrhea/ menstrual disorders.
General disorders and administration site conditions	Very common: fatigue Common: ecchymosis Uncommon: hypothermia Very rare: malaise, pyrexia, drug interaction Not known: weakness.
Investigations	Very rare: weight decreased Not known: weight increased.

Injury, poisoning and procedural complications	Very common: fall Common: laceration, inflicted injury Rare: drug administration error Very rare: overdose

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions https://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

Symptoms associated with overdoses of tetrabenazine 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.
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system drugs, ATC code: N07XX06

Mechanism of action

Tetrabenazine is a synthetic derivative of benzylquinolizine that causes depletion of dopamine and other monoamines in the central nervous system. The precise mechanism by which tetrabenazine exerts its effects is unknown but is believed to be related to its effect as a reversible depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals.

Studies conducted *in vitro* and *in vivo* have shown that tetrabenazine is a selective inhibitor of monoamine transportation into pre-synaptic neuronal vesicles, by reversible inhibition of the VMAT2 (vesicular monoamine transporter 2), which is principally located in the central nervous system. Studies have shown that α-dihydrotetrabenazine, one of the principal metabolite of tetrabenazine, has a similar affinity and more significant selectivity for VMAT2.

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

Neurotransmitter depletion by a single dose of tetrabenazine is reversible and lasts only a few hours.

5.2. Pharmacokinetic properties

Absorption and Distribution

Tetrabenazine is quickly and mostly absorbed after oral administration. Its absorption is not affected by the taking of food.

Clinical testing has shown that a single oral dose of tetrabenazine undergoes extensive (>75%) absorption from the gastro-intestinal tract.

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 hepatic metabolism of tetrabenazine to α-HTBZ and β-HTBZ. α-HTBZ and β-HTBZ are metabolized principally by CYP2D6. Peak plasma concentrations (Cmax) of α-HTBZ and β-HTBZ are reached within 1 to 1½ hours post-dosing. α-HTBZ and β-HTBZ are subsequently metabolized to another major circulating metabolite, O-dealkylated-HTBZ, for which Cmax is reached approximately 2 hours post-dosing.

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%.

Biotransformation

The metabolism of tetrabenazine is complex, initially proceeding via the formation of alpha and beta dihydrotetrabenazine. α-HTBZ and β-HTBZ, major circulating metabolites, have half-lives of 4-8 hours and 2-4 hours, respectively. The majority of the observed metabolites appear to be formed from these dihydrotetrabenazines as a result of O-dealkylation, hydroxylation and conjugation.

Elimination

After oral administration, tetrabenazine is extensively hepatically metabolized, and the metabolites are primarily renally eliminated. Clinical testing has shown that subjects with liver impairment have substantially reduced first-pass systemic metabolism of tetrabenazine, resulting in increased exposure to the parent compound compared to healthy subjects. The conversion of tetrabenazine to alpha and beta dihydrotetrabenazine appears to be slower in subjects with liver impairment as is the subsequent elimination of these metabolites.

No significant build-up has been observed after daily administration. The elimination half-life of dihydrotetrabenazine is approximately five hours.

Tetrabenazine is mostly eliminated in metabolised form in urine (less than 2% of tetrabenazine is excreted in unchanged form).

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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

In repeated dose toxicity studies orally administered tetrabenazine is generally well tolerated across all animal species tested. Most effects observed are related to the pharmacological parameters of the drug and reflect central monoamine depletion. These signs typically include hypoactivity, lethargy, squinted eyes, or eyes closed. They last up to several hours after dosing and in some species at high doses interfere with normal food intake with consequent decreased or suppressed body weight gain. Across all animal species tested dose-dependent sedation is the dose limiting effect and the principal adverse effect following oral administration of tetrabenazine.

Tetrabenazine and metabolites α-HTBZ and β-HTBZ were negative in the in vitro bacterial reverse mutation assay. Tetrabenazine was clastogenic in the in vitro chromosome aberration assay in Chinese hamster ovary cells in the presence of metabolic activation. α-HTBZ and β-HTBZ were clastogenic in the in vitro chromosome aberration assay in Chinese hamster lung cells in the presence and absence of metabolic activation. Tetrabenazine was negative in male mice and rats but equivocal in female rats in in vivo micronucleus tests.

Tetrabenazine did not cause an increase in any tumour type when administered for 26 weeks in the transgenic p53 heterozygous mouse model at doses up to 30 mg/kg/day. Tetrabenazine was non-carcinogenic when administered for 94 weeks to male rats at doses up to 12 mg/kg/day.

Tetrabenazine was not teratogenic to rats or rabbits at the maximum recommended human dose (MRHD) (3 or 13-fold, respectively). In prenatal/postnatal toxicity studies, tetrabenazine increased stillborn pups and neonatal mortality as well as delayed pup maturation in rats. These effects could either be indirect effects due to inadequate maternal care or a direct effect of tetrabenazine on the pups. The no-effect dose was 0.5 times the MRHD.

In a fertility and early embryonic development study at systemic exposures below clinical levels there was no effect on pregnancy or in utero survival in rats but oestrous cycle length was increased and a delay in fertility was seen in female rats. Reproduction was unaffected in male rats.

Tetrabenazine and metabolites accumulate in melanin-containing tissues in partially pigmented rats. A single oral administration of 14C-tetrabenazine to Lister Hooded rats resulted in high levels of radioactivity that persisted in pigmented tissues (eye, uveal tract and pigmented fur) and were still measurable 21 days after administration while all other tissues were BLQ (Below Limit of Quantification).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Motetis tablet contains iron oxide yellow, lactose monohydrate, magnesium stearate, pregelatinised maize starch and purified talc.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at or below 25°C.

6.5. Nature and contents of container

HDPE bottle pack with child-resistant caps, containing 112 tablets.

6.6. Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd P O Box 45 027
Auckland 0651 New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

29 November 2011

10. DATE OF REVISION OF THE TEXT

26 May 2020

Summary table of changes

Section changed	Summary of new information
4.2 Dose and method of administration	Added: “Discontinuation of treatment” section Added: “Resumption of treatment” section Updated: “Special population section” section
4.3 Contraindications	Added: “taking or have taken within 14 days a” monoamine oxidase inhibitor Added: “untreated or inadequately treated” depression. “patients who are actively suicidal”. Added: “with impaired hepatic function, Child-Pugh5 to 9
4.4 Special warning and precautions for use	Added: dosage information Updated: Depression”/suicidality” section Added: “Anger and aggression” section Updated: “Tardive dyskinesia” section Updated: “Neuroleptic malignant syndrome” Added: “Cardiac effects” section Added: “QTc prolongation” section Added: “Cardiac disease” section Added: “Akathisia, restlessness and agitation” section Added: “Sedation and somnolence” section Added: “Orthostatic hypotension” section Added: “Hyperprolactinemia” section Added: “Binding to melanin-containing issues” section Added: “Drug-disease interactions” section Added: “Laboratory test” section. Added: “Elderly” section Added: “Paediatric population” section.
4.5 Interaction with other medicines and other forms of interaction	Updated: “patients taking CYP2D6 inhibitors” Updated: “levodopa” Updated: “MAOIs” Updated: “concomitant use of neuroleptic drugs” Updated: “antihypertensive drugs and beta blockers” Updated: “interaction with CNS depressants” Added: “Medicines known to prolong QTc” Updated: “reserpine” Added: “digoxin” Added: “paediatric population”
4.6 Fertility, pregnancy and lactation	Updated
4.7 Effects on ability to drive	Updated
4.8 Undesirable effects	Added: neutropenia, hypersensitivity, decreased appetite, dehydration, increased appetite, irritability, obsessive compulsive, aggression, anger, suicidal ideation, suicidal attempt, nervousness, sedation, somnolence, drowsiness, extrapyramidal event, insomnia, bradykinesia, lethargy, dizziness, dysarthria, headache, tremor, memory loss, blepharospasm, hypertension, hypertensive crisis, hyperhidrosis, rash, pruritus, urticaria, dysuria, urinary tract infection, irregular menstrual cycle, ecchymosis, malaise, pyrexia, drug interaction. Added new section “Respiratory, thoracic and mediastinal disorders. Added new section “Hepatobiliary disorders”

	Added new section “Renal and urinary disorders” Added new section “Investigations” Added new section “injury, poisoning and procedural complications”
4.9 Overdose	Updated
5.2 Pharmacokinetics properties	Added new information re distribution and elimination
5.3 preclinical safety data	Added information re in clastogenicity, carcinogenicity and reproduction toxicity.