SCHEDULING STATUS

S5

1. NAME OF MEDICINE:

RISTABBS 0.5 mg tablets

RISTABBS 1 mg tablets

RISTABBS 2 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

RISTABBS 0.5: Each OD tablet contains 0,5 mg risperidone.

RISTABBS 1: Each OD tablet contains 1 mg risperidone.

RISTABBS 2: Each OD tablet contains 2 mg risperidone.

Contains: Aspartame and Mannitol

RISTABBS 0.5 contains 2 mg aspartame and 32,10 mg mannitol.

RISTABBS 1 contains 2 mg aspartame and 32,10 mg mannitol.

RISTABBS 2 contains 2 mg aspartame and 30,80 mg mannitol.

For full list of excipients, **see section 6.1.**

3. PHARMACEUTICAL FORM:

RISTABBS 0.5 mg: Yellow coloured, mottled, round, flat faced beveled edged tablets, debossed with ‘C’ on one side and ‘01’ on the other with characteristic flavour.

RISTABBS 1 mg: White, round, flat faced beveled edged tablets, debossed with ‘C’ on the side and ‘02’ on the other with characteristics flavour.

RISTABBS 2 mg: Blue colored, mottled, round, flat faced beveled edged tablets, debossed with ‘C’ on one side and ‘03’ on the other with characteristic flavour.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

RISTABBS is indicated for the treatment of:

Acute and chronic schizophrenic psychoses and related psychosis in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness) and/or the negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. **RISTABBS** also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. In patients who have shown an initial treatment response, **RISTABBS** is also effective in maintaining the clinical improvement.

Mania in bipolar disorder. These episodes are characterised by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for

sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

Conduct and other disruptive behaviour disorders in children (aged 5 – 12 years), with subaverage intellectual functioning or mental retardation in whom destructive behaviours (e.g., aggression, impulsivity and self-injurious behaviours) are prominent.

4.2 Posology and method of administration

Posology

- **Schizophrenia**

Adults:

RISTABBS may be given once or twice daily.

Patients should start with 2 mg/day **RISTABBS**. The dosage may be increased on the second day to 4 mg/day. From then on, the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses of between 4 mg/day and 8 mg/day. Doses above 6 mg/day (when administered twice daily) were associated with more extrapyramidal symptoms and other adverse effects and are not generally recommended. In some patients, particularly with first episode acute psychosis, a slower titration phase and a lower starting and maintenance dose may be appropriate.

Doses above 10 mg/day have not been shown to be superior in efficacy to lower doses and may cause an increased incidence of side-effects such as extrapyramidal

symptoms. Dosages above 10 mg/day should only be considered if the benefits outweigh the risk. The maximum total daily dose is 16 mg/day.

A benzodiazepine may be added to **RISTABBS** if additional sedation is required.

Special population

Elderly patients and patients with renal and hepatic impairment:

A starting dose of 0,5 mg twice daily is recommended. This dosage can be individually adjusted with 0,5 mg twice daily increments to 1 - 2 mg twice daily.

Paediatric population:

Not for children under 15 years as efficacy and safety in children under the age of 15 years have not been demonstrated in schizophrenia.

- **Mania in bipolar disorders**

RISTABBS should be administered on a once daily schedule, starting with 2 or 3 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Efficacy was demonstrated in flexible doses over a range of 1 to 6 mg per day.

The continued use of **RISTABBS** must be evaluated and justified on an ongoing basis.

Experience is lacking in bipolar mania in children and adolescents less than 18 years of age.

- **Conduct and other Disruptive Behaviour Disorders (DBD) in children 5 - 12 years of age.**

Patients < 50 kg:

A starting dose of 0,01 mg/kg once daily is recommended. This dosage can be individually adjusted by increments of 0,01 mg/kg once daily not more frequently than every other day, if needed. The recommended maintenance dose is 0,02 – 0,04 mg/kg once daily. The mean dose is 0,03 mg/kg once daily.

The continued use of **RISTABBS** must be evaluated and justified on an ongoing basis.

Experience is lacking in children aged less than 5 years.

Renal and hepatic impairment:

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than normal adults. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone.

Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal or hepatic impairment.

RISTABBS should be used with caution in these groups of patients.

Method of administration:

RISTABBS tablets are for oral use. Food does not affect the absorption of **RISTABBS** tablets.

Switching from other antipsychotics to **RISTABBS**:

When medically appropriate, gradual discontinuation of the previous treatment, while **RISTABBS** therapy is initiated, is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate **RISTABBS** therapy in place of the next scheduled injection. The need for continuing existing anti-Parkinson medications should be re-evaluated periodically.

4.3 Contraindications

- **RISTABBS** is contraindicated in patients with known hypersensitivity to risperidone or to any of the excipients listed in section 6.1.
- Conduct and other disruptive behaviour disorders in children: **RISTABBS** is contraindicated in children under 5 years of age as efficacy and safety in these children have not been demonstrated.
- Parkinson's disease and Lewy Body Dementia (see section 4.4).

4.4 Special warnings and precautions for use

Elderly Patients with Dementia

Overall Mortality

Elderly patients with dementia treated with atypical antipsychotic medicines have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic medicines, including **RISTABBS**. In placebo-controlled trials

with oral risperidone as in **RISTABBS** in this population, the incidence of mortality was 4,0 % for **RISTABBS**-treated patients compared to 3,1 % for placebo-treated patients. The mean age (range) of patients who died was 86 years (range 67-100).

Concomitant use with furosemide

In risperidone as in **RISTABBS** placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide and risperidone (7,3 %; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3,1 %; mean age 84 years, range 70-96) or furosemide alone (4,1 %; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone as in **RISTABBS** was observed in two of the four clinical trials.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant medication with risperidone as in **RISTABBS**. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CAE)

In placebo-controlled clinical trials in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischaemic attacks), including fatalities, in patients treated with risperidone

as in **RISTABBS** compared to patients receiving placebo (mean age 85 years; range 73-97 years).

Orthostatic Hypotension

Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur, especially during the initial dose-titration period. **RISTABBS** should be used with caution in patients with known cardiovascular disease, and the dosage should be gradually titrated as recommended. A dose reduction should be considered if hypotension occurs.

Leucopoenia, Neutropaenia, and Agranulocytosis

Events of leucopoenia, neutropaenia and agranulocytosis have been reported with risperidone as in **RISTABBS**. Agranulocytosis has been reported during post-marketing surveillance.

Patients with a history of a clinically significant low white blood cell count (WBC) or a medicine-induced leucopoenia/neutropaenia should be monitored during therapy and discontinuation of **RISTABBS** should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropaenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropaenia (absolute neutrophil count < 1 X 10^9/L) should discontinue **RISTABBS** and have their WBC followed until recovery.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with risperidone as in **RISTABBS**. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with **RISTABBS** and preventive measures undertaken.

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)

RISTABBS has been associated with the induction of tardive dyskinesia (TD) characterised by potentially irreversible rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. TD appears to be most prominent in the elderly especially elderly females. If signs and symptoms of tardive dyskinesia appear, the discontinuation of **RISTABBS** should be considered.

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome, a potentially fatal symptom complex, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels has been reported to occur in association with risperidone as in **RISTABBS**. Additional signs may include elevated creatine phosphokinase levels, myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, **RISTABBS**, should be discontinued.

Parkinson's disease/Lewy Body dementia and NMS

Patients with Parkinson's disease or Dementia with Lewy Bodies (DLB) have an increased risk of Neuroleptic Malignant Syndrome (NMS) as well as having an

increased sensitivity to antipsychotic medications (see section 4.3). Manifestation of this increased sensitivity can include confusion, obtundation and postural instability with frequent falls, in addition to extrapyramidal symptoms. In addition, in clinical trials, elderly patients have a higher mortality than placebo treated elderly patients. (see section 4.3).

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with risperidone as in **RISTABBS**.

Patients with an established diagnosis of diabetes mellitus who are starting on **RISTABBS** should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with **RISTABBS** should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with **RISTABBS** should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when risperidone as in **RISTABBS** were discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of risperidone as in **RISTABBS**.

Hyperprolactinemia

Hyperprolactinemia is a common side effect of treatment with risperidone as in **RISTABBS**. Evaluation of the prolactin plasma level is recommended in patients with

evidence of possible prolactin-related side effects (e.g., gynaecomastia, menstrual disorders, anovulation, fertility disorder, decreased libido, erectile dysfunction, galactorrhoea).

Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history.

Risperidone as in **RISTABBS** should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

Weight gain

Significant weight gain has been reported. Monitoring weight gain is advisable when **RISTABBS** is being used. Patients may be advised to refrain from excessive eating in view of the possibility of weight gain.

QT Interval

Caution should be exercised when **RISTABBS** is prescribed in patients with a history of cardiac dysrhythmias, in patients with congenital long QT syndrome, and in concomitant use with medicines known to prolong the QT interval.

Priapism

Medicines with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with risperidone as in **RISTABBS** during post-marketing surveillance (see section 4.9).

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature may occur. Appropriate care is advised when prescribing **RISTABBS** to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Antiemetic Effect

An antiemetic effect was observed in preclinical studies with risperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain medicines or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including **RISTABBS**.

IFIS may increase the risk of eye complications during and after the operation. Current or past use of risperidone as in **RISTABBS** should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping

RISTABBS prior to cataract surgery has not been established and must be weighed against the risk of stopping **RISTABBS** therapy.

Renal and hepatic impairment:

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than adults with normal renal function. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone (see section 4.2). Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including risperidone as in **RISTABBS**.

IFIS may increase the risk of eye complications during and after the operation. Current or past use of risperidone as in **RISTABBS** should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping risperidone as in **RISTABBS** prior to cataract surgery has not been established and must be weighed against the risk of stopping risperidone as in **RISTABBS** therapy.

Seizures

RISTABBS should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Paediatric population

Before **RISTABBS** is prescribed to a child or adolescent with conduct disorder they should be fully assessed for physical and social causes of the aggressive behaviour such as pain or inappropriate environmental demands.

The sedative effect of risperidone as in **RISTABBS** should be closely monitored in this population because of possible consequences on learning ability. A change in the time of administration of risperidone could improve the impact of the sedation on attention faculties of children and adolescents.

Risperidone was associated with mean increases in body weight and body mass index (BMI). Baseline weight measurement prior to treatment and regular weight monitoring are recommended. Changes in height in the long-term open-label extension studies were within expected age-appropriate norms. The effect of long-term risperidone treatment on sexual maturation and height has not been adequately studied.

Because of the potential effects of prolonged hyperprolactinaemia on growth and sexual maturation in children and adolescents, regular clinical evaluation of endocrinological status should be considered, including measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects.

Results from a small post-marketing observational study showed that risperidone-exposed subjects between the ages of 8-16 years were on average approximately 3.0 to 4.8 cm taller than those who received other atypical antipsychotic medications. This study was not adequate to determine whether exposure to risperidone had any

impact on final adult height, or whether the result was due to a direct effect of risperidone on bone growth, or the effect of the underlying disease itself on bone growth, or the result of better control of the underlying disease with resulting increase in linear growth. During treatment with risperidone as in **RISTABBS** regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

For specific posology recommendations in children and adolescents see section 4.2.

Aspartame intolerance

This medicine contains 2 mg aspartame in each dosage unit which is equivalent to 2 mg/weight. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Mannitol intolerance

May have a mild laxative effect.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per OD tablet, that is to say essentially “sodium free”.

4.5 Interactions with other medicines and other forms of interaction

Pharmacodynamic-related interactions

Medicines known to prolong the QT interval.

Caution is advised when prescribing **RISTABBS** with medicines known to prolong the QT interval, such as antidysrhythmics (e.g., quinidine, disopyramide, procainamide, propafenone, amiodarone, sotalol), tricyclic antidepressant (i.e., amitriptyline), tetracyclic antidepressants (i.e., maprotiline), some antihistamines, other antipsychotics, some antimalarials (i.e., quinine and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesaemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

Centrally-acting medicines and alcohol

RISTABBS should be used with caution in combination with other centrally-acting substances notably including alcohol, opiates, antihistamines and benzodiazepines due to the increased risk of sedation.

Levodopa and dopamine agonists

RISTABBS may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Psychostimulants

The combined use of psychostimulants (e.g., methylphenidate) with **RISTABBS** can lead to extrapyramidal symptoms upon change of either or both treatments (**see section 4.4**).

Medicines with hypotensive effect

Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone as in **RISTABBS** and antihypertensive treatment.

Paliperidone

Concomitant use of oral **RISTABBS** with paliperidone is not recommended as paliperidone is the active metabolite of **RISTABBS** and the combination of the two may lead to additive active antipsychotic fraction exposure.

Pharmacokinetic-related interactions

*Food does not affect the absorption of **RISTABBS**.*

RISTABBS is mainly metabolised through CYP2D6, and to a lesser extent through CYP3A4. Both **RISTABBS** and its active metabolite 9-hydroxy-risperidone are substrates of P-glycoprotein (P-gp). Substances that modify CYP2D6 activity, or substances strongly inhibiting or inducing CYP3A4 and/or P-gp activity, may influence the pharmacokinetics of the risperidone active antipsychotic fraction.

Strong CYP2D6 inhibitors

Co-administration of **RISTABBS** with a strong CYP2D6 inhibitor may increase the plasma concentrations of **RISTABBS**, but less so of the active antipsychotic fraction. Higher doses of a strong CYP2D6 inhibitor may elevate concentrations of the risperidone active antipsychotic fraction (e.g., paroxetine, see below). It is expected that other CYP2D6 inhibitors, such as quinidine, may affect the plasma concentrations of risperidone in a similar way. When concomitant paroxetine,

quinidine, or another strong CYP2D6 inhibitor, especially at higher doses, is initiated or discontinued, the physician should re-evaluate the dosing of **RISTABBS**.

CYP3A4 and/or P-gp inhibitors

Co-administration of **RISTABBS** with a strong CYP3A4 and/or P-gp inhibitor may substantially elevate plasma concentrations of the risperidone active antipsychotic fraction. When concomitant itraconazole or another strong CYP3A4 and/or P-gp inhibitor is initiated or discontinued, the medical practitioner should re-evaluate the dosing of **RISTABBS**.

CYP3A4 and/or P-gp inducers

Co-administration of **RISTABBS** with a strong CYP3A4 and/or P-gp inducer may decrease the plasma concentrations of the risperidone active antipsychotic fraction. When concomitant carbamazepine or another strong CYP3A4 and/or P-gp inducer is initiated or discontinued, the medical practitioner should re-evaluate the dosing of **RISTABBS**. CYP3A4 inducers exert their effect in a time-dependent manner and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

Highly protein-bound drugs

When **RISTABBS** is taken together with highly protein-bound medicines, there is no clinically relevant displacement of either medicine from the plasma proteins.

When using concomitant medication, the corresponding label should be consulted for information on the route of metabolism and the possible need to adjust dosage.

Paediatric population

Interaction studies have only been performed in adults. The relevance of the results from these studies in paediatric patients is unknown.

The combined use of psychostimulants (e.g., methylphenidate) with risperidone as in **RISTABBS** in children and adolescents did not alter the pharmacokinetics and efficacy of risperidone.

Examples

Examples of medicines that may potentially interact or that were shown not to interact with **RISTABBS** are listed below:

*Effect of other medicines on the pharmacokinetics of **RISTABBS***

Antibacterials:

- Erythromycin, a moderate CYP3A4 inhibitor and P-gp inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction.
- Rifampicin, a strong CYP3A4 inducer and a P-gp inducer, decreased the plasma concentrations of the active antipsychotic fraction.

Anticholinesterases:

- Donepezil and galantamine, both CYP2D6 and CYP3A4 substrates, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction.

Antiepileptics:

- Carbamazepine, a strong CYP3A4 inducer and a P-gp inducer, has been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone. Similar effects may be observed with e.g., phenytoin and phenobarbital which also induce CYP3A4 hepatic enzyme, as well as P-glycoprotein.
- Topiramate modestly reduced the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.

Antifungals:

- Itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of the active antipsychotic fraction by about 70%, at risperidone doses of 2 to 8 mg/day.
- Ketoconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of risperidone and decreased the plasma concentrations of 9-hydroxy-risperidone.

Antipsychotics:

- Phenothiazines may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Antivirals:

- Protease inhibitors: No formal study data are available; however, since ritonavir is a strong CYP3A4 inhibitor and a weak CYP2D6 inhibitor, ritonavir and ritonavir-boosted protease inhibitors potentially raise concentrations of the risperidone active antipsychotic fraction.

Beta-blockers:

- Some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Calcium channel blockers:

- Verapamil, a moderate inhibitor of CYP3A4 and an inhibitor of P-gp, increases the plasma concentration of risperidone and the active antipsychotic fraction.

Gastrointestinal medicines:

- H_2-receptor antagonists: Cimetidine and ranitidine, both weak inhibitors of CYP2D6 and CYP3A4, increased the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction.

SSRIs and tricyclic antidepressants:

- Fluoxetine, a strong CYP2D6 inhibitor, increases the plasma concentration of risperidone, but less so of the active antipsychotic fraction.
- Paroxetine, a strong CYP2D6 inhibitor, increases the plasma concentrations of risperidone, but, at dosages up to 20 mg/day, less so of the active

antipsychotic fraction. However, higher doses of paroxetine may elevate concentrations of the risperidone active antipsychotic fraction.

- Tricyclic antidepressants may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction.
- Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100 mg/day are not associated with clinically significant changes in concentrations of the risperidone active antipsychotic fraction. However, doses higher than 100 mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.

*Effect of **RISTABBS** on the pharmacokinetics of other medicines*

Antiepileptics:

- Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate.

Antipsychotics:

- Aripiprazole, a CYP2D6 and CYP3A4 substrate: risperidone tablets or injections did not affect the pharmacokinetics of the sum of aripiprazole and its active metabolite, dehydroaripiprazole.

Digitalis glycosides:

- Risperidone does not show a clinically relevant effect on the pharmacokinetics of digoxin.

Lithium:

- Risperidone does not show a clinically relevant effect on the pharmacokinetics of lithium.

*Concomitant use of **RISTABBS** with furosemide*

- See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

4.6 Fertility, pregnancy, and lactation

Pregnancy

RISTABBS safety in pregnancy has not been established (see section 4.4).

Although, in experimental animals, **RISTABBS** did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed. No teratogenic effect of risperidone was noted in any study.

Neonates exposed to antipsychotic medicines (including **RISTABBS**) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may vary in severity following delivery. These symptoms in the neonates may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder.

Therefore, **RISTABBS** should only be used during pregnancy if the benefits outweigh the risks.

Lactation

RISTABBS safety in lactation has not been established (see section 4.4).

In animal studies risperidone and 9-hydroxy- risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk. Therefore, women receiving **RISTABBS** should not breastfeed

Fertility

Medicines that antagonize dopamine D2 receptors, **RISTABBS** elevates prolactin level. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients.

There were no relevant effects observed in the non-clinical studies**.**

4.7 Effects on ability to drive and use machines

RISTABBS may impair mental alertness. Patients should therefore be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

The following adverse reactions have been identified or suspected in the clinical trials programme for **RISTABBS**.

System Organ Class	**Frequency**	**Side effects**
Infections and infestations	*Frequent*	Pneumonia, influenza, bronchitis, upper respiratory tract infection, urinary tract infection.
	Less frequent	Sinusitis, viral infection, ear infection, tonsillitis, cellulitis, otitis media, eye infection, localised infection, acarodermatitis, respiratory tract infection, cystitis, onychomycosis, otitis media chronic.
Blood and lymphatic system disorders	*Less frequency*	Anaemia, neutropaenia, granulocytopaenia
Immune system disorders	*Less frequency*	Hypersensitivity, angioedema, drug hypersensitivity.
Endocrine disorders	*Frequent*	Hyperprolactinaemia.
	Less frequent	Inappropriate antidiuretic hormone secretion, glucose urine present.

Metabolism and nutrition disorders	*Frequent*	Increased appetite, decreased appetite.
	Less frequent	Anorexia, polydipsia, diabetes mellitus, hyperglycaemia, weight decreased, blood cholesterol increased, water intoxication, hypoglycaemia, hyperinsulinaemia, blood triglycerides increased, diabetic ketoacidosis.
Psychiatric disorders	*Frequent*	Insomnia, anxiety, agitation, sleep disorder, depression
	Less frequent	Confusional state, decreased libido, listless, nervousness, nightmare, anorgasmia, blunted affect, somnambulism, sleep-related eating disorder.
Nervous system disorders	*Frequent*	Parkinsonism, headache, akathisia, dizziness, tremor, dystonia, somnolence,

		sedation, lethargy, dyskinesia.
	Less frequent	Unresponsive to stimuli, loss of consciousness, syncope, depressed level of consciousness, cerebrovascular accident, transient ischaemic attack, dysarthria, disturbance in attention, hypersomnia, postural dizziness, balance disorder, tardive dyskinesia, speech disorder, coordination abnormal, hypoaesthesia, head titubation, neuroleptic malignant syndrome, diabetic coma, cerebrovascular disorder, cerebral ischaemia, movement disorder.
Eye disorders	*Frequent*	Blurred vision.

	Less frequent	Conjunctivitis, ocular hyperaemia, eye discharge, eye swelling, dry eye, increased lacrimation, photophobia, reduced visual acuity, eye rolling, glaucoma.
Ear and labyrinth disorders	*Less frequent*	Ear pain, tinnitus, vertigo.
Cardiac disorders	*Frequent*	Tachycardia
	Less frequent	Atrioventricular block, bundle branch block, sinus bradycardia, palpitations, atrial fibrillation, conduction disorder, electrocardiogram QT prolonged, electrocardiogram abnormal, sinus dysrhythmia.
Vascular disorders	*Frequent*	hypertension
	Less frequent	Hypotension, orthostatic hypotension, flushing, pulmonary embolism, venous thrombosis.

Respiratory, thoracic and mediastinal disorders	*Frequent*	Dyspnoea, epistaxis, cough, nasal congestion, pharyngolaryngeal pain.
	Less frequent	Wheezing, pneumonia aspiration, pulmonary congestion, respiratory disorder, rales, respiratory tract congestion, dysphonia, sleep apnoea syndrome, hyperventilation.
Gastrointestinal disorders	*Frequent*	Vomiting, diarrhoea, constipation, nausea, abdominal pain, dyspepsia, dry mouth, stomach discomfort, toothache.
	Less frequent	Dysphagia, gastritis, faecal incontinence, faecaloma, lip swelling, cheilitis
Skin and subcutaneous tissue disorders	*Frequent*	Rash, erythema
	Less frequent	Skin lesion, skin disorder, pruritus, acne, skin discolouration, seborrhoeic dermatitis, dry skin,

		hyperkeratosis, dandruff, urticaria, alopecia, eczema, drug eruption.
Musculoskeletal and connective tissue disorders	*Frequent*	Arthralgia, back pain, pain in extremity
	Less frequent	Muscular weakness, myalgia, neck pain, joint swelling, posture abnormal, joint stiffness, musculoskeletal chest pain, rhabdomyolysis, muscle spasms, musculoskeletal pain, back pain, arthralgia, blood creatine phosphokinase increased, joint stiffness.
Renal and urinary disorders	*Frequent*	Enuresis
	Less frequent	Dysuria, urinary incontinence, pollakiuria, urinary retention.
Pregnancy, puerperium, and neonatal conditions	*Less frequent*	Drug withdrawal syndrome neonatal.

Reproductive system and breast disorders	*Less frequent*	Amenorrhoea, sexual dysfunction, erectile dysfunction, ejaculation disorder, galactorrhoea, gynaecomastia, menstrual disorder, vaginal discharge, breast pain, breast discomfort, priapism, menstruation delayed, breast engorgement, breast enlargement, breast discharge.
General disorders and administration site conditions	*Frequent*	Pyrexia, fatigue, peripheral oedema, asthenia, chest pain, pain.
	Less frequent	Face oedema, gait disturbance, feeling abnormal, sluggishness, influenza like illness, thirst, chest discomfort, chills, generalised oedema, drug withdrawal syndrome, peripheral coldness.

Hepatobiliary disorders	*Less frequent*	Transaminases increased, gamma-glutamyltransferase increased, hepatic enzyme increased, jaundice.
Injury, poisoning and procedural complications	*Frequent*	Fall.
	Less frequent	Procedural pain.
Investigations	*Frequent*	Increased blood prolactin, increased weight
	Less frequent	Abnormal electrocardiogram, increased blood glucose, increased transaminases, decreased white blood cell count, increased body temperature, increased eosinophil count, decreased haemoglobin, increased blood creatine phosphokinase, decreased body temperature.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to

SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications: hppts://www.sahpra.or.za/Publications/Index/8.

4.9 Overdose

Reported signs and symptoms have been those resulting from an exaggeration of the medicine's known pharmacological effects. Symptoms of acute overdosage include drowsiness, sedation, hypotension, tachycardia and extrapyramidal symptoms. In overdose, QT-prolongation and convulsions have been reported. *Torsade de pointes* has been reported in association with combined overdose of oral risperidone as in **RISTABBS** and paroxetine.

In the case of acute overdosage, the possibility of multiple medicine involvement should be considered.

Treatment:

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible dysrhythmias. Since there is no known antidote if accidental poisoning or overdosage is suspected, appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic medicines. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological classification: A.2.6.5 Central nervous system depressants. Miscellaneous structures.

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX08.

Mechanism of action

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT2 and dopaminergic D2 receptors. Risperidone binds also to alpha1-adrenergic receptors, and, with lower affinity, to H1 histaminergic and alpha2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D2 antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical antipsychotics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 Pharmacokinetic properties

Risperidone is metabolised to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone (see *Biotransformation and Elimination*).

Absorption

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absolute oral bioavailability of risperidone is

70 % (CV=25 %). The relative oral bioavailability of risperidone from a tablet is 94 % (CV=10 %) compared with a solution. The absorption is not affected by food and thus risperidone can be given with or without meals. Steady-state of risperidone is reached within 1 day in most patients. Steady-state of 9-hydroxy-risperidone is reached within 4-5 days of dosing.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, risperidone is bound to albumin and alpha1-acid glycoprotein. The plasma protein binding of risperidone is 90 %, that of 9-hydroxyrisperidone is 77 %.

Biotransformation

Risperidone is metabolised by CYP 2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. CYP 2D6 is subject to genetic polymorphism. Extensive CYP 2D6 metabolisers convert risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP 2D6 metabolisers convert it much more slowly. Although extensive metabolisers have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolisers, the pharmacokinetics of risperidone and 9-hydroxy-risperidone combined (i.e., the active antipsychotic fraction), after single and multiple doses, are similar in extensive and poor metabolisers of CYP 2D6.

Another metabolic pathway of risperidone is N-dealkylation. In vitro studies in human liver microsomes showed that risperidone at clinically relevant concentration does

not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP 1A2, CYP 2A6, CYP 2C8/9/10, CYP 2D6, CYP 2E1, CYP 3A4, and CYP 3A5.

Elimination

One week after administration, 70 % of the dose is excreted in the urine and 14 % in the faeces. In urine, risperidone plus 9-hydroxy-risperidone represent 35-45 % of the dose. The remainder is inactive metabolites. After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy-risperidone and of the active antipsychotic fraction is 24 hours.

Linearity/non-linearity

Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.

Elderly, hepatic and renal impairment

A single dose study showed higher active plasma concentrations and a reduced clearance of the active antipsychotic fraction by 30 % in the elderly and 50 % in patients with moderate renal insufficiency. In patients with severe renal insufficiency the clearance was one third that of normal. The plasma concentrations of risperidone were normal in patients with liver insufficiency, but the mean free fraction of risperidone in plasma was increased by about 35 %.

Paediatric population

The Pharmacokinetics of risperidone, 9-hydroxy-risperidone and active moety in children are similar to those in adults.

6. Pharmaceutical particulars

6.1 List of excipients

Acesulfame potassium, acetone, aspartame, basic butylated fumarate, colloidal silicon dioxide, ferric oxide red & yellow, isopropyl alcohol, low-substituted hydroxypropyl cellulose, magnesium aluminometasilicate, mannitol, peppermint flavour, sodium chloride, sodium lauryl sulfate, sodium stearyl fumarate, strawberry flavour, talc.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25˚C

Protect from moisture and sunlight

6.5 Nature and contents of container

RISTABBS 0.5 mg, 1 mg & 2 mg Orally Disintegrating Tablets: Forming laminate aluminium based film and Lidding laminate soft tempered aluminium foil in cold

formable blister strips of 10 tablets per strip packed in an outer carton containing 30 tablets.

6.6 Special precautions for disposal and other handling

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

7. Holder of certificate of registration

Innovata Pharmaceuticals (Pty) Ltd

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. Registration numbers

TBI

9. Date of first authorization/Renewal of the authorization

TBI

10. Date of revision of the text

TBI

REFERENCES:

1. Reference 1: RISPERLET PI, Janssen Pharmaceuticals (Pty) Ltd: 20 November 2020.
2. Reference 2: Risperidone 1 mg. SmPC

   Date of first authorization/Date of renewal of the authorization: 1st April 2008.

   Renewal of authorization: 1st April 2008

   Date of revision of the text: 7th December 2020

   Name of registration holder: Accord Healthcare Limited

   Sage House

   319 Pinner Road

   North Harrow

   Middlesex

   HA1 4HF

   United Kingdom.

3. Reference 3: Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668)

   Excipients and information for the package leaflet

22 November 2019

EMA/CHMP/302620/2017 Rev. 1*