APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S5

PROPRIETARY NAME (AND DOSAGE FORM):

RUTRA SOLUTION 1 mg/ml (Solution)

COMPOSITION:

Each ml contains 1 mg Risperidone.

Preservative: Benzoic acid…….0.2 %

PHARMACOLOGICAL CLASSIFICATION:

A.2.6.5 Central nervous system depressants. Miscellaneous structures.

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Risperidone is an antipsychotic of the benzisoxazol derivatives. It is a selective monoaminergic antagonist.

Risperidone has affinity for serotonin-5-HT_2, dopamine-D_2, H_1-histamine, alpha$_1$- and alpha$_2$-adrenergic receptors.

Risperidone has no affinity for cholinergic receptors. It is a dopamine D_2-antagonist.

Pharmacokinetics:

Risperidone is completely absorbed after oral administration. Peak plasma concentrations are attained within 1 to 2 hours. Food does not affect the absorption of risperidone.

Risperidone is metabolized by cytochrome CYP2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. Risperidone and 9-hydroxy-risperidone form the active antipsychotic fraction.

After oral administration to psychotic patients, risperidone's half-life is about 3 hours. The elimination half-life of 9-hydroxy-risperidone and the active antipsychotic fraction is 24 hours.

Steady state is reached within 1 day for risperidone in most patients and 4-5 days for 9-hydroxyrisperidone.

Risperidone plasma concentration is dose-proportional within the therapeutic dose-range.

Risperidone is bound to albumin and alpha$_1$-acid glycoprotein. Plasma protein binding of risperidone is 88% and 77% for 9-hydroxy-risperidone. One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In the urine, risperidone and 9-hydroxy-risperidone represent 35 - 45% of the dose.

Risperidone showed significantly higher active plasma concentrations and slower elimination in the elderly and in patients with moderately severe renal insufficiency. The plasma concentrations of risperidone were normal in patients with mild to moderate liver insufficiency.

The pharmacokinetics of risperidone, 9-hydroxy-risperidone and the active moiety in children are similar to those in adults.

INDICATIONS:

RUTRA SOLUTION 1 mg/ml is indicated for the treatment of:

- Acute and chronic schizophrenic psychoses and related psychosis in which positive symptoms and/or the negative symptoms are prominent. **RUTRA SOLUTION 1 mg/ml** also alleviates affective symptoms associated with schizophrenia. In patients who have shown an initial treatment response, **RUTRA SOLUTION 1 mg/ml** is also effective in maintaining the clinical improvement.
- Behavioural disturbances in patients with dementia in whom symptoms such as aggressiveness, activity disturbances or psychotic symptoms are prominent.
- Conduct and other disruptive behaviour disorders in children (aged 5 - 12 years), with sub-average intellectual functioning or mental retardation in whom destructive behaviours are prominent.

CONTRA-INDICATIONS:

RUTRA SOLUTION 1 mg/ml is contra-indicated in patients with known sensitivity to any of the components of the medicine.

Conduct and other disruptive behaviour disorders in children: **RUTRA SOLUTION 1 mg/ml** is contra-indicated in children under 5 years of age as efficacy and safety in these children have not been demonstrated.

Lewy antibody dementia (see **WARNINGS**).

WARNINGS:

Tardive dyskinesia:

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, involuntary dyskinetic movements may

develop in patients treated with **RUTRA SOLUTION 1 mg/ml**. Although this syndrome of TD appears to be most prevalent in the elderly, especially elderly females, it is impossible to predict at the onset of treatment which patients are likely to develop TD (see **Special Precautions**).

Neuroleptic Malignant Syndrome:

Neuroleptic Malignant Syndrome (NMS) is a potentially fatal symptom complex that has been reported in association with the use of **RUTRA SOLUTION 1 mg/ml**. Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, cardiac arrhythmias and diaphoresis). Additional signs may include elevated creatine phosphokinase (CPK) levels, myoglobinuria (rhabdomyolysis), and acute renal failure (see **Special Precautions**).

Concomitant use with furosemide:

In **RUTRA SOLUTION 1 mg/ml** placebo controlled trials in elderly patients with dementia, there was a higher mortality in patients treated with furosemide and **RUTRA SOLUTION 1 mg/ml** when compared to patients treated with **RUTRA SOLUTION 1 mg/ml** alone. Caution is advised in these patients. Dehydration was an overall risk for mortality and should be carefully avoided in these patients.

Hyperglycaemia and diabetes mellitus:

Hyperglycaemia, in some cases extreme and associated with ketoacidosis and hyperosmolar coma or death, has been reported in patients treated with **RUTRA SOLUTION 1 mg/ml**. Patients with an established diagnosis of diabetes mellitus who are started on **RUTRA SOLUTION 1 mg/ml** 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 **RUTRA SOLUTION 1 mg/ml** should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with **RUTRA SOLUTION 1 mg/ml** should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when **RUTRA SOLUTION 1 mg/ml** was discontinued. However, some patients required continuation of anti-diabetic treatment despite discontinuation of **RUTRA SOLUTION 1 mg/ml**.

Cerebrovascular Adverse Events:

Cerebrovascular adverse events (CAE), including cerebrovascular accidents and transient ischaemic attacks, have been reported during treatment with **RUTRA SOLUTION 1 mg/ml**. In placebo-controlled clinical trials in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events, including cerebrovascular accidents and transient ischaemic attacks, in patients treated with **RUTRA SOLUTION 1 mg/ml**

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

Dementia associated with Parkinson's disease and senile dementia:

Doctors should weigh the risks versus the benefits when prescribing **RUTRA SOLUTION 1 mg/ml** to patients with Parkinson's Disease or Dementia with Lewy bodies (DLB) since both groups may be at risk of Neuroleptic Malignant Syndrome (NMS) as well as having an increased sensitivity to antipsychotic medications such as **RUTRA SOLUTION 1 mg/ml**. Manifestations 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 **RUTRA SOLUTION 1 mg/ml** treated patients had a higher mortality than placebo treated elderly patients.

The risk of using **RUTRA SOLUTION 1 mg/ml** in combination with other medicines has not been systematically evaluated. Given the primary CNS depressive effects of **RUTRA SOLUTION 1 mg/ml**, it should be used with caution in combination with alcohol and other centrally acting medicines. **RUTRA SOLUTION 1 mg/ml** may antagonise the effect of levodopa and other dopamine agonists.

Alpha-blocking activity:

Due to the alpha-blocking activity of **RUTRA SOLUTION 1 mg/ml**, (orthostatic) hypotension can occur, especially during the initial dose-titration period. **RUTRA SOLUTION 1 mg/ml** 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.

Other:

Seizures have been reported after treatment with **RUTRA SOLUTION 1 mg/ml**. Caution is recommended when treating patients with epilepsy.

INTERACTIONS:

Carbamazepine has been shown to decrease the plasma levels of the active antipsychotic fraction of risperidone by about 50%. Similar effects may be observed with other hepatic enzyme inducers. On discontinuation of carbamazepine or other hepatic enzyme inducers the dosage of risperidone should be re-evaluated and, if necessary, decreased.

Valproate: valproate Tmax increased from 1.3 hours to 2.0 hours.

Topiramate: modest decrease in risperidone bioavailability, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentration of risperidone but not that of the antipsychotic fraction. Fluoxetine and paroxetine increased the plasma concentration of risperidone but less so of the antipsychotic fraction. Fluoxetine kinetics were not changed in combination with **RUTRA SOLUTION 1 mg/ml**. When concomitant fluoxetine or paroxetine is initiated or discontinued, the dosing of **RUTRA SOLUTION 1 mg/ml** should be re-evaluated.

Amitriptyline: non-significant interactions.

Venlafaxine: Risperidone AUC increased and risperidone clearance decreased, but there was no effect on 9-OH-risperidone and the active moiety.

Quetiapine: no significant interaction.

Clozapine: no significant interaction.

Lithium: Cmax and AUC of lithium were non-significant increased, but Tmax of lithium was increased from 2.4 hours to 3.0 h.

Erythromycin: non-significant increase in risperidone exposure.

There were non-significant effects on risperidone kinetics or that of the active fraction in combination with donepezil or galantamine.

Cimetidine and ranitidine increased the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction.

When **RUTRA SOLUTION 1 mg/ml** is taken together with other highly protein-bound medicines (e.g. diazepam, warfarin, digoxin, imipramine and propranolol), there is no clinically relevant displacement of either agent from the plasma proteins.

See **Special Precautions** and **WARNINGS** for use regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

PREGNANCY AND LACTATION:

The safety of **RUTRA SOLUTION 1 mg/ml** in pregnancy and lactating women has not been established.

Reversible extrapyramidal symptoms, including hypertonia, hypotonia, jitteriness, tremor, muscle rigidity, twitching and convulsions, feeding disorder and withdrawal symptoms have been observed in neonates following postmarketing use of **RUTRA SOLUTION 1 mg/ml** during the last trimester of pregnancy.

Risperidone and 9-hydroxy-risperidone are excreted in human breast milk. Therefore, women receiving **RUTRA SOLUTION 1 mg/ml** should not breast feed (see **CONTRA-INDICATIONS)**.

DOSAGE AND DIRECTIONS FOR USE:

Schizophrenia:

Switching from other antipsychotics to **RUTRA SOLUTION 1 mg/ml:**

When medically appropriate, gradual discontinuation of the previous treatment, while **RUTRA SOLUTION 1 mg/ml** therapy is initiated, is recommended. Also if medically appropriate, when switching patients from depot antipsychotics, initiate **RUTRA SOLUTION 1 mg/ml** therapy in place of the next scheduled injection. The need for continuing existing anti-Parkinson medications should be re-evaluated periodically.

Adults

RUTRA SOLUTION 1 mg/ml may be given once or twice daily.

Patients should start with 2 mg/day. 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 **RUTRA SOLUTION 1 mg/ml** if additional sedation is required.

Elderly patients

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.

Children

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

Behavioural disturbances in adult patients with dementia:

A starting dose of 0.25 mg twice daily is recommended. This dosage can be individually adjusted by increments of

0.25 mg twice daily, not more frequently than every other day, if needed. The optimum dose is 0.5 mg twice daily for most patients. Some patients, however, may benefit from doses up to 1 mg twice daily.

Once patients have reached their target dose, a once-daily dosing regimen can be considered. The continued use of **RUTRA SOLUTION 1 mg/ml** must be evaluated and justified on an ongoing basis.

Conduct and other disruptive behaviour disorders in children 5-12 years of age:

Subjects < 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 **RUTRA SOLUTION 1 mg/ml** must be evaluated and justified on an ongoing basis.

Experience is lacking in children aged less than 5 years (see **CONTRA-INDICATIONS**).

Renal- and liver impairment:

Caution should be exercised with these groups of patients, as clinical experience is lacking in these patient populations. It is recommended to halve both the starting dose and the subsequent dose increments.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and frequency (wherever applicable).

General disorders

Frequent:

Weight gain, headache, fatigue.

The following side-effects have been reported and frequencies are unknown:

Angioedema and other allergic reactions.

Blood and the lymphatic system disorders

The following side-effects have been reported and frequencies are unknown:

A decrease in neutrophil and/or thrombocyte count has been reported.

Respiratory system disorders

Frequent:

Rhinitis.

Endocrine disorders

Less frequent:

Body temperature disregulation.

The following side-effects have been reported and frequencies are unknown:

Water intoxication, either due to polydipsia or the syndrome of inappropriate secretion of the antidiuretic hormone (SIADH).

Increased plasma prolactin levels and associated manifestations (see **Reproductive system** and **Special Precautions**).

Psychiatric disorders

Frequent:

Insomnia, agitation, anxiety, somnolence, impaired concentration.

In some instances it has been difficult to differentiate adverse events from symptoms of the underlying psychosis.

Central and peripheral nervous system disorders

Frequent:

Extrapyramidal disorder, dizziness.

Dose dependent extrapyramidal symptoms, including tremor, rigidity, bradykinesia, oculogyric crisis, akathisia and acute dystonia, hypokinesia. These may be reversible upon dose reduction and/or administration of anti-Parkinson medication, if necessary.

Less frequent:

Dose dependent extrapyramidal symptoms, including hypersalivation and hyperkinesia. These may be reversible upon dose reduction and/or administration of anti-Parkinson medication, if necessary.

Tardive dyskinesia (see **Special Precautions)**.

Neuroleptic Malignant Syndrome (see **Special Precautions**).

Cerebrovascular accidents have been observed during treatment with **RUTRA SOLUTION 1 mg/ml**.

The following side-effects have been reported and frequencies are unknown:

Sedation.

Eye disorders

Frequent:

Blurred vision.

Vascular disorders

Less frequent:

(Orthostatic) hypotension, (reflex) tachycardia.

The following side-effects have been reported and frequencies are unknown:

Hypertension.

Gastro-intestinal disorders

Frequent:

Constipation, dyspepsia, nausea.

Less frequent:

Abdominal pain, vomiting.

Skin and subcutaneous tissue disorders

Frequent:

Skin rash.

Urinary system disorders

The following side-effects have been reported and frequencies are unknown:

Urinary incontinence.

Reproductive system disorders

Less frequent:

Priapism.

Galactorrhoea, amenorrhoea (see **Special Precautions)**.

The following side-effects have been reported and frequencies are unknown:

Erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction.

Gynaecomastia, disturbances in the menstrual cycle (see **Special Precautions)**.

Special Precautions:

Tardive dyskinesia:

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, involuntary dyskinetic movements may develop in patients treated wlth **RUTRA SOLUTION 1 mg/ml**. Although this syndrome of TD appears to be most prevalent in the elderly, especially elderly females, it is impossible to predict at the onset of treatment which

patients are likely to develop TD.

It has been suggested that the occurrence of Parkinsonian side-effects is a predictor for the development of TD. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of the antipsychotic administered to the patient increase. However, the syndrome can develop, although less commonly, after relatively brief periods of treatment at low doses. There is no known treatment for an established case of TD. The syndrome may remit partially or completely if the antipsychotic medicine treatment is withdrawn.

RUTRA SOLUTION 1 mg/ml treatment itself, however, may suppress the signs and symptoms of TD, thereby masking the underlying process. The effect of symptom suppression upon the long-term course of TD is unknown. In view of these considerations, **RUTRA SOLUTION 1 mg/ml** should be prescribed in a manner that is most likely to minimise the risk of TD. **RUTRA SOLUTION 1 mg/ml** should be reserved for patients who appear to be obtaining substantial benefit from the medicine. In such patients the smallest dose and the shortest duration of treatment should be sought. The benefit for continued treatment should be reassessed periodically. If signs and symptoms of TD appear in a patient on antipsychotics, **RUTRA SOLUTION 1 mg/ml** discontinuation should be considered. However, some patients may require treatment despite the presence of this syndrome.

Neuroleptic Malignant Syndrome:

Neuroleptic Malignant Syndrome (NMS) is a potentially fatal symptom complex that has been reported in association with the use of **RUTRA SOLUTION 1 mg/ml**. Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, cardiac arrhythmias and diaphoresis). Additional signs may include elevated creatine phosphokinase (CPK) levels, myoglobinuria (rhabdomyolysis), and acute renal failure. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illnesses (e.g. pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, medicine fever and primary central nervous system pathology. The management of NMS should include

1. Immediate discontinuation of all antipsychotic medicines and other drugs not essential to concurrent therapy;
2. Intensive symptomatic treatment and medical monitoring; and
3. Treatment of any concomitant serious medical problems for which specific treatments are available.

There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic medicine treatment after recovery from NMS, the potential reintroduction of medicine therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Seizures have been reported after treatment with **RUTRA SOLUTION 1 mg/ml**. Caution is recommended when treating patients with epilepsy.

A dose-dependent increase in plasma prolactin concentration may occur. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea. Premenopausal women who develop secondary amenorrhoea of greater than six months duration should receive appropriate preventative therapy to avoid hypo-oestrogenic bone loss.

Concomitant use with furosemide:

In **RUTRA SOLUTION 1 mg/ml** placebo controlled trials in elderly patients with dementia, there was a higher mortality in patients treated with furosemide and **RUTRA SOLUTION 1 mg/ml** when compared to patients treated with **RUTRA SOLUTION 1 mg/ml** alone. Caution is advised in these patients. Dehydration was an overall risk for mortality and should be carefully avoided in these patients.

Effects on ability to drive or operate machinery:

RUTRA SOLUTION 1 mg/ml may impair mental alertness. Patients should therefore be advised not to drive or operate machinery until their individual susceptibility is known.

It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and patients with renal or liver insufficiency.

Caution should be used when prescribing **RUTRA SOLUTION 1 mg/ml** to patients with Parkinson disease since, theoretically, it might cause a deterioration of the disease.

Patients may be advised to refrain from excessive eating in view of the possibility of weight gain.

Hyperglycaemia and exacerbation of pre-existing diabetes mellitus have been reported on **RUTRA SOLUTION 1 mg/ml** treatment (see **WARNINGS**).

Benign pituitary adenomas have been reported during postmarketing surveillance. No causal association could be detected.

Alpha-blocking activity:

Due to the alpha-blocking activity of **RUTRA SOLUTION 1 mg/ml**, (orthostatic) hypotension can occur especially during the initial dose-titration period. **RUTRA SOLUTION 1 mg/ml** 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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, cases of QT-prolongation have been reported.

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

Treatment:

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and 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 arrhythmias.

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 agents. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

IDENTIFICATION:

A clear, colourless liquid.

PRESENTATION:

1. Glass bottle:

100 ml solution packed in 125 ml amber coloured, Type III glass bottle, 28 mm neck finish and press in bottle adapter suitable for 28 mm neck, with 28 mm – 400 CR closure with F 217 expanded polyethylene wad.

Pack size: One 125 ml amber coloured glass bottle packed in a printed carton with package insert.

2. HDPE bottle:

100 ml solution packed in 115 ml translucent HDPE container of 28 mm neck finish with 28 mm – 400 CR closure with F 217 expanded polyethylene wad.

Pack size: One 115 ml HDPE container packed in a printed carton with package insert.

STORAGE INSTRUCTIONS:

Store below 30 °C. Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

41/2.6.5/1056

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