APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM:

AUROPERDAL 0.5 mg (Tablet)

AUROPERDAL 1 mg (Tablet)

AUROPERDAL 2 mg (Tablet)

AUROPERDAL 3 mg (Tablet)

AUROPERDAL 4 mg (Tablet)

COMPOSITION:

AUROPERDAL 0.5 mg: Each film-coated tablet contains 0,5 mg risperidone.

AUROPERDAL 1 mg: Each film-coated tablet contains 1 mg risperidone.

AUROPERDAL 2 mg: Each film-coated tablet contains 2 mg risperidone.

AUROPERDAL 3 mg: Each film-coated tablet contains 3 mg risperidone.

AUROPERDAL 4 mg: Each film-coated tablet contains 4 mg risperidone.

PHARMACOLOGICAL CLASSIFICATION:

A.2.6.5 Central nervous system depressants. Miscellaneous structures.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Risperidone is an antipsychotic of the benzisoxazol derivatives. It is a selective monoaminergic antagonist. **AUROPERDAL** has affinity for serotonin-5-HT_2, dopamine-D_2, H_1-histamine, α_1- and α_2 -adrenergic receptors. Risperidone has no affinity for cholinergic receptors. It is a D_2-antagonist.

Pharmacokinetics:

AUROPERDAL is readily absorbed after oral doses, peak plasma concentrations being reached within 1 to 2 hours. It is extensively metabolized in the liver by hydroxylation to its main active metabolite, 9-hydroxyrisperidone. Hydroxylation is mediated by the cytochrome P450 isoenzyme CYP2D6. Excretion is mainly in the urine and to a lesser extent, in the faeces. Risperidone and 9-hydroxyrisperidone are about 88 % and 77 % bound to plasma proteins, respectively. A mean value of 19,5 hours has been reported for the terminal elimination half-life of the active fraction following oral administration of risperidone.

Steady state is reached within 1 day for risperidone in most patients and 4-5 days for 9-hydroxy-risperidone. Risperidone plasma concentration is dose proportional within the therapeutic dose range.

One week after administration 70 % of the dose is excreted in the urine and 14 % in the faeces. Risperidone showed higher active plasma concentrations and slower elimination in the elderly and in patients with renal insufficiency. The plasma concentrations were normal in patients with liver insufficiency. The pharmacokinetics of risperidone and the active metabolite, 9-hydroxyrisperidone, in children are similar to those in adults.

INDICATIONS:

AUROPERDAL is indicated in the treatment of:

- acute and chronic schizophrenic psychoses and related psychosis in which positive symptoms and/or the negative symptoms are prominent. **AUROPERDAL** also alleviates affective symptoms associated with schizophrenia. In patients who have shown an initial treatment response, **AUROPERDAL** 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 subaverage intellectual functioning or mental retardation in whom destructive behaviours are prominent.

CONTRA-INDICATIONS:

AUROPERDAL is contra-indicated in patients with known sensitivity to the medicine.

Safety of **AUROPERDAL** in pregnancy or lactating women has not been established.

Risperidone and 9-hydroxy-risperidone are excreted in human breast milk. Therefore, women receiving **AUROPERDAL** should not breast feed.

Conduct and other disruptive behaviour disorders in children: **AUROPERDAL** is contra-indicated in children under 5 years as efficacy and safety in children under the age of 5 years as efficacy and safety in children under the age of 5 years have not been demonstrated.

Lewy body dementia (see "**WARNINGS AND SPECIAL PRECAUTIONS"**).

WARNINGS AND SPECIAL PRECAUTIONS:

Tardive dyskinesia:

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, involuntary dyskinetic movements may develop in patients treated with **AUROPERDAL**. 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.

The antipsychotic drug treatment itself however, may suppress the signs and symptoms of TO, thereby masking the underlying process. The effect of symptom suppression upon the long-term course of TD is unknown. In view of these considerations, **AUROPERDAL** should be prescribed in a manner that is most likely to minimise the risk of TD. As with any antipsychotic medicine, **AUROPERDAL** 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 antipsychotic, medicine 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 **AUROPERDAL**. 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.

Concomitant use with furosemide:

Caution is advised in patients treated with furosemide due to possible dehydration (see **"INTERACTIONS"**).

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 **AUROPERDAL**. Patients with an established diagnosis of diabetes mellitus who are started on **AUROPERDAL** 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 **AUROPERDAL** should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with **AUROPERDAL** should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when **AUROPERDAL** was discontinued. However, some patients required continuation of anti-diabetic treatment despite discontinuation of **AUROPERDAL**.

Cerebrovascular adverse events:

Cerebrovascular adverse events (CAE), including cerebrovascular accidents and transient ischaemic attacks, have been reported during treatment with **AUROPERDAL**. 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 **AUROPERDAL** 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 **AUROPERDAL** 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 **AUROPERDAL**. 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 **AUROPERDAL** treated patients had a higher mortality than placebo treated elderly patients.

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

Alpha-blocking activity:

Due to the alpha-blocking activity of **AUROPERDAL**, (orthostatic) hypotension can occur, especially during the initial dose-titration period. **AUROPERDAL** 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.

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 **AUROPERDAL** (see "**SIDE EFFECTS"**).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Other:

Seizures have been reported after treatment with **AUROPERDAL**. Caution is recommended when treating patients with epilepsy.

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

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

Water intoxication, either due to polydipsia or the syndrome of inappropriate secretion of the antidiuretic hormone (SIADH), and body temperature disregulation, has been reported.

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

Effect on ability to drive and use machines:

AUROPERDAL may impair mental alertness. Therefore patients should be advised not to drive or operate machinery until their individual susceptibility is known.

INTERACTIONS:

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

Lithium: Cmax and AUC of lithium were non significantly increased but Tmax of lithium was increased from 2,4 hours to 3,0 hours.

AUROPERDAL should be used with caution in combination with alcohol and other centrally acting medicines. It may antagonise the effect of levodopa and other dopamine agonists.

Carbamazepine has been shown to decrease the plasma levels of the active antipsychotic fraction of **AUROPERDAL** 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 **AUROPERDAL** should be re-evaluated and, if necessary, decreased.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentration of risperidone but not that of the antipsychotic fraction. Fluoxetine and paroxetine may increase the plasma concentration of risperidone but less so of the anti-psychotic fraction. When either fluoxetine or paroxetine is initiated or discontinued the dosing of **AURODERPAL** should be re-evaluated.

When **AUROPERDAL** is taken together with other highly protein-bound medicines (e.g. diazepam, warfarin, digitoxin, imipramine and propranolol), there is no clinically relevant displacement of either agent from the plasma proteins.

Furosemide: In placebo controlled trials in elderly patients with dementia, there was a higher mortality in patients treated with furosemide and risperidone when compared to patients treated with risperidone alone. Caution is advised in these patients. Dehydration was an overall risk for mortality and should be carefully avoided in these patients.

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

PREGNANCY AND LACTATION:

Safety of **AUROPERDAL** in pregnancy or lactating women has not been established.

Risperidone and 9-hydroxy-risperidone are excreted in human breast milk. Therefore, women receiving **AUROPERDAL** should not breast feed.

Reversible extrapyramidal symptoms, including hypertonia, hypotonia, jitteriness, tremor, muscle rigidity, twitching and convulsions, feeding disorder and withdrawal symptoms were observed in neonates following post marketing use of risperidone during the last trimester of pregnancy.

DOSAGE AND DIRECTIONS FOR USE:

Schizophrenia:

Switching from other antipsychotic to AUROPERDAL:

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

Adults:

AUROPERDAL may be given once or twice daily.

Patients should start with 2 mg/day **AUROPERDAL**. 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 **AUROPERDAL** if additional sedation is required.

Renal- and liver-diseased patients:

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.

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 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 **AUROPERDAL** must be evaluated and justified on an ongoing basis.

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

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 **AUROPERDAL** must be evaluated and justified on an ongoing basis.

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

SIDE EFFECTS:

Gastrointestinal disorders:

Frequent: Dyspepsia, nausea, vomiting, constipation, diarrhoea.

Less frequent: Abdominal pain.

Nervous system disorders:

Frequent: Headache, anxiety, insomnia, agitation, and extrapyradimal disorder. Sedation has been reported more frequently in children and adolescents than in adults, dizziness, fatigue, concentration difficulties, akathisia, somnolence, asthenia, drowsiness, lassitude, increased dream activity, increased duration of sleep.

Less frequent: Mania, hypothermia, tardive dyskinesia, neuroleptic malignant syndrome, cerebrovascular accident.

Frequency not known: Seizures.

Endocrine disorders:

Less frequent: Weight gain, aggrevation of diabetes mellitus or diabetic ketoacidosis, hyperglycaemia.

Eye Disorders:

Less frequent: Floppy iris syndrome (intaoperative)

Respiratory, thoracic and mediastinal disorders:

Frequent: Rhinitis, dyspnoea, cough, decreased salivation or dryness of mouth, pharyngitis, upper respiratory tract infection.

Frequency not known: Apnoea.

Reproductive system and breast disorders:

Frequent: Priapism, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction.

Less frequent: Amenorrhoea, galactorhoea, gynaecomastia.

Renal and urinary disorders:

Less frequent: Urinary incontinence, water intoxication, either due to polydipsia or the syndrome of inappropriate secretion of the anti-diuretic hormone (SIAHD) hyponatraemia. Micturition disturbances or polyuria.

Skin and subcutaneous tissue disorders:

Frequent: Rash and other allergic reactions have been observed.

Less frequent: Dry skin, increased skin pigmentation, increased sweating, photosensitivity, seborrhea.

Vascular disorders:

Less frequent: Hypertension, reflex tachycardia, orthostatic hypotension, palpitations, chest pain, reflex tachycardia or tachycardia, cardiovascular adverse events including stroke and transient ischaemic attacks.

Cerebrovascular accidents have been observed during treatment with risperidone.

Musculoskeletal disorders:

Less frequent: Back pain, arthralgia.

General disorders:

Frequency not known: Angioedema, anaphylactic reaction.

Investigations:

Mild fall in neutrophil and/or thrombocytes count has been reported.

A dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhea.

Premenopausal women who develop secondary amenorrhea of greater than six months duration should receive appropriate preventative therapy to avoid hypo-oestrogenic bone loss.

The following dose dependent extra pyramidal symptoms have been observed: tremor, rigidity, hyper salivation, bradykinesia, oculogyric crisis, akathisia (hyperkinesia) and acute dystonia, hypokinesia. These are usually mild and reversible upon dose reduction and/or administration of anti-Parkinson medication, if necessary.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms of acute overdosage include drowsiness, sedation, hypotension, tachycardia and extra pyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported.

In the case of acute over dosage, the possibility of multiple medicine involvement 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 cases of severe exrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

IDENTIFICATION:

AUROPERDAL 0.5 mg: Green coloured film coated biconvex caplets, debossed on one side with "A" and on the other side with "50". Score line between "5" and "0".

AUROPERDAL 1 mg: White coloured film coated biconvex caplets, debossed on one side with "A" and on the other side with "51". Score line between "5" and "1".

AUROPERDAL 2 mg: Light orange coloured film coated biconvex caplets, debossed on one side with "A" and on the other side with "52" Score line between "5" and "2".

AUROPERDAL 3 mg: Yellow coloured film coated biconvex caplets, debossed on one side with "A" and on the other side with "53". Score line between "5" and "3".

AUROPERDAL 4 mg: Green coloured film coated biconvex caplets, debossed on one side with "A" and on the other side with "54". Score line between "5" and "4".

PRESENTATION:

Tablets are packed in clear 250 micron PVC film laminated with 25 micron PE, coated with 90 gsm PVdC and 25 micron printed aluminium foil. Each blister contains 10 tablets.

Pack size for **AUROPERDAL 0.5 mg**: Each carton contains 2 blisters of 10 tablets each.

Pack size for **AUROPERDAL 1 mg, AUROPERDAL 2 mg**, **AUROPERDAL 3 mg** and **AUROPERDAL 4 mg**: Each carton contains 3 blisters of 10 tablets each.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Do not remove from the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

AUROPERDAL 0.5 mg: 42/2.6.5/0330

AUROPERDAL 1 mg: 42/2.6.5/0331

AUROPERDAL 2 mg: 42/2.6.5/0332

AUROPERDAL 3 mg: 42/2.6.5/0333

AUROPERDAL 4 mg: 42/2.6.5/0334

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF

REGISTRATION:

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