Risperidone

Amidrex OD-3

3 mg Orally Disintegrating Tablet
Antipsychotic

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FORMULATION:
Each orally disintegrating tablet contains:
Risperidone USP .... 3 mg

PRODUCT DESCRIPTION:
White to off white coloured, round, biconvex orally disintegrating uncoated tablet having both sides plain.

PHARMACOLOGICAL PROPERTIES:
PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Other antipsychotics
Mechanism of action
Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT$_2$ and dopaminergic D$_2$ receptors. Risperidone binds also to alpha$_1$-adrenergic receptors, and with lower affinity, to H$_1$-histaminergic and alpha$_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D$_2$ 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.
Pharmacodynamic effects
Schizophrenia
The efficacy of risperidone in the short-term treatment of schizophrenia was established in four studies, 4- to 8-weeks in duration, which enrolled over 2500 patients who met DSM-IV criteria for schizophrenia. In a 6-week, placebo-controlled trial involving titration of risperidone in doses up to 10 mg/day administered twice daily, risperidone was superior to placebo on the Brief Psychiatric Rating Scale (BPRS) total score. In an 8-week, placebo-controlled trial involving four fixed doses of risperidone (2, 6, 10, and 16 mg/day, administered twice daily), all four risperidone groups were superior to placebo on the Positive and Negative Syndrome Scale (PANSS) total score. In an 8-week, dose comparison trial involving five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day administered twice-daily), the 4, 8, and 16 mg/day risperidone dose groups were superior to the 1 mg risperidone dose group on PANSS total score. In a 4-week, placebo-controlled dose comparison trial involving two fixed doses of risperidone (4 and 8 mg/day administered once daily), both risperidone dose groups were superior to placebo on several PANSS measures, including total PANSS and a response measure (>20% reduction in PANSS total score). In a longer-term trial, adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medicinal product were randomised to risperidone 2 to 8 mg/day or to haloperidol for 1 to 2 years of observation for relapse. Patients receiving risperidone experienced a significantly longer time to relapse over this time period compared to those receiving haloperidol.
Manic episodes in bipolar disorder
The efficacy of risperidone monotherapy in the acute treatment of manic episodes associated with bipolar I disorder was demonstrated in three double-blind, placebo-controlled monotherapy studies in approximately 820 patients who had bipolar I disorder, based on DSM-IV criteria. In the three studies, risperidone 1 to 6 mg/day (starting dose 3 mg in two studies and 2 mg in one study) was shown to be significantly superior to placebo on the pre-specified primary endpoint, i.e., the change from baseline in total Young Mania Rating Scale (YMRS) score at Week 3. Secondary efficacy outcomes were generally consistent with the primary outcome. The percentage of patients with a decrease of 50% in total YMRS score from baseline to the 3-week endpoint was significantly higher for risperidone than for placebo. One of the three studies included a haloperidol arm and a 9-week double-blind maintenance phase. Efficacy was maintained throughout the 9-week maintenance treatment period. Change from baseline in total YMRS showed continued improvement and was comparable between risperidone and haloperidol at Week 12. The efficacy of risperidone in addition to mood stabilisers in the treatment of acute mania was demonstrated in one of two 3-week double-blind studies in approximately 300 patients who met the DSM-IV criteria for bipolar I disorder. In one 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day in addition to lithium or valproate was superior to lithium or valproate alone on the pre-specified primary endpoint, i.e., the change from baseline in YMRS total score at Week 3. In a second 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day, combined with lithium, valproate, or carbamazepine was not superior to lithium, valproate, or carbamazepine alone in the reduction of YMRS total score. A possible explanation for the failure of this study was induction of risperidone and 9-hydroxy-risperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxy-risperidone. When the carbamazepine group was excluded in a post-hoc analysis, risperidone combined with lithium or valproate was superior to lithium or valproate alone in the reduction of YMRS total score.
Persistent aggression in dementia
The efficacy of risperidone in the treatment of Behavioural and Psychological Symptoms of Dementia (BPSD), which includes behavioural disturbances, such as aggressiveness, agitation, psychosis, activity, and affective disturbances was demonstrated in three double-blind, placebo-controlled studies in 1150 elderly patients with moderate to severe dementia. One study included fixed risperidone doses of 0.5, 1, and 2 mg/day. Two flexible-dose studies included risperidone dose groups in the range of 0.5 to 4 mg/day and 0.5 to 2 mg/day, respectively. Risperidone showed statistically significant and clinically important effectiveness in treating aggression and less consistently in treating agitation and psychosis in elderly dementia patients (as measured by the Behavioural Pathology in Alzheimer's Disease Rating Scale [BEHAVE-AD] and the Cohen-Mansfield Agitation Inventory [CMAI]). The treatment effect of risperidone was independent of Mini-Mental State Examination (MMSE) score (and consequently of the severity of dementia); of sedative properties of risperidone; of the presence or absence of psychosis; and of the type of dementia, Alzheimer's, vascular, or mixed.
Conduct disorder
The efficacy of risperidone in the short-term treatment of disruptive behaviours was demonstrated in two double-blind placebo-controlled studies in approximately 240 patients 5 to 12 years of age with a DSM-IV diagnosis of disruptive behaviour disorders (DBD) and borderline intellectual functioning or mild or moderate mental retardation/learning disorder. In the two studies, risperidone 0.02 to 0.06 mg/kg/day was significantly superior to placebo on the pre-specified primary endpoint, i.e., the change from baseline in the Conduct Problem subscale of the Nisonger-Child Behaviour Rating Form (N-CBRF) at Week 6.

PHARMACOKINETIC PROPERTIES:
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 alpha$_1$-acid glycoprotein. The plasma protein binding of risperidone is 90%, that of 9-hydroxyrisperidone is 77%.
Biotransformation and elimination
Risperidone is metabolized by CYP2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. CYP2D6 is subject to genetic polymorphism. Extensive CYP2D6 metabolizers convert risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolizers, 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 metabolizers of CYP2D6.
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 metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. One week after administration, 70% of the dose is excreted in the urine and 14% in the feces. 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
Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.
Elderly, hepatic and renal impairment
A single-dose study showed on average a 43% higher active antipsychotic fraction plasma concentrations, a 38% longer half-life and a reduced clearance of the active antipsychotic fraction by 30% in the elderly.Higher active antipsychotic fraction plasma concentrations and a reduced clearance of the active antipsychotic fraction by on average 60% were observed in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency, but the mean free fraction of risperidone in plasma was increased by about 35%.
Pediatric patients
The pharmacokinetics of risperidone, 9-hydroxy-risperidone and the active antipsychotic fraction in children are similar to those in adults.
Gender, race and smoking habits.
A population pharmacokinetic analysis revealed no apparent effect of gender, race or smoking habits on the pharmacokinetics of risperidone or the active antipsychotic fraction.

INDICATIONS:
Risperidone (Amidrex OD-3) is indicated for the treatment of schizophrenia.
Risperidone (Amidrex OD-3) is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.
Risperidone (Amidrex OD-3) is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.
Risperidone (Amidrex OD-3) is indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviors requires pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programmed, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

DOSAGE AND ADMINISTRATION:
Schizophrenia
Adults
Risperidone (Amidrex OD-3) may be given once daily or twice daily.
Patients should start with 2 mg/day risperidone. The dosage may be increased on the second day to 4 mg. Subsequently, the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6 mg. In some patients, a slower titration phase and a lower starting and maintenance dose may be appropriate.
Doses above 10 mg/day have not demonstrated superior efficacy to lower doses and may cause increased incidence of extrapyramidal symptoms. Safety of doses above 16 mg/day has not been evaluated, and are therefore not recommended.
Elderly
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 to 2 mg twice daily.
Pediatric population
Risperidone is not recommended for use in children below age 18 with schizophrenia due to a lack of data on efficacy.
Manic episodes in bipolar disorder
Adults
Risperidone (Amidrex OD-3) should be administered on a once daily schedule, starting with 2 mg risperidone. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Risperidone can be administered in flexible doses over a range of 1 to 6 mg per day to optimize each patient's level of efficacy and tolerability. Daily doses over 6 mg risperidone have not been investigated in patients with manic episodes.
As with all symptomatic treatments, the continued use of (Amidrex OD-3) must be evaluated and justified on an ongoing basis.
Elderly
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 to 2 mg twice daily. Since clinical experience in elderly is limited, caution should be exercised.
Pediatric population
Risperidone (Amidrex OD-3) is not recommended for use in children below age 18 with bipolar mania due to a lack of data on efficacy.
Persistent aggression in patients with moderate to severe Alzheimer's 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. Risperidone (Amidrex OD-3) should not be used more than 6 weeks in patients with persistent aggression in Alzheimer's dementia. During treatment, patients must be evaluated frequently and regularly, and the need for continuing treatment reassessed.
Conduct disorder
Children and adolescents from 5 to 18 years of age
For subjects 50 kg, a starting dose of 0.5 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.5 mg once daily not more frequently than every other day, if needed. The optimum dose is 1 mg once daily for most patients. Some patients, however, may benefit from 0.5 mg once daily while others may require 1.5 mg once daily. For subjects <50 kg, a starting dose of 0.25 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg once daily not more frequently than every other day, if needed. The optimum dose is 0.5 mg once daily for most patients. Some patients, however, may benefit from 0.25 mg once daily while others may require 0.75 mg once daily.
As with all symptomatic treatments, the continued use of Risperidone (Amidrex OD-3) must be evaluated and justified on an ongoing basis.
Risperidone (Amidrex OD-3) is not recommended in children less than 5 years of age, as there is no experience in children less than 5 years of age with this disorder.
Renal and hepatic impairment
Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than in adults with normal renal function. 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.
Risperidone (Amidrex OD-3) should be used with caution in these groups of patients.
Or as prescribed by the physician.

CONTRAINDICATIONS:
Hypersensitivity to the active substance or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Elderly patients with dementia
Overall mortality
Elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotics, including Risperidone. In placebo-controlled trials with Risperidone in this population, the incidence of mortality was 4.0% for Risperidone treated patients compared to 3.1% for placebo-treated patients. The odds ratio (95% exact confidence interval) was 1.21 (0.7, 2.1). The mean age (range) of patients who died was 86 years (range 67-100). Data from two large observational studies showed that elderly people with dementia who are treated with conventional antipsychotics are also at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Concomitant use with furosemide
In the Risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus 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 was observed in two of the four clinical trials. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.
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 or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. 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 (CVAE)
In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence (approximately 3-fold increased) of CVAEs, such as stroke (including fatalities) and transient ischemic attack in patients treated with Risperidone (Amidrex OD-3) compared with patients treated with placebo (mean age 85 years; range 73 to 97). The pooled data from six placebo-controlled studies in mainly elderly patients (>65 years of age) with dementia showed that CVAEs (serious and non-serious, combined) occurred in 3.3% (33/1009) of patients treated with risperidone and 1.2% (8/712) of patients treated with placebo. The odds ratio (95% exact confidence interval) was 2.96 (1.34, 7.50). The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Risperidone (Amidrex OD-3) should be used with caution in patients with risk factors for stroke.
The risk of CVAEs was significantly higher in patients with mixed or vascular type of dementia when compared to Alzheimer's dementia. Therefore, patients with other types of dementias than Alzheimer's should not be treated with risperidone.
Physicians are advised to assess the risks and benefits of the use of Risperidone (Amidrex OD-3) in elderly patients with dementia, taking into account risk predictors for stroke in the individual patient. Patients/caregivers should be cautioned to immediately report signs and symptoms of potential CVAEs such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems. All treatment options should be considered without delay, including discontinuation of risperidone.
Risperidone (Amidrex OD-3) should only be used short term for persistent aggression in patients with moderate to severe Alzheimer's dementia to supplement non-pharmacological approaches which have had limited or no efficacy and when there is potential risk of harm to self or others.
Patients should be reassessed regularly, and the need for continuing treatment reassessed.

Orthostatic hypotension
Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur, especially during the initial dose-titration period. Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment. Risperidone should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended. A dose reduction should be considered if hypotension occurs.

Leukopenia, neutropenia, and agranulocytosis
Events of leukopenia, neutropenia and agranulocytosis have been reported with antipsychotic agents, including Risperidone (Amidrex OD-3). Agranulocytosis has been reported very rarely (< 1/10,000 patients) during post-marketing surveillance.
Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of Risperidone (Amidrex OD-3) 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 neutropenia 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 neutropenia (absolute neutrophil count < 1 X 109/L) should discontinue Risperidone (Amidrex OD-3) and have their WBC followed until recovery.

Tardive dyskinesia/extrapyramidal symptoms (TD/EPS)
Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterized by rhythmical involuntary movements, predominantly of the tongue and/or face. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics should be considered.

Neuroleptic malignant syndrome (NMS)
Neuroleptic Malignant Syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics, including Risperidone (Amidrex OD-3), should be discontinued.

Parkinson's disease and dementia with Lewy bodies
Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including Risperidone (Amidrex OD-3), to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB). Parkinson's Disease may worsen with risperidone. Both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medicinal products; these patients were excluded from clinical trials. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Hyperglycemia and diabetes mellitus
Hyperglycemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment with Risperidone (Amidrex OD-3). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Association with ketoacidosis has been reported very rarely and rarely with diabetic coma. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any atypical antipsychotic, including Risperidone (Amidrex OD-3), should be monitored for symptoms of hyperglycemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus should be monitored regularly for worsening of glucose control.

Weight gain
Significant weight has been reported with Risperidone (Amidrex OD-3) use. Weight should be monitored regularly.

Hyperprolactinemia
Hyperprolactinemia is a common side-effect of treatment with Risperidone tablet. Evaluation of the prolactin plasma level is recommended in patients with evidence of possible prolactin-related side-effects (e.g. gynecomastia, menstrual disorders, anovulation, fertility disorder, decreased libido, erectile dysfunction, and galactorrhea).
Tissue culture studies suggest that cell growth in human breast tumors 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 tablet should be used with caution in patients with pre-existing hyperprolactinemia and in patients with possible prolactin-dependent tumors.

QT prolongation
QT prolongation has very rarely been reported post-marketing. As with other antipsychotics, caution should be exercised when risperidone is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia, or electrolyte disturbances (hypokalaemia, hypomagnesemia), as it may increase the risk of arrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.

Seizures
Risperidone (Amidrex OD-3) should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Priapism
Priapism may occur with Risperidone (Amidrex OD-3) treatment due to its alpha-adrenergic blocking effects.

Body temperature regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. Appropriate care is advised when prescribing Risperidone (Amidrex OD-3) 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 treatment 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 tumor.

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 Dosage and Administration).

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. 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 Risperidone (Amidrex OD-3) and preventative measures undertaken.

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 Risperidone (Amidrex OD-3).

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.

Children and adolescents
Before risperidone is prescribed to a child or adolescent with conduct disorder they should be fully assessed for physical and social causes of the aggressive behavior such as pain or inappropriate environmental demands.
The sedative effect of risperidone 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). 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 have not been adequately studied.
Because of the potential effects of prolonged hyperprolactinemia 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.
During treatment with risperidone regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.
For specific posology recommendations in children and adolescents see Dosage and Administration.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, such as class I antiarrhythmics (e.g., quinidine, disopyramide, procainamide), class III antiarrhythmics (e.g., amiodarone, sotalol), tricyclic antidepressant (i.e., amitriptyline), tetracyclic antidepressants (i.e., maprotiline), some antihistaminics, other antipsychotics, some antimalarials (i.e., quinine and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

Potential for Risperidone (Amidrex OD-3) to affect other medicinal products
Risperidone 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.
Risperidone (Amidrex OD-3) 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.
Clinically significant hypotension has been observed post-marketing with concomitant use of risperidone and antihypertensive treatment.
Risperidone (Amidrex OD-3) does not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

Potential for other medicinal products to affect Risperidone (Amidrex OD-3)
Carbamazepine has been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone. Similar effects may be observed with e.g. rifampicin, phenytoin and phenobarbital which also induce CYP3A4 hepatic enzyme as well as P-glycoprotein. When carbamazepine or other CYP3A4 hepatic enzyme/P-glycoprotein (P-gp) inducers are initiated or discontinued, the physician should re-evaluate the dosing of Risperidone (Amidrex OD-3).
Fluoxetine and paroxetine, CYP2D6 inhibitors, increase the plasma concentration of risperidone, but less so of the active antipsychotic fraction. It is expected that other CYP2D6 inhibitors, such as quinidine, may affect the plasma concentrations of risperidone in a similar way. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone (Amidrex OD-3).
Verapamil, an inhibitor of CYP3A4 and P-gp, increases the plasma concentration of risperidone.
Galantamine and donepezil do not show a clinically relevant effect on the pharmacokinetics of risperidone and on the active antipsychotic fraction.
Phenothiazines, tricyclic antidepressants, and some beta-blockers 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. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction.
The combined use of psychostimulants (e.g., methylphenidate) with Risperidone (Amidrex OD-3) in children and adolescents did not alter the pharmacokinetics and efficacy of Risperidone (Amidrex OD-3).
See Special Warnings and Precautions for use regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.
Concomitant use of oral Risperidone (Amidrex OD-3) with paliperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive active antipsychotic fraction exposure.

Pediatric population
Interaction studies have only been performed in adults.

Highly Protein-bound Drugs
When Risperidone is taken together with highly protein-bound drugs, there is no clinically relevant displacement of either drug 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.

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-hydroxyrisperidone.

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

Effect of other medicinal products on the pharmacokinetics of risperidone
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.

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.

PREGNANCY AND LACTATION:
Pregnancy
There are no adequate data from the use of risperidone in pregnant women. According to post marketing data reversible extrapyramidal symptoms in the neonate were observed following the use of risperidone during the last trimester of pregnancy. Consequently, newborns should be monitored carefully. Risperidone was not teratogenic in animal studies but other types of reproductive toxicity were seen. The potential risk for humans is unknown. Therefore, Risperidone (Amidrex OD-3) should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.
Lactation
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 in small quantities. There are no data available on adverse reactions in breastfeeding infants. Therefore, the advantage of breastfeeding should be weighed against the potential risks for the child.

Effects on ability to drive and use machines
Risperidone (Amidrex OD-3) can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

ADVERSE DRUG REACTIONS:
The most frequently reported adverse drug reactions (ADRs) (incidence 10%) are: Parkinsonism, headache, and insomnia.
The following are all the ADRs that were reported in clinical trials and post marketing. The following terms and frequencies are applied: very common (1/10), common (1/100 to <1/10), uncommon (1/1000 to <1/100), rare (1/10,000 to <1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available clinical trial data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse Drug Reactions by System Organ Class and Frequency.

Investigations:
Common: Blood prolactin increased, Weight increased; Uncommon: Electrocardiogram QT prolonged, Electrocardiogram abnormal, Blood glucose increased, Transaminases increased, White blood cell count decreased, Body temperature increased, Eosinophil count increased, Haemoglobin decreased, Blood creatinine phosphokinase increased; Rare: Body temperature decreased.
Cardiac disorders:
Common: Tachycardia; Uncommon: Atrioventricular block, Bundle branch block, Atrial fibrillation, Sinus bradycardia, Palpitations.
Blood and lymphatic system disorders:
Uncommon: Anemia, Thrombocytopenia; Rare: Granulocytopenia; Not known: Agranulocytosis.
Nervous system disorders:
Very common: Parkinsonism, Headache; Common: Akathisia, Dizziness, Tremor, Dystonia, Somnolence, Sedation, Lethargy, Dyskinesia; Uncommon: Unresponsive to stimuli, Loss of consciousness, Syncope, Depressed level of consciousness, Cerebrovascular accident, Transient ischemic attack, Dysarthria, Disturbance in attention, Hypersomnia, Dizziness postural, Balance disorder, Tardive dyskinesia, Speech disorder, Coordination abnormal, Hypoesthesia; Rare: Neuroleptic malignant syndrome, Diabetic coma, Cerebrovascular disorder, Cerebral ischemia, Movement disorder.
Eye disorders:
Common: Vision blurred Uncommon: Conjunctivitis, Ocular hyperemia, Eye discharge, Eye swelling, Dry eye, Lacrimation increased, Photophobia Rare: Visual acuity reduced, Eye rolling, Glaucoma.
Ear and labyrinth disorders:
Uncommon: Ear pain, Tinnitus
Respiratory, thoracic and mediastinal disorders
Common: Dyspnea, Epistaxis, Cough, Nasal congestion, Pharyngolaryngeal pain Uncommon: Wheezing, Pneumonia aspiration, Pulmonary congestion, Respiratory disorder, Rales, Respiratory tract congestion, Dysphonia Rare: Sleep apnea syndrome, Hyperventilation.
Gastrointestinal disorders:
Common: Vomiting, Diarrhea, Constipation, Nausea, Abdominal pain, Dyspepsia, Dry mouth, Stomach discomfort Uncommon: Dysphagia, Gastritis, Fecal incontinence, Fecaloma Rare: Intestinal obstruction, Pancreatitis, Lip swelling, Cheilitis.
Renal and urinary disorders:
Common: Enuresis Uncommon: Dysuria, Urinary incontinence, Pollakiuria
Skin and subcutaneous tissue disorders:
Common: Rash, Erythema Uncommon: Angioedema, Skin lesion, Skin disorder, Pruritus, Acne, Skin discoloration, Alopecia, Seborrheic dermatitis, Dry skin, Hyperkeratosis Rare: Dandruff.
Musculoskeletal and connective tissue disorders:
Common: Arthralgia, Back pain, Pain in extremity Uncommon: Muscular weakness, Myalgia, Neck pain, Joint swelling, Posture abnormal, Joint stiffness, Musculoskeletal chest pain Rare: Rhabdomyolysis.
Endocrine disorders:
Rare: Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders:
Common: Increased appetite, decreased appetite Uncommon: Anorexia, Polydipsia Very rare: Diabetic ketoacidosis Not known: Water intoxication.
Infections and infestations:
Common: Pneumonia, Influenza, Bronchitis, Upper respiratory tract infection, Urinary tract infection Uncommon: Sinusitis, Viral infection, Ear infection, Tonsillitis, Cellulitis, Otitis media, Eye infection, Localized infection, Acarodermatitis, Respiratory tract infection, Cystitis, Onychomycosis Rare: Otitis media chronic.
Vascular disorders:
Uncommon: Hypotension, Orthostatic hypotension, Flushing.
General disorders and administration site conditions:
Common: Pyrexia, Fatigue, Peripheral edema, Asthenia, Chest pain Uncommon: Face edema, Gait disturbance, Feeling abnormal, Sluggishness, Influenza like illness, Thirst, Chest discomfort, Chills Rare: Generalized edema, Hypothermia, Drug withdrawal syndrome, Peripheral coldness.
Immune system disorders:
Uncommon: Hypersensitivity Rare: Drug hypersensitivity Not known: Anaphylactic reaction.
Hepatobiliary disorders:
Rare: Jaundice.
Reproductive system and breast disorders:
Uncommon: Amenorrhea, Sexual dysfunction, Erectile dysfunction, Ejaculation disorder, Galactorrhea, Gynecomastia, Menstrual disorder, Vaginal discharge, Not known: Priapism.
Psychiatric disorders:
Very common: Insomnia Common: Anxiety, Agitation, Sleep disorder Uncommon: Confusional state, Mania, Libido decreased, Listlessness, Nervousness Rare: Anorgasmia, Blunted affect.

OVERDOSE AND TREATMENT:
In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of risperidone. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT-prolongation and convulsions have been reported. Torsade de Pointes has been reported in association with combined overdose of Risperidone (Amidrex OD-3) and paroxetine. In case of acute overdose, the possibility of multiple drug 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 only when drug intake was less than one hour before. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. There is no specific antidote to Risperidone (Amidrex OD-3). Therefore, 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, an anticholinergic medicinal product should be administered. Close medical supervision and monitoring should continue until the patient recovers.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT:
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

AVAILABILITY:
Alu/Alu Blister Pack x 10's (Box of 30's)

Registration No.: DRP-12013
Date of First Authorization: May 30, 2022
Date of Revision of Package Insert: October 10, 2023

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