JOSWE

Respal®

Risperidone (E.P)

QUALITATIVE & QUANTITATIVE COMPOSITION

The tablets may contain 1 mg, 2 mg or 4 mg risperidone (E.P).

CLINICAL PARTICULARS

Therapeutic indications

Respal is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Respal also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Posology and method of administration

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

Adults: Respal may be given once daily or twice daily. Patients should be titrated to 6 mg gradually over three days. Acute or chronic patients, should start with 2 mg/day Risperidone. The dosage should be increased to 4 mg on the second day and 6 mg on the third day. From then on the dosage can be maintained unchanged, or further individualized, if needed. The usual optimal dosage is 4 to 8 mg/day. However, some patients may benefit from lower doses. A slower titration phase may be medically appropriate. Doses above 10 mg/day have not been shown to be superior in efficacy to lower doses and may cause extrapyramidal symptoms. Since the safety of doses above 16 mg/day has not been evaluated, doses above this level should not be used. A benzodiazepine may be added to Risperidone when additional sedation is required.

Elderly: A starting dose of 0.5 mg b.i.d is recommended. This dosage can be individually adjusted with 0.5 mg b.i.d increments to 1 to 2 mg b.i.d. Risperidone is well tolerated by the elderly.

Contra-indications: This product is contraindicated in patients with a known hypersensitivity to Risperidone.

Special warnings and special precautions for use: Due to the alpha-blocking activity of Risperidone, (orthostatic) hypotension can occur, especially during the initial dose-titration period. Risperidone should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolaemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended (see posology and method of administration). A dose reduction should be considered if hypotension occurs. Drugs 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. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. Because Risperidone has a lower potential to induce extrapyramidal symptoms than classical neuroleptics, it should have a reduced risk of inducing tradive dyskinesia as compared to classical neuroleptics. If signs and symptoms of tradive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered. The Neuroleptic Malignant Syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels has been reported to occur with classical neuroleptics. In this event, all antipsychotic drugs, including Risperidone should be discontinued. It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and in patients with renal or liver insufficiency. Caution is also due when prescribing Risperidone to patients with Parkinson's disease since , theoretically, it might cause a deterioration of the disease. Classical neuroleptics are known to lower the seizure threshold. 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.

Atypical -second generation- antipsychotic medications (Olanzapine, Aripiprazole, Risperidone & Quetiapine) are not approved for the treatment of dementia-related psychosis because of the increased risk of death compared to placebo.

Interaction with other medicaments and other forms of interaction

The risk of using Risperidone in combination with other drugs have not been systemically evaluated. Given the primary CNS effects of Risperidone it should be used with caution in combination with other centrally acting drugs. Risperidone may antagonize the effect of levodopa and other dopamine-agonists. Carbamazepine has been shown to decrease the plasma levels of the active antipsychotic fraction of Risperidone. 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. Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of the antipsychotic fraction. Fluoxetine may increase the plasma concentration of risperidone but less so of the antipsychotic fraction. When Risperidone is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

Pregnancy and lactation: The safety of Risperidone for use during human pregnancy has not been established. Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed. No teratogenic effect of risperidone was noted in any study. Therefore, Risperidone should only be used during pregnancy if the benefits outweigh the risks. In animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. . It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk. Therefore, women receiving Risperidone should not breast feed.

Effects on ability to drive and use machines: Risperidone may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

Undesirable effects: Risperidone is generally well tolerated. In many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease. Adverse events observed in association with the use of Risperidone are listed below:

Common: Insomnia, agitation, anxiety, headache.

Less common: Somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, urinary incontinence, rhinitis, rash and other allergic reactions. Risperidone has a lower propensity to induce extrapyramidal symptoms than classical neuroleptics, however, in some cases the following extrapyramidal symptoms may occur: tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia. These are usually mild and are reversible upon dose reduction and/or administration of antiparkinson medication, if necessary. Occasionally, (orthostatic) hypotension, (reflex) tachycardia or hypertension have been observed following administration of Risperidone (see special warnings and special precautions for use). A mild fall in neutrophil and/or thrombocyte

count has been reported. Risperidone can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoa. Weight gain (see special warnings and special precautions for use), oedema and increased hepatic enzyme levels have been observed during treatment with Risperidone. As with classical neuroleptics, the following have occasionally been reported in psychotic patients: water intoxication due to either polydipsia or the syndrome of inappropriate secretion of antiduretic hormone (SIADH), tardive dyskinesia, neuroleptic malignant syndrome, body temperature disregulation and seizures.

Overdose:

Symptoms: In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. Overdosages of up to 360 mg have been reported. The available evidence suggests a wide safety margin. In overdose, rare cases of QT-prolongation have been reported. In case of acute overdosage, 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. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrythmias.There is no specific antidote to Risperidone. 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, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic properties: 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 neuroleptics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and effective symptoms of schizophrenia.

Pharmacokinetic properties: Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absorption is not affected by food and thus risperidone can be given with or without meals. Risperidone is metabolized by cytochrome P-450 IID6 to 9-hydroxy-risperidone which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. Another metabolic pathway of risperidone is N-dealkylation. 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. 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. Risperidone plasma concentrations are dose-proportional within the therapeutic dose range. Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and alpha1-acid glycoprotein. The plasma protein binding of risperidone is 88%, that of 9-hydroxy-risperidone is 77%. One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, risperidone plus 9-hydroxy-risperidone represent 35-45% of the dose. The reminder are inactive metabolites. A single-dose study showed higher active plasma concentrations and a slower elimination of risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency.

Storage Conditions:

Store below 30°C.

Don't use after the expiry date.

Presentation:

Respal 1: 20 film coated tablet

Respal 2: 20 film coated tablet

Respal 4: 20 film coated tablet

- A medicament is a product that affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who dispensed the medicament.
- The doctor and the pharmacist are experts in medicine.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep medicaments out of the reach of children.

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