Front

SEZODON™

(R i s p e r i d o n e)

Tablet

سیزوڈون

COMPOSITION:

Sezodon Tablet 1 mg:
Each film coated tablet contains:
Risperidone ..... 1 mg.

Product Specs.: USP

Sezodon Tablet 2 mg:
Each film coated tablet contains:
Risperidone ..... 2 mg.

Product Specs.: USP

Sezodon Tablet 4 mg:
Each film coated tablet contains:
Risperidone ..... 4 mg.

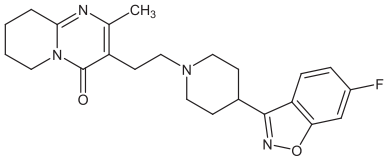
Product Specs.: USP

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Sezodon is not approved for use in patients with dementia-related psychosis.

DESCRIPTION:

SEZODON contains risperidone, an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)- 1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



CLINICAL PHARMACOLOGY:

Mechanism of Action: The mechanism of action of risperidone in schizophrenia is unclear. The drug's therapeutic activity in schizophrenia could be mediated through a combination of dopamine Type 2 (D2) and serotonin Type 2 (5HT2) receptor antagonism. The clinical effect from risperidone results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone (paliperidone). Antagonism at receptors other than D2 and 5HT2 may explain some of the other effects of risperidone.

Pharmacodynamics: Risperidone is a monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 (5HT2), dopamine Type 2 (D2), α1 and α2 adrenergic, and H1 histaminergic receptors. Risperidone showed low to moderate affinity (Ki of 47 to 253 nM) for the serotonin 5HT1C, 5HT1D, and 5HT1A receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10-5 M) for cholinergic muscarinic or β1 and β2 adrenergic receptors.

Pharmacokinetics:

Absorption: Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution. Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg twice daily). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Distribution: Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α1-acid glycoprotein. The plasma protein binding of risperidone is approximately 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance

Elimination:

Metabolism: Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers.

Excretion: Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of 14C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces. The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Special Populations:

Pregnancy: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including Sezodon, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at http://womensmentalhealth.org/clinical-andresearch-programs/pregnancyregistry/

Lactation: Limited data from published literature reports the presence of risperidone and its metabolite, 9-hydroxyrisperidone, in human breast milk at relative infant dose ranging between 2.3% and 4.7% of the maternal weight-adjusted dosage. There are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to risperidone (see Clinical Considerations). There is no information on the effects of risperidone on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Sezodon and any potential adverse effects on the breastfed child from Sezodon.

Geriatric use: In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients.

Pediatric: Schizophrenia The efficacy and safety of Sezodon in the treatment of schizophrenia were demonstrated in 417 adolescents, aged 13 to 17 years, in two short-term (6 and 8 weeks, respectively) doubleblind controlled. Additional safety and efficacy information was also assessed in one long-term (6-month) open-label extension study in 284 of these adolescent patients with schizophrenia. Safety and effectiveness of Sezodon in children less than 13 years of age with schizophrenia have not been established. Bipolar I Disorder The efficacy and safety of Sezodon in the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in 169 children and adolescent patients, aged 10 to 17 years, were demonstrated in one double-blind, placebo-controlled, 3-week trial. Safety and effectiveness of Sezodon in children less than 10 years of age with bipolar disorder have not been established.

Autistic disorder. The efficacy and safety of Sezodon in the treatment of irritability associated with autistic disorder were established in two 8-week, double-blind, placebo-controlled trials in 156 children and adolescent patients, aged 5 to 16 years. Additional safety information was also assessed in a long-term study in patients with autistic disorder, or in short- and long-term studies in more than 1200 pediatric patients with psychiatric disorders other than autistic disorder, schizophrenia, or bipolar mania who were of similar age and weight, and who received similar dosages of Sezodon as patients treated for irritability associated with autistic disorder. The pharmacokinetics of risperidone and 9-hydroxyrisperidone in children were similar to those in adults after correcting for the difference in body weight.

Geriatric use: Clinical studies of Sezodon in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg twice daily followed by careful titration. Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

Renal impairment: In patients with moderate to severe (Clcr 59 to 15 mL/min) renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60%, compared to young healthy subjects. Sezodon doses should be reduced in patients with renal disease.

Hepatic impairment: While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α1-acid glycoprotein. Sezodon doses should be reduced in patients with liver disease.

Patients with parkinson's disease or lewy body dementia: Patients with Parkinson's Disease or Dementia with Lewy Bodies can experience increased sensitivity to Sezodon. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

INDICATIONS AND USAGE:

Schizophrenia: Sezodon (risperidone) is indicated for the treatment of schizophrenia. Efficacy was established in 4 short-term trials in adults, 2 short-term trials in adolescents (ages 13 to 17 years), and one long-term maintenance trial in adults.

Bipolar mania monotherapy: Sezodon is indicated for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder. Efficacy was established in 2 short-term trials in adults and one short-term trial in children and adolescents (ages 10 to 17 years).

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Adjunctive therapy: Sezodon adjunctive therapy with lithium or valproate is indicated for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder. Efficacy was established in one short-term trial in adults.

Irritability associated with autistic disorder: Sezodon is indicated for the treatment of irritability associated with autistic disorder, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. Efficacy was established in 3 short-term trials in children and adolescents (ages 5 to 17 years).

	Initial Dose	Titration (Increments)	Target Dose	Effective Dose Range
Schizophrenia: adults	2 mg / day	1 to 2 mg daily	4 to 8 mg daily	4 to 16 mg / day
Schizophrenia: adolescents	0.5 mg / day	0.5 to 1 mg daily	3 mg / day	1 to 6 mg / day
Bipolar mania adults	2 to 3 mg / day	1 mg daily	1 to 6 mg / day	1 to 6 mg / day
Bipolar mania: children and adolescents	0.5 mg / day	0.5 to 1 mg daily	2.5 mg / day	1 to 6 mg / day
Irritability in austistic disorder:	0.25 mg Can increase to 0.5 mg by Day 4: (body weight less than 20 kg) 0.5 mg Can increase to 1 mg by Day 4: (body weight greater than or equal to 20 kg)	After Day 4, at intervals of> 2 weeks: 0.25 mg (body weight less thank 20 kg) 0.5 mg: (body weight greater than or equal to 20 kg)	0.5 mg: (body weight greater than or equal to 20 kg) 1 mg: (body weight greater than or equal to 20 kg)	0.5 to 3 mg / day

Schizophrenia

Adults: Usual Initial Dose Sezodon can be administered once or twice daily. Initial dosing is 2 mg per day. May increase the dose at intervals of 24 hours or greater, in increments of 1 to 2 mg per day, as tolerated, to a recommended dose of 4 to 8 mg per day. In some patients, slower titration may be appropriate. Efficacy has been demonstrated in a range of 4 mg to 16 mg per day. However, doses above 6 mg per day for twice daily dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are generally not recommended. In a single study supporting once-daily dosing, the efficacy results were generally stronger f or 8 mg than for 4 mg. The safety of doses above 16 mg per day has not been evaluated in clinical trials.

Maintenance treatment: While it is unknown how long a patient with schizophrenia should remain on Sezodon, the effectiveness of Sezodon 2 mg per day to 8 mg per day at delaying relapse was demonstrated in a controlled trial in adult patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. Both adult and adolescent patients who respond acutely should generally be maintained on their effective dose beyond the acute episode. Patients should be periodically reassessed to determine the need for maintenance treatment.

Adolescents: The initial dose is 0.5 mg once daily, administered as a single-daily dose in the morning or evening. The dose may be adjusted at intervals of 24 hours or greater, in increments of 0.5 mg or 1 mg per day, as tolerated, to a recommended dose of 3 mg per day. Although efficacy has been demonstrated in studies of adolescent patients with schizophrenia at doses between 1 mg to 6 mg per day, no additional benefit was observed above 3 mg per day, and higher doses were associated with more adverse events. Doses higher than 6 mg per day have not been studied. Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

Switching from other antipsychotics: There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to Sezodon, or treating patients with concomitant antipsychotics.

Bipolar Mania:

Adults: The initial dose range is 2 mg to 3 mg per day. The dose may be adjusted at intervals of 24 hours or greater, in increments of 1 mg per day. The effective dose range is 1 mg to 6 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3 week) anti-manic efficacy was demonstrated in a flexible dosage range of 1 mg to 6 mg per day. Sezodon doses higher than 6 mg per day were not studied.

Pediatrics: The initial dose is 0.5 mg once daily, administered as a single-daily dose in the morning or evening. The dose may be adjusted at intervals of 24 hours or greater, in increments of 0.5 mg or 1 mg per day, as tolerated, to the recommended target dose of 1 mg to 2.5 mg per day. Although efficacy has been demonstrated in studies of pediatric patients with bipolar mania at doses between 0.5 mg and 6 mg per day, no additional benefit was observed above 2.5 mg per day, and higher doses were associated with more adverse events. Doses higher than 6 mg per day have not been studied. Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

Maintenance therapy: There is no body of evidence available from controlled trials to guide a clinician in the longerterm management of a patient who improves during treatment of an acute manic episode with Sezodon. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of Sezodon in such longer-term treatment (i.e., beyond 3 weeks). The physician who elects to use Sezodon for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Irritability Associated with Autistic Disorder – Pediatrics (Children and Adolescents): The dosage of Sezodon should be individualized according to the response and tolerability of the patient. The total daily dose of Sezodon can be administered once daily, or half the total daily dose can be administered twice daily. For patients with body weight less than 20 kg, initiate dosing at 0.25 mg per day. For patients with body weight greater than or equal to 20 kg, initiate dosing at 0.5 mg per day. After a minimum of four days, the dose may be increased to the recommended dose of 0.5 mg per day for patients less than 20 kg and 1.0 mg per day for patients greater than or equal to 20 kg. Maintain this dose for a minimum of 14 days. In patients not achieving sufficient clinical response, the dose may be increased at intervals of 2 weeks or greater, in increments of 0.25 mg per day for patients less than 20 kg, or increments of 0.5 mg per day for patients greater than or equal to 20 kg. The effective dose range is 0.5 mg to 3 mg per day. No dosing data are available for children who weigh less than 15 kg. Once sufficient clinical response has been achieved and maintained, consider gradually lowering the dose to achieve the optimal balance of efficacy and safety. The physician who elects to use Sezodon for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient. Patients experiencing persistent somnolence may benefit from a once-daily dose administered at bedtime or administering half the daily dose twice daily, or a reduction of the dose.

Dosing in patients with severe renal or hepatic impairment: For patients with severe renal impairment (Clcr< 30 mL/min) or hepatic impairment (10-15 points on Child Pugh System), the initial starting dose is 0.5 mg twice daily. The dose may be increased in increments of 0.5 mg or less, administered twice daily. For doses above 1.5 mg twice daily, increase in intervals of one week or greater.

Dose adjustments for specific drug interactions: When Sezodon is co-administered with enzyme inducers (e.g., carbamazepine), the dose of Sezodon should be increased up to double the patient's usual dose. It may be necessary to decrease the Sezodon dose when enzyme inducers such as carbamazepine are discontinued. Similar effect may be expected with co-administration of Sezodon with other enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital). When fluoxetine or paroxetine is co-administered with Sezodon, the dose of sezodon should be reduced. The Sezodon dose should not exceed 8 mg per day in adults when co-administered with these drugs. When initiating therapy, Sezodon should be titrated slowly. It may be necessary to increase the Sezodon dose when enzyme inhibitors such as fluoxetine or paroxetine are discontinued.

CONTRAINDICATIONS:

Sezodon is contraindicated in patients with a known hypersensitivity to either risperidone or paliperidone, or to any of the excipients in the Sezodon formulation. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported in patients treated with risperidone and in patients treated with paliperidone. Paliperidone is a metabolite of risperidone.

WARNINGS AND PRECAUTIONS:

Increased Mortality in Elderly Patients with Dementia-Related Psychosis Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. 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. In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus Sezodon when compared to patients treated with Sezodon alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed.

ADVERSE REACTIONS:

The most common adverse reactions in clinical trials (>5% and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain.

DRUG INTERACTIONS:

Carbamazepine and other enzyme inducers decrease plasma concentrations of risperidone. Increase the Sezodon dose up to double the patient's usual dose. Titrate slowly. Fluoxetine, paroxetine, and other CYP 2D6 enzyme inhibitors increase plasma concentrations of risperidone. Reduce the initial dose. Do not exceed a final dose of 8 mg per day of Sezodon.

INSTRUCTIONS:

- Store below 30°C.
- Protect from heat, sunlight and moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

Sezodon Tablet 1 mg	:	Pack of 1 x 10 tablets.
Sezodon Tablet 2 mg	:	Pack of 1 x 10 tablets.
Sezodon Tablet 4 mg	:	Pack of 1 x 10 tablets.

ہدایات:

۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

گرمی، دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATIONS PLEASE CONTACT:

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CCL Pharmaceuticals (Pvt.) Ltd.
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