PRODUCT MONOGRAPH

PR RIVA-OXAZEPAM

(Oxazepam, USP)

10 mg, 15 mg and 30 mg Tablets

ANXIOLYTIC-SEDATIVE

Laboratoire Riva Inc.
660 Industriel Blvd.
Blainville, Quebec, Canada.
J7C 3V4
www.labriva.com

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THERAPEUTICA CLASSIFICATION

ANXIOLYTIC-SEDATIVE

ACTION:

RIVA-OXAZEPAM, (Oxazepam Tablets), a benzodiazepine, is a Central Nervous System (CNS) depressant. Oxazepam possesses anxiolytic and sedative properties of value in the symptomatic relief of manifest anxiety and tension states in psychoneurotic patients.

Following an oral dose, peak plasma levels of oxazepam are reached in 3-4 hours and its half-life is estimated to be approximately 11 hours. Oxazepam is conjugated to a pharmacologically inactive glucuronide. Excretion is primarily in the urine, as the glucuronide, with the faeces containing approximately 21% of unchanged drug. After the administration of a single oral dose, most of the drug is excreted within 48 hours.

Plasma binding of oxazepam in normal subjects is approximately 89%.

INDICATIONS:

RIVA-OXAZEPAM, (Oxazepam Tablets), is useful for the short-term symptomatic relief of excessive anxiety and tension in patients with anxiety neurosis.

Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

RIVA-OXAZEPAM also may be of value in relieving the symptoms of acute alcoholic withdrawal, including acute agitation and impending delirium tremens.

CONTRAINDICATIONS:

RIVA-OXAZEPAM, (Oxazepam Tablets), is contraindicated in patients with previous history of hypersensitivity reactions to oxazepam, infants, patients with a history of glaucoma and patients with myasthenia gravis.

WARNING AND PRECAUTIONS:

Use in Pregnancy: Several studies have suggested increased risk of congenital malformations associated with the use of anxiolytic-sedative agents such as diazepam, chlordiazepoxide and meprobamate during the first trimester of pregnancy. Oxazepam, a benzodiazepine derivative, has not been studied adequately to determine whether it too, may be associated with an increased risk of fetal abnormality. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. If the drug is prescribed to a woman of child-bearing potential, she should be warned to contact her physician regarding discontinuation of the drug if she intends to become or suspects that she is pregnant.

In the Elderly: In elderly or debilitated patients or those with organic brain syndromes, even low doses of oxazepam may produce symptoms of CNS depression such as: ataxia, over sedation, or other possible adverse reactions. Caution should be exercised in administering oxazepam to these patients. Oxazepam should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac complications. This is particularly true in the elderly patient. Treatment should be initiated with very low initial doses and increments, if required, should be made gradually in order to avoid oversedation or neurological impairment.

Use in Children: Oxazepam is not indicated in children under 6 years or age. The dosage for children 6-12 years of age has not been established.

In Emotional Disorders: Oxazepam is not recommended in severely depressed or psychotic patients. Caution is required in the treatment of patients with evidence of depression who may develop suicidal tendencies. Oxazepam should not be used in patients with non-pathologic anxiety with characterological and personality disorders or those with obsessive-compulsive neurosis.

Psychotic patients may react with excessive stimulation when treated with this drug, and oxazepam should not be used in patients suspected of having a psychotic underlay to their anxiety.

Dependence Liability: Tolerance or dependence on oxazepam may develop. Therefore, the drug should not be administered to individuals prone to drug abuse and the dose should not be increased if tolerance develops. Since withdrawal symptoms may occur, oxazepam should not be discontinued abruptly in patients who may have received the drug in large doses for prolonged periods of time.

Potentiation of Drug Effects: Patients should be advised to abstain from alcohol and other CNS depressant drugs during treatment with oxazepam. Phenothiazines, barbiturates, monoamine oxidase inhibitors and other psychotropic drugs might potentiate the action of oxazepam and usually should not be given concurrently.

Epileptic Patients: Since oxazepam may occasionally exacerbate grand mal seizures, caution is required when it is used in epileptic patients and an adjustment may be necessary in their anticonvulsive medication. Abrupt withdrawal of oxazepam in these patients should be avoided.

General Precautions: Since patients may become excessively sedated or drowsy while taking oxazepam, they should be warned not to undertake activities requiring mental alertness, judgment and physical coordination, such as driving or operating machinery, particularly in the early phases of dosage adjustment.

Caution should be employed when oxazepam is administered to patients with impaired hepatic or renal function, and blood counts and liver function tests should be performed regularly in patients receiving large doses or therapy for a prolonged period.

ADVERSE REACTIONS:

As with other benzodiazepines, adverse reactions most commonly observed include: drowsiness, dizziness, fatigue and ataxia.

Other adverse reactions reported are: headache, vertigo, diplopia, blurred vision, weakness, hypotension, impairment of memory, slurred speech, sluggish response, hypoactivity, dysarthria, depression, euphoria, anorexia, nausea, constipation, incontinence or urinary retention, changes in libido, urticaria, skin rashes, generalized exfoliative dermatitis, tremors, edema and changes in the EEG pattern (increased fast activity).

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Drug dependence after withdrawal, abstinence symptoms such as anxiety, muscle twitches, convulsions or delirium with psychotic manifestations may occur.

Release of hostility and other paradoxical reactions such as irritability, excitability, rage, hallucination, increased muscle spasticity and sleep disturbances may occur with oxazepam. Leukopenia, jaundice, hypersensitivity reactions and abnormal kidney and liver function tests have been reported with this class of drugs.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice

SYMPTOMS AND TREATMENT OF OVERDOSAGE:

Symptoms of overdosage with oxazepam include somnolence, muscle weakness, ataxia, dysarthria and particularly in children, paradoxical excitement may occur. In more severe cases, diminished reflexes, confusion and coma may ensue. Fatalities rarely occur except when other drugs, alcohol or aggravating factors are involved. Hypotension and respiratory depressions are not found frequently unless other drugs have been associated.

There is no specific antidote. Gastric lavage performed early after ingestion of the drug may be beneficial. Management consists of supportive measures and close supervision and monitoring. Cardiovascular and central nervous system stimulants may be used, if necessary. Although oxazepam as a relatively long half-life, the use of dialysis is of questionable value.

For management of a suspected drug overdose, contact your regional poison control centre immediately.

DOSAGE AND ADMINISTRATION:

As with other benzodiazepines, the dosage of oxazepam must be individualized and carefully titrated in order to avoid excessive sedation or mental and motor impairment. As with other anxiolytic-sedatives, short courses of treatment should usually be the rule for the symptomatic relief of excessive anxiety and the initial course of treatment should not last longer than one week without re-assessment of the need for a limited extension. If necessary, drug dosage can be adjusted after one week of treatment. Initially, not more than one week's supply of the drug should be provided and automatic prescription renewals should not be allowed. Subsequent prescriptions, when required, should be limited to short courses of therapy.

The adult dosage is 30-120 mg daily, in 3 divided doses, according to severity of symptoms and patient response. Initiate treatment by lower dose and increase gradually.

In Elderly and Debilitated Patients: The recommended dosage is 5 mg once or twice daily, as tolerated. Initiate treatment always by the lowest dose and increase gradually as needed and tolerated.

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DOSAGE FORMS:

10 mg - Light yellow, round, flat-faced tablet with "R" score "10" on one side and plain on the other side.
15 mg - Yellow, round, flat-faced tablet with "R" score "15" on one side and plain on the other side.
30 mg - White, round, flat-faced tablet with "R" score "30" on one side and plain on the other side.

COMPOSITION

RIVA-OXAZEPAM 10 & 15 mg: ln addition to oxazepam, each tablet contains the nonmedicinal ingredients D & C Yellow #10 Aluminium Lake, FD&C Yellow # 6 Aluminium Lake, lactose, magnesium stearate, microcrystalline cellulose and starch.

RIVA-OXAZEPAM 30 mg: ln addition to oxazepam, each tablet contains the nonmedicinal ingredients lactose, magnesium stearate, microcrystalline cellulose and starch.

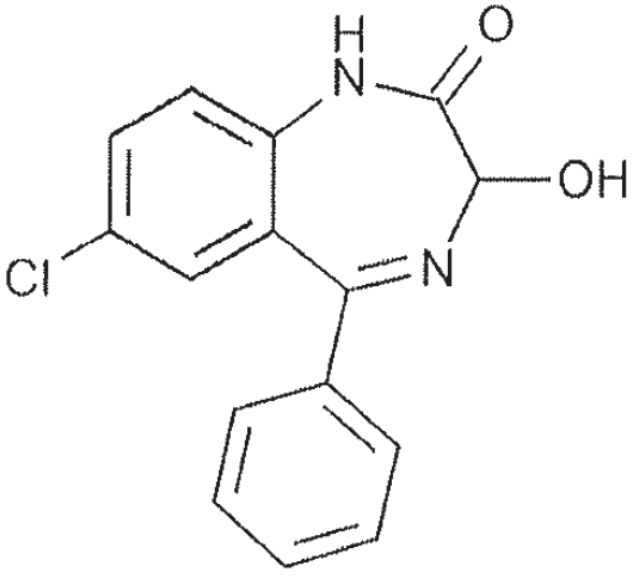
STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature 15-30°C.

AVAILABILITY

All strengths available in bottles of 500 tablets.

CHEMISTRY AND PHARMACOLOGY:
Oxazepam is 7-chloro-l,3-dihydro-3-hydroxy-5-phenyl-2H-l.4-benzodiazepin-2-one and has the following structural formula:



PHARMACOLOGY:
Oxazepam is a benzodiazepine derivative with a wide spectrum of pharmacological effects upon the central nervous system, qualitatively similar to chlordiazepoxide and diazepam, but less potent.

In tests in laboratory animals, oxazepam has weak activity as an antifighting, anticonvulsant agent and also as a muscle relaxant. At the highest dose treated, 40 mg/kg, p.o., oxazepam reduced only moderately the activity of aggressive behavior of cynomolgus monkeys.

Oxazepam depressed discreet trial and continuous avoidance behavior in rats but was inactive in squirrel monkeys at a dose of 20 mg/kg, p.o. At lower doses, however, oxazepam produced an increase in the rate of avoidance responding i.e., stimulation.

In continuous avoidance tests, oxazepam prevented the stimulant effect of tetrabenazine in iproniazid - pretreated rats at a M.E.D. (medium effective dose) of 1.0 mg/kg i.p., which had no behavioral effect in normal rats. However, its potency was 20 times less than that of diazepam (M.E.D.-0.05 mg/kg i.p.).

When administered to rats at a dose of 10 mg/kg i.p., oxazepam produced attenuation of conflict behavior without a considerable reduction in the inter-trial response rate usually due to ataxia and motor incoordination.

The anticonvulsant activity of oxazepam in mice was found to be in the same degree of potency as that of diazepam and greater than that shown by chlordiazepoxide using either pentylenetetrazol or maximal electroshock as agonists.

Utilization of suppression of the polysynaptic linguomandibular reflex in immobilized cats as a

measure of central muscle relaxant effect demonstrated that oxazepam has less relaxant activity than diazepam and was about equipotent to chlordiazepoxide.

TOXICOLOGY:

Acute Toxicity: The oral LD_{50} in mice and rats, is greater than 5000 mg/kg.

Subacute Toxicity: Fatty metamorphosis of the liver occurred in rats in six-week studies with oxazepam administered in the diet at 0.5%. No liver necrosis or fibrosis occurred.

Dogs were treated for 4 weeks with doses of 480 and 960 mg/kg p.o. Two out of eight dogs at the high dose died with evidence of circulatory collapse.

Chronic Toxicity: Oxazepam was administered to rats in the diet at levels of 0, 0.015, 0.03, 0.06 and 0.12% in a 55-56 week study. Increase in the organ-body weight ratio were seen for the liver at the 3 upper levels (0.03, 0.06 and 0.12%). An increase in kidney weight occurred in males at the two upper levels. The changes were considered reversible.

REPRODUCTION STUDIES:

In mice, reproduction studies in which oxazepam was administered orally at doses of 25, 50 and 100 mg/ kg/day on days 7 through 14 of the gestation period showed no effect on mortality, litter size and in the number of deaths of the young in the first few days after birth.

In rats on two consecutive matings, the percent of females conceiving and giving birth to viable young was 50% and 55% compared to an average of 87.5% for the controls, when oxazepam was administered in the diet at 0.06%. The average litter size for this same group for the two phases was 9.8 and 11.6 and 11.9 for controls. No gross abnormalities were detected in the offspring.

REFRENCES:

Product Monograph: OXPAM TABLETS (Oxazepam, USP) by Biomed 2002 Inc. Date of Revision: October 3, 2014, Control No.: 177866.