New Zealand Data Sheet

1. PRODUCT NAME

Ox-Pam 10mg Tablet
Ox-Pam 15mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ox-Pam 10mg tablet contains 10mg oxazepam
Ox-Pam 15mg tablet contains 15mg oxazepam
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ox-Pam 10mg tablet: white, round, flat tablet with a diameter of 7.94mm and a bisecting score on one side.

Ox-Pam 15mg tablet: yellow, round, flat tablet with a diameter of 7.94mm and a bisecting score on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Oxazepam is indicated in adults for:

- Short-term relief (2 – 4 weeks) of anxiety, especially anxiety associated with mental depression.
- Relief of acute alcohol withdrawal symptoms.

4.2. Dose and method of administration

Dose, frequency of administration and duration of therapy should be individualised according to patient response. All patients should be monitored and therapy should be re-evaluated before any extension of treatment.

As an anxiolytic, the lowest effective dose should be employed, for the shortest time possible. Dosage regimes should not exceed beyond 4 weeks. Treatment should be withdrawn gradually to minimise possible withdrawal symptoms.

<u>Dose</u>
Adults:
10mg to 30mg three to four times daily.

Elderly/debilitated population:
10mg three to four times daily.

Children:
Not recommended for children.

Method of Administration
For oral administration

4.3. Contraindications

- Known hypersensitivity to benzodiazepines or any other ingredient in the tablet
- Acute alcohol intoxication
- Coma
- Shock
- Acute closed-angle glaucoma
- Hepatic function impairment (minimal risk)
- Hyperkinesia
- Hypoalbuminaemia, intolerance to the benzodiazepine prescribed
- Severe mental depression
- Myasthenia gravis
- Organic brain disorders
- Psychoses
- Pulmonary disease
- Renal function impairment
- Suicidal tendencies

4.4. Special warnings and precautions for use

Dependence and withdrawal

Prolonged use of oxazepam may lead to development of dependence of the barbiturate-alcohol type. This type of dependence is characterised by: a strong need to continue taking the medicine associated with a tendency to increase the dose, a psychic dependence on the effects of the medicine and a physical dependence on the effects of the medicine for maintenance of homeostasis. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse or in patients with marked personality disorders. Regular monitoring in such patients is essential.

Benzodiazepines should be prescribed for short periods only. Continuous long-term use is not recommended.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency. More serious manifestations of withdrawal are more common in patients who have received excessive doses over a prolonged period, or in patients who have been dependent on alcohol or other narcotic drugs in the past.

Withdrawal symptoms may occur with abrupt cessation of benzodiazepines following normal therapeutic doses given for short periods of time. Following prolonged use at therapeutic doses, withdrawal from the medication should be gradual to reduce the risk of withdrawal reactions. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Patients should be advised to consult their physician before either increasing the dose or abruptly discontinuing the medication.

A sudden discontinuation of benzodiazepines may result in convulsion. Particular care should be taken in patients with epilepsy, and other patients who have had a history of seizures, alcohol or drug dependence.

Rebound phenomenon has been described in the context of benzodiazepine use. Rebound insomnia, anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased.

In some cases, patients taking Benzodiazepines have developed protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months.

Abuse

Abuse of benzodiazepines has been reported. Benzodiazepines should be used in caution in patients with a history of alcohol or drug abuse, dependence on CNS depressants, those known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative.

Before prescribing and throughout treatment, assess each patient's risk for abuse, misuse, and addiction. Use of benzodiazepines, particularly patients at elevated risk, necessitates counselling about the risks and proper use. Repeat prescriptions should not be given without medical review.

Tolerance

Tolerance to benzodiazepines may develop from continued therapy. There is evidence that tolerance develops to the sedative effect of benzodiazepines.

Psychiatric reaction

Abnormal psychological reactions to benzodiazepines have been reported. Rare behavioural effects include paradoxical aggressive outbursts, excitement, confusion and the uncovering of depression with suicidal tendencies.

Extreme caution should be used in prescribing benzodiazepines to patients with personality disorders as disinhibiting effects may manifest in various ways. Suicide may be precipitated in patients who are depressed, aggressive behaviour towards self and others may also be precipitated.

Risks from concomitant use with opioids

Concomitant use of benzodiazepines, including oxazepam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe oxazepam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation oxazepam is used with opioids *(see Section 4.5 Interactions with other medicines and other forms of interaction)*.

Specific patient groups

Elderly

Caution is required when giving oxazepam to elderly or debilitated patients. Elderly patients are usually more sensitive to the CNS effects of benzodiazepines. It is recommended that dosage be limited to the smallest effective dose and increased gradually *(see section 4.2)*, if necessary, to decrease the possibility of development of ataxia, dizziness and over sedation.

Paediatric population

Children should not be given oxazepam *(see section 4.2).* Children, especially the very young, are usually more sensitive to the CNS effects of benzodiazepines. Prolonged CNS depression may be produced in the neonate because of inability to biotransform the benzodiazepine into inactive metabolites.

Care should also be exercised in patients with arteriosclerosis, renal, hepatic or respiratory dysfunction *(see section 4.3 Contraindications)*.

Care may be needed in epileptic patients, in whom the initiation or abrupt withdrawal of benzodiazepine therapy has occasionally provoked seizures.

Oxazepam may enhance the effects of other CNS depressants and alcohol, therefore should be used with extreme caution in patients with a history of alcohol or drug abuse.

4.5. Interaction with other medicines and other forms of interaction

Oxazepam has the potential to interact with the following:

Other addictive medications

Prolonged concurrent use may increase the risk of habituation.

Alcohol and CNS depression-producing medications

Increased CNS depressant effects.

Opioids

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation (*see section 4.4).*

Tricyclic antidepressants
Possible increase of CNS depressant effects.

Carbamazepine
Causes decreased metabolism of hepatically metabolised benzodiazepines.

Levodopa
Concurrent use may decrease the therapeutic effects of levodopa.

Magnesium sulphate, parenteral
Concurrent use may potentiate the CNS depressant effects of benzodiazepine hypnotics.

Probenecid
Concurrent use may impair glucuronide conjugation of oxazepam resulting in increased effects and possibly excessive sedation.

Zidovudine
Concurrent use may competitively inhibit hepatic glucuronisation and decrease the clearance of zidovudine, thereby potentiating the toxicity of zidovudine.

Tests interference- Glucose test
Oxazepam may give a positive result for the laboratory estimation of glucose.

4.6. Fertility, pregnancy and lactation

Pregnancy
Oxazepam may cross the placenta. There may be a risk of congenital malformations during the first trimester of pregnancy. Risk-benefit must be carefully considered.
Chronic usage of benzodiazepines during pregnancy may cause physical dependence with resulting withdrawal symptoms in the neonate. Use of benzodiazepine hypnotics during the last weeks of pregnancy may result in neonatal CNS depression.

Use of benzodiazepines just prior to or during labour may cause neonatal flaccidity. Furthermore, benzodiazepines may cause hypotonia, respiratory depression and hypothermia in the newborn infant if used in high doses during labour.
Withdrawal symptoms in newborn infants have been reported with prolonged use of this class of drugs.

Breast-feeding
Oxazepam may be excreted in breast milk. Since neonates metabolise benzodiazepines more slowly than adults and accumulation of the benzodiazepine and/or its metabolites may occur, use by nursing mothers may cause sedation, and

possibly feeding difficulties and weight loss in the infant. If oxazepam is required by a nursing mother, an alternate method of infant feeding should be used.

Fertility

Female mice fed diets containing 0.05% or 0.75% oxazepam were reported to exhibit significant decreases in the frequency of vaginal oestrus.

4.7. Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.

Patients should be advised that, like all medicines of this type, Ox-Pam may modify their performance at skilled tasks to a varying degree depending on dosage, administration and individual susceptibility. Patients should be further advised that alcohol may intensify any impairment and should be avoided during treatment.

4.8. Undesirable effects

Blood and lymphatic system disorders

Blood dyscrasias, leucopenia.

Psychiatric disorders

Mild drowsiness*, disorientation, dreams, †nightmares, lethargy, amnesia (see below), mild excitatory effects with stimulation of affect**, numbed emotions, reduced alertness, †restlessness, †agitation, †irritability, †delusions, †rages, †psychoses, †inappropriate behaviour, behavioural adverse effects including paradoxical †aggressive outbursts, excitement, †hallucinations, confusion, uncovering of depression with suicidal tendencies. ***

†These are more likely to occur in children and the elderly.

Nervous system disorders

Dizziness, light-headedness*, ataxia, vertigo, headache, syncope, slurred speech, tremor, dysarthria.

Eye disorders

Blurred vision, double vision.

Vascular disorders

Hypotension.

Gastrointestinal disorders
Nausea, salivation changes, gastrointestinal disturbances.

Hepatobiliary disorders
Increased liver enzymes, jaundice.

Skin and subcutaneous tissue disorders
Minor diffuse skin rashes (morbilliform, urticarial and macropapular).

Musculoskeletal and connective tissue disorders
Muscle weakness.

Renal and urinary disorders
Incontinence, urinary retention.

Reproductive system and breast disorders
Altered libido.

General disorders and administration site conditions
Fever, oedema, fatigue.

* Commonly seen in the first few days of therapy. If this becomes troublesome dosage should be reduced.
** Reported in psychiatric patients and usually occur within the first few weeks of therapy.
*** Extreme caution should therefore be exercised in prescribing benzodiazepines to patients with personality disorders.

Amnesia
Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

Dependence
When used at the appropriate recommended dosage for short term treatment of anxiety the dependence potential of oxazepam is low. However, the risk of dependence increases with higher doses and longer-term use and is further increased in patients with a history of alcoholism, drug abuse or in patients with marked personality disorders.

Withdrawal

As with all benzodiazepines, withdrawal may be associated with physiological and psychological symptoms including depression, persistent tinnitus, involuntary movements, paraesthesia, perceptual changes, confusion, convulsions, muscle cramps, abdominal cramps and vomiting.

Symptoms such as anxiety, depression, headache, insomnia, tension and sweating have been reported following abrupt discontinuation of benzodiazepines and these symptoms may be difficult to distinguish from the original symptoms of anxiety.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

Symptoms

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, ataxia, dysarthria, nystagmus and lethargy, in more serious cases, symptoms may include hypotension, respiratory depression and rarely coma.

As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol).

Treatment

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Following overdose with oral benzodiazepines activated charcoal should be considered to reduce absorption, provided they are not too drowsy. Special attention should be paid to respiratory and cardiovascular functions in intensive care. Supportive measures are indicated depending on the patients clinical state. The patient is likely to sleep and therefore a clear airway should be maintained.

Dialysis is of little or no value in poisoning by benzodiazepines.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group: Psycholeptics, anxiolytics, benzodiazepine derivatives
ATC code: N05BA

Mechanism of action

Oxazepam is a benzodiazepine compound having anti-convulsant, sedative, muscle relaxant and amnesic properties. In general, benzodiazepines act as depressants of the central nervous system (CNS), producing all levels of CNS depression from mild sedation to hypnosis to coma depending on dose.

The precise sites and mechanisms of action have not been completely established. Although various mechanisms of action have been proposed, it is believed that benzodiazepines enhance or facilitate the inhibitory neurotransmitter action of gamma-aminobutyric acid (GABA), which is one of the major inhibitory neurotransmitters in the brain and mediates both pre- and post-synaptic inhibition in all regions of the CNS, following interaction between the benzodiazepine and a specific neuronal membrane receptor.

Benzodiazepines reportedly act as agonists at the benzodiazepine receptors, which have been shown to form a component of the benzodiazepine-GABA-receptor-chloride ionophore complex. Most anxiolytics appear to act through at least one of the components of this complex to enhance the inhibitory action of GABA. Other actions of benzodiazepines, such as sedative, anticonvulsant and muscle relaxant effects, may be mediated through a similar mechanism, although different receptor subtypes may be involved.

5.2. Pharmacokinetic properties

Oxazepam is well absorbed from the gastrointestinal tract and reaches peak plasma concentrations about 2 hours after ingestion.

Oxazepam is about 85-97% bound to plasma protein and has been reported to have an elimination half-life ranging from about 3 to 21 hours. It is largely metabolised to the inactive glucuronide which is excreted in the urine.

After single oral doses, onset of action depends largely upon absorption rate. After multiple doses, effects depend partly upon rate and extent of medicine accumulation, which in turn relate to elimination half-life and clearance.

During multiple-dosage, accumulation is minimal and a steady-state plasma concentration is usually attained within a few days after initiation of therapy. Following termination of treatment, blood concentrations are subclinical in 24 hours and return rapidly to zero (in about four days).

5.3. Preclinical safety data

Studies on the mutagenic potential of oxazepam have not been done.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Oxazepam 10mg tablets: maize starch, lactose monohydrate and magnesium stearate.

Oxazepam 15mg tablets: maize starch, lactose monohydrate, magnesium stearate, quinoline yellow and sunset yellow FCF.

6.2. Incompatibilities

None known.

6.3. Shelf life

36 months from date of manufacture.

6.4. Special precautions for storage

Store at or below 25°C.

Protect from light.

6.5. Nature and contents of container

Oxazepam tablets are contained in a HDPE plastic bottle.

Pack size of 100 tablets.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

Class C5 Controlled Drug

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

18 October 1979

10. DATE OF REVISION OF THE TEXT

28 February 2022

Summary table of changes

Section Changed	Summary of new information
4.3	Section updated to align information with international oxazepam product information.
4.4	Section updated to align with international safety information as per Medsafe's request.