SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Oxazepam 15mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg of oxazepam.

Excipient with known effect:
Lactose monohydrate – 95 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Pale yellow tablet marked “OM” break line “15” on one side and “G” on the other

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Oxazepam tablets are indicated for the short-term relief (2-4 weeks) only of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short term psychosomatic, organic or psychotic illness.

The use of Oxazepam to treat short-term ‘mild’ anxiety is considered to be inappropriate and unsuitable.

4.2 Posology and method of administration

Posology
All patients taking oxazepam should be carefully monitored and routine repeat prescriptions should be avoided. Patients who have taken benzodiazepines for a long time may require an extended withdrawal period during which doses are reduced. Long-term chronic use is not recommended.

Adults

Severe anxiety: The recommended dosage is 15-30mg three or four times daily.

Insomnia associated with anxiety

Most patients need a dose of 15-25mg but some patients may need up to 50mg. The dose should be taken one hour before retiring.

Elderly patients and those who are particularly sensitive to benzodiazepines

The recommended dosage is 10-20mg three or four times daily.

Children

Oxazepam is not recommended for the treatment of anxiety or insomnia in children.

Treatment of anxiety should not be continued beyond 8-12 weeks including a tapering off period.

Treatment of insomnia should be as short as possible. Generally, the duration of treatment varies from a few days to two weeks with a maximum, including tapering off process of four weeks.

In all cases, the dosage of Oxazepam should be titrated according to the needs of the individual patient and the lowest effective dose necessary to control symptoms should be used for the shortest possible time. The maximum dose should not be exceeded. In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status with special expertise.

Method of administration

For oral administration only.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Myasthenia gravis, hypersensitivity to benzodiazepines, phobic or obsessional states, chronic psychosis, respiratory depression, acute pulmonary insufficiency, sleep apnoea syndrome, severe hepatic insufficiency.

4.4 Special warnings and precautions for use

Tolerance
Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Dependence
Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. 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. Therefore, benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

Once physical dependence has developed, abrupt discontinuation of benzodiazepines may be associated with physiological and psychological symptoms of withdrawal including extreme anxiety, headache, muscle pain, insomnia, 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.

Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in 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 dosage be decreased gradually.

Duration of treatment
The duration of treatment should be as short as possible (see also section 4.2) depending on the indication, but should not exceed 4 weeks for insomnia and eight to twelve weeks in case of anxiety, including a tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.

It may be useful to inform the patient when treatment is started it will be of limited duration and explain precisely how the dosage will be progressively decreased. Moreover, it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is discontinued.

There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

When benzodiazepines with a long duration are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Psychiatric and paradoxical reaction
Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the medicinal product should be discontinued. They are more likely to occur in children and elderly.

Amnesia
Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk to patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see section 4.8).

Specific patient groups
Benzodiazepines should not be used alone to treat depression or anxiety associated with depression.
Benzodiazepines are not recommended for the primary treatment of psychotic illness or marked personality disorder. Suicide may be precipitated in patients who are depressed and aggressive behaviour toward self and others may be precipitated.

A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy, renal impairment, muscle weakness or porphyria.

Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum.

Elderly should be given a reduced dose (see section 4.2).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Elderly
Elderly or debilitated patients may be more susceptible to the effects of oxazepam; therefore, these patients should be monitored frequently and have their dosage adjusted carefully according to patient response (see section 4.2 Posology and method of administration).
Due to the myorelaxant effect there is a risk of falls and consequently fractures in the elderly.

Thyroid disease
An increase in oxazepam dose or frequency may be necessary in patients with hyperthyroidism due to increased clearance and shorter half-life of oxazepam.
A decrease in oxazepam dose may be necessary in patients with hypothyroidism.

Loss or bereavement

In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.

Risk from concomitant use of opioids:
Concomitant use of Oxazepam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Oxazepam with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe Oxazepam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Take into account the combination of benzodiazepines with central nervous system (CNS) depressants. Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anaesthetics and sedating antihistamines, lofexidine, nabilone and tizanidine. In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence.

Oestrogen-containing contraceptives (concurrent use may cause a decrease in plasma levels of oxazepam).

Antibacterials (rifampicin may increase the metabolism of oxazepam).

Antivirals (concurrent use of zidovudine with benzodiazepines may decrease zidovudine clearance. Ritonavir may inhibit benzodiazepine hepatic metabolism). The clinical significance of these interactions has yet to be established.

Antiepileptic drugs (concurrent use of phenytoin may cause oxazepam serum levels to fall. Side effects may be more evident with hydantoins or barbiturates).

Antihypertensives (enhanced hypotensive effects. Enhances sedative effect with alpha blockers or moxonidine).

Dopaminergics (concurrent use with benzodiazepines may decrease the therapeutic effects of levodopa).

Baclofen (enhanced sedative effect).

Probenecid (may increase effects and possibility of excessive sedation).

Benzodiazepines in combination with 4-hydroxybutanoic acid (sodium oxybate) may cause an increased respiratory depression.

Administration of theophylline or aminophylline may reduce the sedative effects of benzodiazepines, including oxazepam.

Opioids:
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Oxazepam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.

Pregnancy
Oxazepam should not be used during pregnancy. An increased risk of congenital malformations associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested in several studies. In humans, umbilical cord blood samples indicate placental transfer of benzodiazepines including oxazepam and their glucuronide metabolites.

Moreover, infants born to mothers who took benzodiazepines chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

If for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected, due to the pharmacological action of the compound.

Breast-feeding
Since benzodiazepines are found in the breast milk, benzodiazepines should not be given to breast feeding mothers.

Fertility
Human data are not available. Animal data showed decreases in frequency of vaginal estrus in mice.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscular 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 (see also section 4.5). As with all patients on CNS depressant drugs, patients should be warned not to drive or operate machinery until it is known that they do not become drowsy or dizzy from Oxazepam.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - o The medicine has been prescribed to treat a medical or dental problem and
    - o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - o It was not affecting your ability to drive safely

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 (see section 4.4).

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
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. Other symptoms such as depression, persistent tinnitus, involuntary movements, paraesthesia, perceptual changes, confusion, convulsions, abdominal and muscle cramps and vomiting may be characteristic of benzodiazepine withdrawal syndrome.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow

Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Toxicity is an extension of the known pharmacological effects,increased GABA activity causing CNS depression. Overdosage 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, rarely coma and very rarely death.

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

Management

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

Activated charcoal treatment is usually not necessary unless the patient has a dangerous co-ingestant. Activated charcoal may be beneficial if dangerous co-ingestants were consumed and the patient can protect their own airway or is intubated.

Gastric lavage and whole bowel irrigation are usually not indicated as severe toxicity is very rare.

While coma and respiratory depression are rare, they may occur with large overdoses or co-ingestion. Supportive care with attention to the airway, breathing and circulation is the mainstay of treatment. Overdose of benzodiazepines as single agents does not generally cause loss of airway reflexes, however when combined with other sedating drugs airway protection may be necessary. Even with large doses patients generally remain haemodynamically stable.

Due to the high protein binding and the high volume of distribution of oxazepam there is no role for active elimination methods such as forced diuresis, haemodialysis or haemoperfusion.

Flumazenil, a specific benzodiazepine antagonist, is available but is rarely indicated. It has a short half-life (approximately one hour). Flumazenil may be indicated to antagonize the central depressive effect in severe cases of intoxication with respiratory depression and/or hypotension. Flumazenil is not to be used in mixed overdose or as a "diagnostic" test. Flumazenil may cause withdrawal states and result in seizures, adrenergic stimulation or autonomic instability in patients chronically receiving benzodiazepines or in those with ventricular dysrhythmias and seizures who are concomitantly using cocaine or tricyclic antidepressants.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives, ATC code: N05BA04

Oxazepam is a benzodiazepine with anticonvulsant, anxiolytic, sedative, muscle relaxant and amnesic properties. Its actions are mediated by enhancement of the activity of aminobutyric acid (GABA), a major inhibitory neurotransmitter in the brain.

5.2 Pharmacokinetic properties

Oxazepam is well absorbed from the gastrointestinal tract and reaches peak plasma concentrations in about 1 - 5 hours. Oxazepam is extensively bound to plasma proteins and has been reported to have a half-life ranging from about 6 to 20 hours. It is the ultimate pharmacologically active metabolite of diazepam and is itself largely metabolised to the inactive glucuronide which is excreted in the urine. Oxazepam has a volume of distribution of 0.4-2.3 $L.kg^{-1}$.

Oxazepam crosses the placental barrier and is excreted in breast milk; lethargy and weight loss may occur in breast fed infants.

5.3 Preclinical Safety Data

There are no preclinical safety data of relevance to the prescriber, which are additional to those already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Maize Starch

Magnesium Stearate ,

Quinoline Yellow

Erythrosine

6.2. Incompatibilities

None

6.3. Shelf Life

3 years

6.4 Special precautions for storage

Store below 25°C.
Store in the original package. Protect from light. Store in a cool dry place.

6.5 Nature and contents of container

Polyethylene container with polyethylene tamper evident caps, fitted with a general polyethylene ullage filler in packs of 100, 250, 500 and 1000 tablets.
PVC/PVdC/Aluminium blisters containing 28 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd t/a Mylan
Station Close
Potters Bar
Herts
EN6 1TL
UK

8. MARKETING AUTHORISATION NUMBER

PL 04569/0103

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th April 1986
Date of latest renewal: 31st January 2003

10 DATE OF REVISION OF THE TEXT

11/10/2018