Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

VABEN TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg Oxazepam.
Excipient with known effect:
Each tablet contains 68.83mg lactose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White tablets.

4. CLINICAL PARTICULARS

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.
- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

4.1 Therapeutic indications

Anxiolytic.

4.2 Posology and method of administration

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

As an anxiolytic, the lowest effective dose should be employed, for the shortest time possible; dosage regimes should not exceed beyond 4 weeks and treatment should always be gradually withdrawn.

Adults:
Anxiety 10-30mg three or four times a day.
Elderly patients and those who are particularly sensitive to benzodiazepines: 10 mg three 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; phobic or obsessional states; chronic psychosis; respiratory depression, acute pulmonary insufficiency; myasthenia gravis; sleep apnoea syndrome; severe hepatic insufficiency.

4.4 Special warnings and precautions for use

Patients should be advised that since their tolerance for alcohol and other CNS depressants will be diminished in the presence of oxazepam, these substances should either be avoided or taken in reduced dosage.

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, or in patients with significant personality disorders.

Dependence may lead to withdrawal symptoms (see section 4.8), especially if treatment is discontinued abruptly.

Rebound insomnia and 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.

It may be useful to inform the patient that treatment will be of limited duration and that it will be discontinued gradually. The patient should also be made aware of the possibility of "rebound" phenomena to minimise anxiety should they occur.

Abuse of benzodiazepines has been reported.

Falls

Due to the potential adverse reactions including ataxia, muscle weakness, dizziness, drowsiness and fatigue (see section 4.8), Benzodiazepines may be associated with an increased risk of falling especially in elderly patients. As a result, caution should be exercised particularly when getting up at night. The elderly should receive a reduced dose (see section 4.2).

Duration of treatment

The duration of treatment should be as short as possible (see 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 tapering off process. Extension beyond these periods should not take place without reevaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to 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 being 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.

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 caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Amnesia

Benzodiazepines may induce anterograde amnesia. This condition usually occurs several hours after ingestion therefore patients should ensure that they will be able to have a period of uninterrupted sleep which is sufficient to allow dissipation of drug effect (e.g., 7-8 hours) wherever possible.

Psychiatric and paradoxical reaction

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behavior and other adverse behavioral 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 the elderly.

Specific patient groups

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). A lower dose is also 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 are not recommended for the primary treatment of psychotic illness or marked personality disorder.

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients). Also, pre-existing depression may emerge during benzodiazepine use.

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

Caution should be used in the treatment of patients with acute narrow-angle glaucoma.

Patients with impaired renal or hepatic function should be monitored frequently and have their dosage adjusted carefully according to response. Lower doses may be sufficient in these patients. The same precautions apply to elderly or debilitated patients and patients with chronic respiratory insufficiency.

Some patients taking benzodiazepines have developed a blood dyscrasia, and some have had elevations in liver enzymes. Periodic haematologic and liver-function assessments are recommended where repeated courses of treatment are considered clinically necessary.

Although hypotension has occurred only rarely, benzodiazepines should be administered with caution to patients in whom a drop in blood pressure might lead to cardiovascular or cerebrovascular complications. This is particularly important in elderly patients.

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

4.5 Interaction with other medicinal products and other forms of interaction

The following drug interactions with oxazepam should be considered:

- Enhancement of other CNS depressant drugs such as barbiturates, antipsychotics, narcotic analgesics (enhancement of euphoria may also occur, leading to an increase in psychic dependence), antidepressants, hypnotics, anticonvulsants, anaesthetics, sedative antihistamines, lofexidine, nabilone and tizanidine.

• 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).

• When taken with muscle relaxants, the overall muscle-relaxing effect may be increased (accumulative) therefore caution is advised, especially in elderly patients and at higher doses (risk of falling, see Section 4.4).

• Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines which are metabolised only by conjugation.

•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).

•Alcohol (concomitant intake with alcohol is not recommended. The sedative effects may be enhanced when oxazepam is used in combination with alcohol. This affects the ability to drive or use machines).

•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).

4.6 Fertility, pregnancy and lactation

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

Benzodiazepines should not be used during pregnancy, especially during the first and last trimesters. Benzodiazepines may cause foetal damage when administered to pregnant women.

There is a possibility that infants born to mothers who take benzodiazepines chronically during the later stages of pregnancy may develop physical dependence. The infant may also develop withdrawal symptoms during the postnatal period such as hypoactivity, hypotonia, hypothermia, respiratory depression, apnoea, feeding problems, and impaired metabolic response to cold stress.

Breastfeeding

The concentration of oxazepam and its conjugate in human breast milk is approximately 10% of the plasma level. Therefore, oxazepam should not be administered to breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, dizziness and impaired muscular function may adversely affect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased (see section 4.5).
This medicine can impair cognitive function and can affect a patient's ability to drive safely. 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.

4.8 Undesirable effects

Adverse reactions, when they occur, are usually observed at the beginning of therapy and generally decrease in severity or disappear with continued use or upon decreasing the dose.

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.

Injury, poisoning and procedural complications

Fall.

***** 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 (see section 4.4).

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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

4.9 Overdose

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, dysarthia, 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).

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, induced vomiting and/or gastric lavage should be undertaken (if ingestion was recent). Alternatively (if there is no advantage in emptying the stomach), activated charcoal should be considered to reduce absorption. 50g for adults and 10-15g for children if they have taken more than 1mg/kg within 1 hour, provided they are not too drowsy. Special attention should be paid to vital signs including 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.

Hypotension, though unlikely, may be controlled with noradrenaline. The dialysability of oxazepam is minimal.

Flumazenil, a benzodiazepine antagonist, is available but should rarely be required. It has a short half-life (about an hour). Flumazenil is **NOT TO BE USED IN MIXED OVERDOSE OR AS A "DIAGNOSTIC" TEST**

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code:N05B A

Oxazepam is a benzodiazepine with anxiolytic, sedative and hypnotic properties and possibly, muscle relaxant and anticonvulsant characteristics.

Oxazepam is a sedative and anxiolytic acting by potentiation of the inhibitory effect of gamma-aminobutyrate by binding to specific receptor sites of the brain stem reticular formation and other parts of the CNS.

5.2 Pharmacokinetic properties

Oxazepam is rapidly and almost completely absorbed from the GI tract and is highly protein bound (approximately 90%). It has been reported to have a half-life ranging from about 6-20 hours. It is the ultimate pharmacologically active metabolite of diazepam and is metabolised by a simple one-step process to a pharmacologically inert compound glucuronide. Peak serum levels are reached in 1-5 hours.

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

Acute oral LD50 in mice is greater than 5000 mg/kg.

Fatty metamorphosis of the liver has been noted in six-week toxicity studies in rats given this product at 0.5% of the diet. Such accumulations of fat are considered reversible, since no liver necrosis or fibrosis is seen.

In vitro mutagenicity reports on Oxazepam are inconclusive.

In a carcinogenicity study, oxazepam was administered with diet to rats for two years. Male rats receiving 30 times the maximum human dose showed a statistical increase, when compared to controls, in benign thyroid follicular cell tumours, testicular interstitial cell adenomas, and prostatic adenomas. An earlier published study reported that mice fed dietary dosages of 35 or 100 times the human daily dose of oxazepam for 9 months developed a dose-related increase in liver adenomas. In an independent analysis of some of the microscopic slides from this mouse study, several of these tumours were classified as liver carcinomas. At this time, there is no evidence that clinical use of oxazepam is associated with tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, corn starch (maize), povidone K25, magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Special precautions for storage

Store below 25°C.

6.4 Nature of container

PVC/Aluminium blister pack, 30 tablets.

7. Registration holder:

Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301,Israel.

Registration number: 022-06-21031

Revised in January 2024.