Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Eskazepam Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg Diazepam.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Round, Light yellow coloured tablet, Plain on one side and break-line on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Anxiety.
2. Insomnia.

Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

3. In the control of muscle spasm including that associated with cerebral spasticity.
In the management of epilepsy.
4. As pre-operative medication in minor surgery.

4.2 Posology and method of administration

Posology

Standard dosage

For optimal effect, the dosage should be carefully individualised. Treatment should begin at the lowest effective dose appropriate to the particular condition.

Duration of treatment

The duration of treatment should be as short as possible (see *section 4.4*) depending on the indication, but should not exceed 4 weeks for insomnia and eight to twelve weeks in cases of anxiety, including 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 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 of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Anxiety states

The recommended dose is:

Adults

- Anxiety or mental health problems: 5mg- 30mg each day, in divided doses.
- To help you sleep: 5mg-15mg at bedtime.
- To help cerebral palsy or other spasticities: 5mg-60mg each day, in divided doses.
- To help control muscle spasm: 5mg-15mg each day, in divided doses.
- To help epilepsy: 2mg-60mg each day, in divided doses.
- To help with alcohol withdrawal symptoms: 5mg-20mg, which may be repeated after 2 to 4 hours if necessary.

- Before dental treatment: 5mg the night before treatment, 5mg on waking and 5mg two hours before the appointment.
- Before an operation: 5mg-20mg

Use in children

For tension and irritability in cerebral spasticity: 5mg-40mg each day, in divided doses.
If your doctor has given your child Eskazepam tablets to take before an operation, the usual dose is 2mg-10mg.

Elderly or Frail

If you are elderly or frail you are likely to be more sensitive to the effects of Eskazepam tablets, such as confusion, and your doctor will give you much lower doses. The dose should not be more than half the adult dose.

Patients with hepatic impairment

Patients with impaired hepatic function should be given a reduced dose.

Method of administration

Eskazepam tablets are for oral administration.

4.3 Contraindications

Myasthenia gravis
Hypersensitivity to benzodiazepines or any of the drug's excipients
Severe respiratory insufficiency
Sleep apnoea syndrome
Severe hepatic insufficiency
Phobic or obsessional states
Chronic psychoses
Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Concomitant use of alcohol/CNS depressants

The concomitant use of Eskazepam tablet with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Eskazepam tablet possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see section 4.5).

Medical history of alcohol or drug abuse

Eskazepam tablet should be used with extreme caution in patients with a history of alcohol or drug abuse.
Eskazepam tablets should be avoided in patients with dependence on CNS depressants including alcohol.
An exception to the latter is the management of acute withdrawal reactions.

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 psychological 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 marked personality disorders. Regular monitoring in such patients is essential, routine repeat prescriptions should be avoided and treatment should be withdrawn gradually.

Withdrawal
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.

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. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

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

Amnesia
It should be borne in mind that benzodiazepines may induce anterograde amnesia. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk. Patients should ensure that they will be able to have an uninterrupted sleep of 7 – 8 hours (see *section 4.8*).

Psychiatric and 'paradoxical' reactions
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 drug should be discontinued. They are more likely to occur in children and older people.

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. Since the safety and effectiveness in paediatric patients below the age of 6 months have not been established, Eskazepam tablets should be used in this age group with extreme caution and only when other therapeutic alternatives are not available.
Older and debilitated patients should be given a reduced dose (see *section 4.2*). Due to the myorelaxant effect there is a risk of falls and consequently hip fractures in older people.
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. In patients with chronic hepatic disease, dosage may need to be reduced.
The usual precautions in treating patients with impaired renal function should be observed. In renal failure the half-life of diazepam is unchanged; therefore no dosage adjustments are required in such patients.
Benzodiazepines are not recommended for the primary treatment of psychotic illness.
Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).
In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.
Patients with rare hereditary problems of galactose intolerance, (the Lapp lactase deficiency or glucose-galactose malabsorption) should not take this medicine because it contains Lactose.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic Drug-Drug Interaction

The oxidative metabolism of diazepam is mediated by CYP3A and CYP2C19 isoenzymes. Oxazepam and temazepam are further conjugated to glucuronic acid.
In consequence substrates, which are modulators of CYP3A and/or of CYP2C19, may potentially alter the pharmacokinetics of diazepam. Drugs like cimetidine, ketoconazole, fluvoxamine, fluoxetine and omeprazole which are CYP3A or CYP2C19 inhibitors may lead to increased and prolonged sedation. There have also been reports that the metabolic elimination of phenytoin is affected by diazepam.
Cisapride may lead to a temporary increase in the sedative effects of orally administered benzodiazepines due to faster absorption.

Pharmacodynamic Drug-Drug Interaction

Enhanced effects on sedation, respiration, and haemodynamics may occur when Eskazepam tablets is co-administered with any centrally acting depressants such as antipsychotics, anxiolytics/sedatives, antidepressants, hypnotics, antiepileptic drugs, narcotic analgesics, anaesthetics and sedative antihistamines or alcohol.
Alcohol should be avoided in patients receiving Eskazepam tablets (see section 4.4).
See section 4.9 for warnings on other central nervous system depressants including alcohol.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies with benzodiazepines have shown minor effects on the foetus while a few studies have reported late behavioural disturbances in offspring exposed *in utero*. Do not use during pregnancy, especially during the first and last trimesters, unless there are compelling reasons.
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.
If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour, effects on the neonate, such as hypothermia, hypotonia, irregularities in the foetal heart rate, poor sucking and moderate respiratory depression, can be expected, due to the pharmacological action of the compound. With newborn infants it must be remembered that the enzyme system involved in the breakdown of the drug is not yet fully developed (especially in premature infants).

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.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

Patients should be advised that, like all medicaments of this type, Eskazepam tablets may modify patients' performance at skilled tasks.

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 *section 4.5*).

Patients should further be advised that alcohol may intensify any impairment and should, therefore, be avoided during Treatment.

4.8 Undesirable effects

Description of selected adverse reactions

The most commonly reported undesirable effects are fatigue, drowsiness and muscle weakness; they are usually dose related.

These phenomena occur predominantly at the start of therapy and usually disappear with prolonged administration.

Nervous System Disorders

Ataxia, dysarthria, slurred speech, headache, tremor, dizziness. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

Psychiatric disorders

Paradoxical reactions such as restlessness, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, psychoses, abnormal behaviour and other adverse behavioural effects are known to occur when using benzodiazepines.

Should this occur, the use of the drug should be discontinued. They are more likely to occur in children and in the elderly.

Confusion, emotional poverty, alertness decreased, depression, libido increased or decreased.

Chronic use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see *section 4.4*)).

Abuse of benzodiazepines has been reported (see *section 4.4*).

Injury, Poisoning and Procedural Complications

There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Gastrointestinal disorders

Nausea, dry mouth or hypersalivation, constipation and other gastrointestinal disturbances

Eye disorders

Diplopia, vision blurred

Vascular disorders

Hypotension, circulatory depression

Investigations

Heart rate irregular, very rarely transaminases increased, blood alkaline phosphatase increased

Renal and urinary disorders

Incontinence, urinary retention

Skin and subcutaneous tissue disorders
Skin reactions
Ear and labyrinth disorders
Vertigo
Cardiac disorders
Cardiac failure including cardiac arrest
Respiratory disorders
Respiratory depression including respiratory failure

Hepatobiliary disorders
Very rarely jaundice
Reporting of suspected adverse reactions
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly by emailing on FDA web site, fda@fdaghana.gov.gh

4.9 Overdose
Symptoms
Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of Eskazepam tablets is seldom life threatening if the drug is taken alone, but may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in older patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.
Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.
Treatment
Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.
Further absorption should be prevented using an appropriate method e.g. treatment within 1-2 hours with activated charcoal. If activated charcoal is used, airway protection is imperative for drowsy patients. In case of mixed ingestion, gastric lavage may be considered, however not as a routine measure.
If CNS depression is severe consider the use of flumazenil, a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this drug.
If excitation occurs, barbiturates should not be used.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Anxiolytic, ATC code: N05BA01
A benzodiazepine with anxiolytic, sedative, muscle-relaxant and anticonvulsant properties. It has little autonomic activity.
5.2 Pharmacokinetic properties
Absorption
Diazepam is rapidly and completely absorbed from the gastrointestinal tract, peak plasma concentrations appearing 30 - 90 minutes after oral ingestion.

Distribution
Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98%). Diazepam and its metabolites cross the blood-brain and placental barriers and are also found in breast milk in concentrations approximately one tenth of those in maternal plasma (see *section 4.6*). The apparent volume of distribution is 1 – 2 l/kg.

Biotransformation
Diazepam is mainly metabolised to the pharmacologically active metabolites such as N-desmethyldiazepam, temazepam and oxazepam.
The oxidative metabolism of diazepam is mediated by CYP3A and CYP2C19 isoenzymes. Oxazepam and temazepam are further conjugated to glucuronic acid.

Elimination
The decline in the plasma concentration-time profile after oral administration is biphasic, an initial rapid and extensive distribution phase being followed by a prolonged terminal elimination phase (half-life up to 48 hours). The terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours. Diazepam and its metabolites are excreted mainly in the urine, predominantly in their conjugated forms. The clearance of diazepam is 20 - 30ml/min.
The metabolite may take 2 weeks to reach steady state.

Pharmacokinetics in special clinical situations
The elimination half-life may be prolonged in the newborn, in older people and in patients with liver disease. In renal failure the half-life of diazepam is unchanged.

5.3 Preclinical safety data

Carcinogenicity
The carcinogenic potential of oral diazepam has been studied in several rodent species. An increase in the incidence of hepatocellular tumours occurred in male mice. No significant increase in the incidence of tumours was observed in female mice, rats, hamsters or gerbils.

Mutagenicity
A number of studies have provided weak evidence of a mutagenic potential at high concentrations which are, however, far above the therapeutic doses in humans.

Impairment of Fertility
Reproductive studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of oral doses of 100 mg/kg/day prior to and during mating and throughout gestation and lactation.

Teratogenicity
Diazepam was found to be teratogenic in mice at dose levels of 45-50mg/kg, 100mg/kg and 140mg/kg/day as well as in hamsters at 280 mg/kg. In contrast, this drug was shown to be non-teratogenic at 80 and 300 mg/kg/day in rats and at 20 and 50 mg/kg/day in rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Magnesium stearate
Talcum
Sunset yellow colour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium foil/PVC blister strips.

Blister strips consisting of 0.02 mm thick aluminium foils with a form packing bottom strip of 0.25mm clear PVC.

Pack sizes: 10 Tablets

Box of 10x50 tablets.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

ESKAY THERAPEUTICS LTD
P.O.BOX 431
DARKUMAN

8 MARKETING AUTHORISATION NUMBER

FDA/SD.103-4214.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of last renewal: July 17th 2019.

10 DATE OF REVISION OF THE TEXT

August 2019