SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Anxicalm 5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Diazepam 5mg.

Excipients: Lactose monohydrate 111.67 mg and Tartrazine (E102) 0.033 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Round, yellow, flat bevel-edged tablet engraved with 'D5' on one face and with a single scoreline on the reverse.

The score line is only to facitilitate breaking for ease of swallowing and not to divide into equal doses..

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 tetanus.

(4) In the management of epilepsy.

(5) As pre-operative medication in minor surgery.

4.2. Posology and method of administration

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 short as possible depending on the indication, but should not exceed four 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

Adults

Usual dose: 2 mg three times daily.
Maximum dose: Up to 30 mg daily in divided doses, adjusted on an individual basis.

Insomnia associated with anxiety: 5 to 15 mg before retiring.

The lowest dose which can control symptoms should be used.

Treatment should not be continued at the full dose beyond 4 weeks.

Long-term chronic use is not recommended.

Treatment should always be tapered off gradually. Patients who have taken benzodiazepines for a prolonged time may require a longer period during which doses are reduced. Specialist help may be appropriate.

Conditions associated with muscle spasm

Adults

Muscle spasm: 2 to 15 mg daily in divided doses.

Management of cerebral spasticity in selected cases: 2 to 60 mg daily in divided doses.

Adjunct to control of muscle spasm in tetanus: 3 to 10 mg/kg body weight daily by nasoduodenal tube. The selected dose should relate to the severity of the case, and in extremely severe cases higher doses have been used.

Children

Control of tension and irritability in cerebral spasticity in selected cases: 2 to 40 mg daily in divided doses

As an adjunct to the control of muscle spasm in tetanus: As for adults.

Premedication

Adults
5 to 20 mg

Children

2 to 10 mg

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

Elderly

Elderly or debilitated patients: Doses should not exceed half those normally recommended.

These patients should be checked regularly at the start of treatment in order to minimise the dosage and/or the frequency of administration to prevent overdose due to accumulation.

Impaired hepatic function

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

Anxicalm tablets are for oral administration

4.3. Contraindications

Myasthenia gravis.

Hypersensitivity to benzodiazepines or any of the drug's excipients listed in section 6.1.

Severe respiratory insufficiency.

Sleep apnoea syndrome.

Severe hepatic insufficiency.

Phobic or obsessional states.

Chronic psychoses.

4.4 Special warnings and precautions for use

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

Medical history of alcohol or drug abuse
Anxicalm should be used with extreme caution in patients with a history of alcohol or drug abuse. Anxicalm 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 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
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 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 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 the elderly.

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.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

Pharmacokinetic Drug-Drug Interaction (DDI)

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.

Known inducers of hepatic enzymes, e.g., rifampicin, may increase the clearance of benzodiazepines.

Cisapride may lead to a temporary increase in the sedative effects of orally administered benzodiazepines due to faster absorption.

Pharmacodynamic Drug-Drug Interaction (DDI)

Enhanced effects on sedation, respiration, and haemodynamics may occur when Anxicalm 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 Anxicalm (see section 4.4).
See section 4.9 for warnings on other central nervous system depressants including alcohol.

4.6. Fertility, pregnancy and lactation

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 trimester, 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.

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, Anxicalm may modify patient's 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

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
An increased risk of falls and fractures has been recorded in elderly benzodiazepine users.

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
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 IMB Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie

4.9. Overdose

Symptoms
Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of Anxicalm 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 only a few hours but it may be more protracted and cyclical, particularly in elderly 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 (Anexate®), 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 contraindicated 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: Benzodiazepine

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 track, 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.

Metabolism
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 under 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 – 30 ml/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 the elderly 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 proved 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 45-50 mg/kg, 100 mg/kg and 140 mg/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

Pregelatinised maize starch
Lactose monohydrate
Sodium laurylsulphate
Sodium starch glycollate (Type A)
Stearic acid
Magnesium stearate
Tartarazine (E102)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Do not store above 25°C.
Keep the container tightly closed.
Store in the original container.

6.5. Nature and contents of container

PP tubular tablet container with LDPE cap.
Pack sizes: 30, 50, 90, 100, 250, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd.,
Waterford Road,
Clonmel,
Co. Tipperary.

8. MARKETING AUTHORISATION NUMBER(S)

PA 126/11/2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th April 1979
Date of last renewal: 25th April 2009

10. DATE OF REVISION OF THE TEXT

April 2014