SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICALPRODUCT

Remedium 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg of diazepam.

Excipient(s) with known effect
Each Remedium 5 mg tablet contains 113.6 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Yellow, round, flat, scored tablets.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Anxiety
Treatment should be as short as possible.The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free. The overall duration of treatment generally should not be more than 8-12 weeks, including a tapering off process.

In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without reevaluation of the patient's status with special expertise.

Insomnia

Treatment 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 certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without reevaluation of the patient's status.

The lowest dose that can control symptoms should be used.

Treatment should not be continued beyond four weeks.

Anxiety states
Severe anxiety states: 15 to 30 mg.

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

Elderly or debilitated patients:
Doses should not exceed half those normally recommended.
Treatment should always be tapered off gradually.
Patients who have been taking benzodiazepines for a long time may require a longer period during which dosage is reduced.

Hepatic/renal impairment: Dosage reduction may also be required in patients with liver or kidney dysfunction.

Children: Not recommended.

Method of Administration
Remedium is for oral administration.

4.3 Contraindications

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

Known hypersensitivity to benzodiazepines or any of the ingredients.

Severe or acute respiratory insufficiency / depression.

Sleep apnoea syndrome.

Severe hepatic insufficiency.

Remedium should not be used in phobic or obsessional states, nor be used alone in the treatment of depression or anxiety associated with depression due to the risk of suicide being precipitated in this patient group. Remedium should not be used for the primary treatment of psychotic illness. In common with other benzodiazepines the use of diazepam may be associated with amnesia and diazepam should not be used in cases of loss or bereavement as psychological adjustments may be inhibited.

4.4 Special warnings and precautions for use

Remedium should be used with caution in patients with renal or hepatic dysfunction (see 4.2 Posology and Method of Administration), chronic pulmonary insufficiency, porphyria, myasthenia gravis, coma, a known history of drug or alcohol abuse, or organic brain changes, particularly arteriosclerosis.

Diazepam may enhance the effects of other CNS depressants; their concurrent use should be avoided.

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. This should be considered when treating patients for more than a few days.
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 (see 4.8 Undesirable effects). It is low when limited to short term use.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms.

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 Posology) 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 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 minimizing 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. 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 also Undesirable Effects).

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 are prone to CNS effects of benzodiazepines and, therefore, should be given a reduced dose (see 4.3 Posology and Method of Administration). 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.

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

As with other benzodiazepines, extreme caution should be used if prescribing diazepam for patients with personality disorders. The disinhibiting effects of benzodiazepines may be manifested as the precipitation of suicide in patients who show aggressive behaviour towards self and others.

Risk from concomitant use of opioids:
Concomitant use of Remedium 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 Remedium with opioids should be reserved for patientsfor whom alternative treatment options are not possible. If a decision is made to prescribe Remedium 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).

Remedium contains lactose

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

*Alcohol:*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.

*Anaesthetics and narcotic analgesics:*Enhancement of the central depressive effect may occur, with enhanced sedation or respiratory and cardiovascular depression. In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence.

Antibacterials: Agents that interfere with metabolism by hepatic enzymes (e.g. erythromycin and isoniazid) may reduce the clearance of benzodiazepines and potentiate their action. Known inducers of hepatic enzymes, for example, rifampicin, may increase the clearance of benzodiazepines.

Antidepressants: Enhanced sedation or respiratory and cardiovascular depression. Diazepam plasma levels increased by concomitant fluvoxamine.

Antiepileptics: Enhanced sedation or respiratory and cardiovascular depression. Known inducers of hepatic enzymes, for example carbamazepine, and phenytoin, may increase the clearance of benzodiazepines. Serum phenytoin levels may rise, fall or remain unaltered. In addition, phenytoin may cause diazepam serum levels to fall. Concomitant sodium valproate may increase serum levels of diazepam, with associated drowsiness.

Antihistamines: Enhanced sedation or respiratory and cardiovascular depression with sedative antihistamines.

Antihypertensives: Enhanced hypotensive effect, enhanced sedative effect with alpha blockers and possibly moxonidine.

Antipsychotics: Enhanced sedation or respiratory and cardiovascular depression. Increased plasma concentrations of zotepine. Severe hypotension, collapse, respiratory depression, potentially fatal respiratory arrest and unconsciousness have been reported in a few patients on benzodiazepines and clozapine. Caution is advised when initiating clozapine therapy in patients taking benzodiazepines.

Antivirals: Amprenavir, and ritonavir have been shown to reduce the clearance benzodiazepines and may potentiate their actions, with risk of extreme sedation and respiratory depression – avoid concomitant use.

Anxiolytics: Enhanced sedation or respiratory and cardiovascular depression with other anxiolytics.

Digoxin: Reduced clearance of digoxin

Disulfiram: has been shown to reduce clearance and may potentiate actions of benzodiazepines.

Dopaminergic agents: diazepam may cause inhibition of levodopa.

Hypnotics: Enhanced sedation or respiratory and cardiovascular depression.

Lofexidine: Enhanced sedation or respiratory and cardiovascular depression

Muscle relaxants: Increased CNS depressant effects with baclofen and tizanidine.

Nabilone: Enhanced sedation or respiratory and cardiovascular depression.

Nicotine: Diazepam metabolism is accelerated by smoking.

Oral contraceptives: Reduce the clearance of benzodiazepines and may potentiate their actions.

*Opioids:*The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Remedium 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).

Sedatives: Enhanced sedation or respiratory and cardiovascular depression.

Theophylline: Diazepam metabolism is accelerated by theophylline.

Ulcer-healing drugs: Cimetidine, and omeprazole may reduce the clearance of benzodiazepines and potentiate their actions.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no evidence regarding the safety of diazepam in pregnancy. Remedium should not be used in pregnancy, especially during the first and third trimesters, unless the benefit is considered to outweigh the risk. If the product is prescribed to a woman of child bearing 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.

There may be a small increase in the risk of congenital malformation, particularly oral cleft, with the use of benzodiazepines in the first trimester. In labour, high single doses or repeated low doses have been reported to produce effects on the neonate, such as hypothermia, hypotonia, moderate respiratory depression and poor suckling (floppy infant syndrome) and irregularities in the foetal heart.

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 post-natal period. A small number of children

exposed in utero to benzodiazepines have shown slow development in the early years but by four years of age have developed normally.

Lactation
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 treated with diazepam tablets should not drive or operate machinery as sedation, amnesia, impaired concentration and impaired muscular function may adversely affect their ability. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.

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.
- it is an offence to drive while under the influence of this medicine.
- however, you would not be committing an offence if:
    - the medicine has been prescribed to treat a medical or dental problem and
    - you have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - it was not affecting your ability to drive safely.

4.8 Undesirable effects

Cardiovascular: Hypotension, particularly with high dosage, bradycardia, chest pain.

CNS: Elderly or debilitated patients are particularly susceptible to the CNS effects of benzodiazepines. It is recommended that dosage be limited to the smallest effective dose and increased gradually, if necessary, to decrease the possibility of development of ataxia, dizziness, and oversedation, which may lead to falls and other accidents (see 4.2 Posology and method of administration).

Disorders of the eye: Visual disturbances

Gastrointestinal: Dry mouth gastrointestinal disturbances

General: Fatigue and a hangover effect.

Haematological: Blood dyscrasias

Hepatic: Raised liver enzymes, jaundice.

Immunological: Hypersensitivity reactions, including anaphylaxis, are rare.

Neurological: Headaches, confusion, slurred speech, tremor, reduced alertness. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at

higher dosages (see 4.4 Special warnings and special precautions for use). Amnestic effects may be associated with inappropriate behaviour.

Psychiatric disorders: Numbed emotions. Pre-existing depression may be unmasked during benzodiazepine use. Paradoxical reactions (including aggressive behaviour, hostility, disinhibition, euphoria, excitation, irritability, increased anxiety, and insomnia) are known to occur with benzodiazepines. They may be quite severe with this product. They are more likely to occur in children and the elderly.

Reproductive disorders: Changes in libido, gynaecomastia.

Respiratory disorders: Rarely, respiratory depression and apnoea, particularly with high dosage.

Urinary: Urinary retention, incontinence.

Withdrawal symptoms: dependence is common after regular use, even in therapeutic doses for short periods, particularly in patients with a history of drug or alcohol abuse or marked personality disorders. Discontinuation of the therapy may result in withdrawal or rebound phenomena (see 4.4 Special Warnings and Special Precautions for Use). Symptoms of benzodiazepine withdrawal include anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances such as hypersensitivity to physical, visual, and auditory stimuli and abnormal taste, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension.

Rare and more serious symptoms include muscle twitching, confusional or paranoid psychosis, convulsions, hallucinations, and a state resembling delirium tremens. Broken sleep with vivid dreams and increased REM sleep may persist for some weeks after withdrawal of benzodiazepines.

Abuse of benzodiazepines has been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product isimportant. It allows continued monitoring of the benefit/risk balance of the medicinalproduct. Healthcare professionals are asked to report any suspected adverse reactions via thenational reporting system:

4.9 Overdose

a) Symptoms

The symptoms of mild overdose may include confusion, impairment of consciousness with somnolence or a sleep-like state, little or no respiratory depression, ataxia, dysarthria, hypotension and muscular weakness. Cardiac rate and rhythm remain normal in the absence of anoxia or severe hypotension.

In severe overdose, deep coma or other manifestations of severe depression of brainstem vital functions, particularly the respiratory centre, may occur.

As drug levels fall severe agitation, insomnia and, possibly, major convulsions may develop.

b) Treatment

Treatment is symptomatic. Respiration, heart rate, blood pressure and body temperature should be monitored in intensive care and supportive measures taken to maintain cardiovascular and respiratory function.

As with other benzodiazepines, overdosage 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.

Activated charcoal may be administered to increase clearance as well as decrease absorption of diazepam.

Flumazenil may be indicated to counteract the central depressive effect of benzodiazepines but expert advice is essential since adverse effects may occur (e.g. convulsions in patients dependent on benzodiazepines).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; Anxiolytics,ATC code: N05BA01

Diazepam has anxiolytic and central muscle relaxant properties. It has little autonomic activity.

5.2 Pharmacokinetic properties

Diazepam is readily and completely absorbed from the gastrointestinal tract.

Diazepam has a biphasic half-life with an initial rapid distribution phase followed by a prolonged terminal elimination phase of one or two days. It is extensively metabolised in the liver. It is excreted in the urine, mainly in the form of its metabolites.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber that are additional to those already includes in other sections.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose
Sodium starch glycolate
Colloidal silicon dioxide
Magnesium stearate
Talc
Maize starch
Povidone
Quinoline yellow E104

6.2 Incompatibilities

None known.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30^{o}C.Protect from light and moisture.

6.5 Nature and contents of container

PVC/Aluminium blisters. Pack-sizes of 40, 100 and 1000 tablets.
PP/PE containers. Pack sizes of 1000 tablets.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

None.

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd
Aharnon Str., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

06760/08171/REN/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of latest renewal: Nov 4, 2021

10. DATE OF REVISION OF THE TEXT

04/07/2023