SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

AREM®, 5 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of AREM contains 5 mg of nitrazepam.

Contains sugar: Lactose monohydrate 357,7 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

White to off-white, flat tablet with bevelled edges, debossed “AREM” on the one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of insomnia.

AREM is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

4.2 Posology and method of administration

Posology

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

The usual dose is one tablet (5 mg) at night, although two tablets (10 mg) may be required.

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

Special populations

Elderly

Elderly or debilitated patients should not be given more than half of the normal adult dose.

Method of administration

For oral administration.

4.3 Contraindications

- Psychotic patients.
- Chronic obstructive lung disease states.
- Patients with a known hypersensitivity towards nitrazepam or other benzodiazepines or to any of the excipients listed in section 6.1.
- Pregnancy (given during labour it crosses the placenta and may cause the floppy-infant syndrome characterised by central respiratory depression, hypothermia and poor sucking).
- Lactating mothers.
- Patients suffering from depression and suicidal tendencies.
- Acute porphyria.

AREM should not be used in patients with pre-existing central nervous system depression or coma, acute pulmonary insufficiency, or sleep apnoea.

4.4 Special warnings and precautions for use

Particular caution should be exercised in:

- The elderly and debilitated - who are at a particular risk of oversedation, respiratory depression, sleep disturbances and ataxia (see section 4.2);
- patients suffering from impairment of renal or hepatic function or from hypoalbuminaemia;
- patients receiving barbiturates or other central nervous system depressants since there is an additive risk of central nervous depression when these medicines are taken together;

- patients with myasthenia gravis on account of pre-existing muscle weakness;
- patients with organic brain changes particularly arteriosclerosis;
- patients with acute closed-angle glaucoma;
- patients with gout.

Monitoring of cardiorespiratory function is recommended when benzodiazepines are used for conscious sedation.

AREM is not recommended for the primary treatment of psychotic illness or chronic psychosis or obsessional states. AREM should not be used alone to treat depression or anxiety with depression (suicide may be precipitated in such patients) (see section 4.3).

AREM should be used with extreme caution in patients with a history of alcohol or drug abuse, patients should be cautioned regarding the additive effect of alcohol.

Concomitant use of nitrazepam (e.g., AREM) 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 medicines such as AREM with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe AREM 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. It is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

If the patient is awoken during the period of maximum medicine activity, recall may be impaired.

Dependence

There is a potential for abuse and the development of physical and psychological dependence, especially with prolonged use and high doses. The risk of dependence 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. 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, mood changes, rebound insomnia, irritability, sweating and diarrhoea.

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 (e.g. AREM), as withdrawal symptoms may develop.

In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. In some instances, withdrawal following excessive dosages may produce confusional states and psychotic manifestations and convulsions. Abuse of the benzodiazepines (e.g., AREM) has been reported.

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

Abnormal psychological reactions to benzodiazepines (e.g.AREM) have been reported. Rare behavioural effects include paradoxical aggressive outbursts, excitement, confusion, restlessness, agitation, irritability, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and the uncovering of depression with suicidal tendencies. Extreme caution should therefore be used in prescribing benzodiazepines (e.g. AREM) to patients with personality disorders. If any of these reactions occur, use of the medicine should be discontinued. These reactions may be quite severe and are more likely to occur in the elderly.

Rebound effects

A transient syndrome whereby the symptoms that led to treatment with AREM recur in an enhanced form may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety 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), but should not exceed 4 weeks for insomnia, 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 AREM is being discontinued.

Benzodiazepines (e.g. AREM) may induce anterograde amnesia. The condition usually occurs 1 to 2 hours after ingesting the product and may last up to several hours. Therefore, to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 7 to 8 hours.

Due to the myorelaxant effect there is a risk of falls and consequently of hip fractures particularly for elderly patients when they get up at night.

Excipients

Patients with the rare hereditary problems of galactose intolerance e.g. total lactase deficiency, glucose-galactose malabsorption should not take AREM.

4.5 Interaction with other medicines and other forms of interaction

The effects of AREM (enhanced sedation or respiratory and cardiovascular depression) may be enhanced by neuroleptics, tranquillisers, alcohol, antidepressants, medicines to treat colds, medicines for seizure, antihistamines, muscle relaxants, antipsychotics, general anaesthetics, other hypnotics or sedatives, opioid analgesics or other medicines that have central depressant properties or that interfere with their metabolism.

The concomitant use of sedative medicines such as benzodiazepines or related medicines such as nitrazepam (e.g., AREM) 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 nitrazepam (e.g., AREM) is used in conjunction with anti-epileptic medicines, side-effects and toxicity may be more evident, particularly with hydantoins or barbiturates or combinations including them. This requires extra care in adjusting dosage in the initial stages of treatment.

Known inhibitors of hepatic enzymes, particularly cytochrome P450 have been shown to reduce the clearance of benzodiazepines and may potentiate their action and known inducers of hepatic enzymes, e.g. rifampicin, may increase the clearance of benzodiazepines (e.g. AREM).

Enhances sedative effect with moxonidine.

Baclofen and tizanidine (enhanced sedative effect).

Cimetidine has also been reported to inhibit the metabolism of AREM.

4.6 Fertility, pregnancy and lactation

Pregnancy

AREM is contraindicated in pregnancy (see section 4.3)

- Pregnancy (given during labour it crosses the placenta and may cause the floppy-infant syndrome characterised by central respiratory depression, hypothermia and poor sucking).

Breastfeeding

AREM is contraindicated in lactating mothers (see section 4.3)

Fertility

Data on the effect of AREM on fertility is not available.

4.7 Effects on ability to drive and use machines

AREM may, particularly at the initiation of therapy, lead to drowsiness or impaired concentration which may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should not drive, climb dangerous heights or operate dangerous machinery where loss of attention might be hazardous.

4.8 Undesirable effects

a) Summary of the safety profile

Common adverse effects include drowsiness during the day, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia and double vision. These phenomena are dose related and occur predominantly at the start of therapy, they usually disappear with repeated administration. The elderly and debilitated patients and in patients receiving high doses are particularly sensitive to the effects of centrally-depressant medicines.

b) Tabulated list of adverse reactions

MedDRA System Organ Class	**Description**
Blood and the lymphatic system disorders	
Less frequent	Blood dyscrasias
Immune system disorders	
Less frequent	Hypersensitivity reactions (anaphylaxia and angiooedema)
Psychiatric disorders	
Less frequent	Sleeping disorders, including insomnia, psychiatric and paradoxical reactions (4), muscular cramps, libido fluctuations
Unknown frequency	Dependence and abuse of benzo-diazepines, amnesia (2), depression (3), withdrawal symptoms (1)
Nervous system disorders	
Frequent	Dizziness, ataxia, drowsiness, headache, lightheadedness
Less frequent	Tremor
Unknown frequency	Dysarthria, hypothermia and tingling and numbness of the hands
Eye disorders	
Less frequent	Visual disturbances, blurred vision
Ear and labyrinth disorders	
Less frequent	Vertigo
Vascular disorders	
Less frequent	Hypotension
Respiratory, thoracic and mediastinal disorders	
Less frequent	Respiratory depression
Gastrointestinal disorders	

Less frequent	Nausea, gastrointestinal upsets, changes in salivation
Hepato-biliary disorders	
Less frequent	Jaundice
Skin and subcutaneous tissue disorders	
Less frequent	Rash, pruritis and other allergic skin reactions, Stevens-Johnson syndrome
Renal and urinary disorders	
Less frequent	Urinary retention/incontinence
Musculoskeletal, connective tissue and bone disorders	
Less frequent	Muscular weakness

(1) Use (even at therapeutic doses) may lead to the development of physical and psychological dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena, a transient syndrome whereby the symptoms that led to treatment with benzodiazepine or benzodiazepine-like medicine recur in an enhanced form. It may be accompanied by other reactions including mood changes, anxiety, convulsions and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually.
(2) Anterograde amnesia may occur during the use of therapeutic doses since the risk is increased at higher doses. Amnesia may be combined with behavioural problems.
(3) Pre-existing depression may be revealed during the use of benzodiazepines (e.g AREM).
(4) Reactions such as restlessness, excitation, irritability, aggressiveness, delusions, rage, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural side effects may occur during benzodiazepine treatment. They can be very serious with AREM. These side effects are observed more frequently in elderly patients.

The benzodiazepines have a moderate potential for abuse.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. Reporting can also be done directly to Adcock Ingram Limited at:

Adcock Ingram Limited:
E-mail: Adcock.aereports@adcock.com
Tel: 011 635 0134

4.9 Overdose

Symptoms:

Overdosage of benzodiazepines (e.g., AREM) is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, dysarthria and lethargy; in more serious cases, the symptoms include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Management:

Activated charcoal should be given to reduce absorption.

Treatment is symptomatic and supportive although the specific benzodiazepine antagonist, flumazenil, may be indicated in emergencies. Flumazenil may also be useful in the diagnosis of benzodiazepine overdosage.

The benzodiazepine antagonist flumazenil is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may trigger seizures.

If excitation occurs, barbiturates should not be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.2 Sedatives, hypnotics

Pharmacotherapeutic group: Hypnotics and Sedatives, Benzodiazepine derivatives,

ATC code: N05CD02.

The major molecular targets of the benzodiazepines are inhibitory neurotransmitter receptors directly activated by the amino acid, gamma-aminobutyric acid (GABA). The half-life is 26 hours ± 3 hours and are increased in the elderly and obese patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycollate

Starch maize

Talc purified

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Store in airtight containers, protected from light and moisture.

Keep in original packaging until required for use.

6.5 Nature and contents of container

30 or 250 tablets are packed in a white polypropylene securitainer with a white low density polyethylene or polypropylene cap, together with a foam or rayon insert and a leaflet.

Not all pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road,

Erand Gardens,
Midrand, 1685

Customer Care: 0860 ADCOCK/ 232625

8. REGISTRATION NUMBER

K/2.2/210

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 28 March 1978

10. DATE OF REVISION OF THE TEXT

23 December 2022