SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Temazepam 10mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of oral solution contains 10mg of temazepam.

Excipients with known effect:

Each 5 ml of oral solution contains 400mg of ethanol (alcohol) and 905mg of sorbitol (E420).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution

A clear, green colour solution with odour of peppermint.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Temazepam is indicated for the short term treatment of sleep disturbances, considered severe or disabling or where insomnia is subjecting the individual to extreme distress. This product is especially useful in those patients for whom particularly rapid onset of hypnotic action is required and for whom the persistence of hypnotic effect after rising would be undesirable.

Temazepam is particularly suitable for patients with transient sleep disorders in whom re-establishment of normal sleep patterns is expected following the resolution of precipitating factors.

It is also indicated for pre-medication for minor surgical and investigative procedures, especially in the case of outpatients.

4.2 Posology and method of administration

Posology

Insomnia

Adults:

The usual dose is 5 - 15ml (10-30mg) orally on retiring; a dose of 10ml (20mg) will be found to be satisfactory for most patients. This may be increased to 15 - 20ml (30 - 40mg) in patients who do not respond to the lower dose. Lower doses may be adequate for some patients, as for the elderly.

Pre-medication

10 - 20ml (20 - 40mg) from half an hour to one hour prior to surgery or investigative procedures.

Elderly:

Elderly patients or those suffering from cerebral vascular changes such as arteriosclerosis are likely to respond to smaller doses. Half the normal dose, 2.5 - 7.5ml (5 - 15mg) may be sufficient for a therapeutic response.

Paediatric population:

Insomnia

Not recommended

Pre-medication

1mg (0.5ml)/kg one hour prior to surgery or investigative procedures.

Treatment should if possible be intermittent. The lowest dose which can control symptoms should be used. It should not be continued beyond 4 weeks.

Long term chronic use is not recommended.

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

Method of administration

For oral administration only.

4.3 Contraindications

- Hypersensitivity to the active substance, to Benzodiazepines or to any of the excipients listed in section 6.1.
- Neuromuscular respiratory weakness including myasthenia gravis (condition may be exacerbated).
- Acute pulmonary insufficiency, severe respiratory depression, sleep apnoea syndrome (risk of further respiratory depression) or CNS depression.
- Severe hepatic insufficiency (may precipitate encephalopathy. Elimination half-life of temazepam may be prolonged).
- Phobic or obsessional state; chronic psychosis (paradoxical reactions may occur. Inadequate evidence of safety and efficacy).
- Mild anxiety states.
- Acute narrow angle glaucoma (due to anticholinergic effects of temazepam).
- As monotherapy in patients with depression or those with anxiety and depression (suicide may be precipitated in these patients).
- Breast-feeding.

4.4 Special warnings and precautions for use

An underlying cause for insomnia should be sought before deciding upon the use of benzodiazepines for symptomatic relief; benzodiazepines should not be used for first line treatment of psychotic illness.

Severe anaphylactic and anaphylactoid reactions, including rare fatal cases of anaphylaxis, have been reported in patients receiving temazepam. Cases of angioedema involving the tongue, glottis, or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including temazepam.

Where temazepam is used as a medication before surgical or investigative procedures, the patients should be accompanied home.

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, 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 minimizing anxiety over such symptoms should they occur while temazepam is being discontinued.

There are indications that, in the case of benzodiazepines with a short duration of action such as temazepam, withdrawal phenomena can become manifest between doses, 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.

Tolerance:

Limit of tolerance in patients with organic cerebral changes (particularly arteriosclerosis) or cardiorespiratory insufficiency may be very wide; care must be taken in adapting the dosage with such patients. Some loss of efficacy to the hypnotic effects of short acting benzodiazepines may develop after repeated use for a few weeks.

Temazepam should be given with caution to patients with chronic pulmonary insufficiency, or those with renal or hepatic dysfunction. Sedatives given to patients with cirrhosis may precipitate encephalopathy.

Doses of 30mg and above are more likely to cause hangover effects to persist into the following day than lower doses, particularly in patients unused to hypnotics and in the elderly. As with all compounds which have an effect on the CNS, patients should be advised not to consume alcohol whilst taking temazepam.

Dependence

In general, the dependence potential of benzodiazepines is low, but this increases when high dosage is used, especially when given over long periods. This is particularly so in patients with a history of alcoholism, drug abuse or in patients with marked personality disorders. Regular monitoring of treatment in such patients is essential, routine repeat prescriptions should be avoided and the treatment should be withdrawn gradually.

Withdrawal effects

Treatment in all patients should be withdrawn gradually as symptoms such as mood changes, nervousness, sleep disturbance, irritability, sweating, headaches, dizziness,

impaired concentration, tinnitus, loss of appetite, tremor, perceptual disturbances, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, orthostatic hypotension, photophobia, hyperacusis, muscle pain, extreme anxiety, tension, restlessness, confusion and diarrhoea have been reported following abrupt cessation of treatment with benzodiazepines in patients receiving even normal therapeutic doses for short periods of time. Abrupt withdrawal following excessive dosage may produce confusion, toxic psychosis, convulsions, derealisation, depersonalisation, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations, epileptic seizures or a condition resembling delirium tremens. Broken sleep with vivid dreams may persist for some weeks after withdrawal.

Rebound symptoms

Symptoms including insomnia and anxiety may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. As this is greater after abrupt discontinuation, the dose should be decreased gradually (see section 4.2).

Amnesia

Anterograde amnesia may occur, most often several hours after ingestion. To reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of

7-8 hours (see also section 4.8). Insufficient sleep may adversely affect the ability to drive/operate machinery etc. (see section 4.7).

Loss or bereavement

Psychological adjustment may be inhibited by benzodiazepines.

Psychiatric and ‘paradoxical’ reactions

Reactions like restlessness, agitation, irritability, aggressiveness, excitement, confusion, delusion, rage, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. These reactions are more likely to occur in children and in the elderly, and extreme caution should be used in prescribing benzodiazepines to patients with personalities disorders. Should this occur, use of the product should be discontinued.

Complex sleep behaviour-related events such as “sleep driving” (i.e. driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in patients who are not fully awake after taking a sedative-hypnotic, including triazolam. These events can occur with sedative-hypnotics, including temazepam, alone at therapeutic doses. The use of alcohol and other CNS depressants with sedative-hypnotics appears to increase the risk of such behaviours, as does the use of sedative-hypnotics at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of sedative-hypnotics should be strongly considered for patients who report such events.

<u>Risk from concomitant use of opioids</u>

Concomitant use of Temazepam 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 Temazepam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Temazepam 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).

Specific patient groups

Patients with depression

Temazepam should not be used alone to treat depression or anxiety associated with depression as suicide may be precipitated in such patients.

Patients with a history of alcohol & drug abuse

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

Patients with phobias and/or chronic psychoses

Temazepam is not recommended (inadequate evidence of efficacy and safety).

Pregnant women

Avoid regular use in pregnant women (risk of neonatal withdrawal symptoms); use only if clear indication such as seizure control (high doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia and respiratory depression) (see also section 4.6).

Excipient Warnings

This product contains liquid sorbitol (E420): Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This product also contains ethanol (alcohol) (E1510). Each 5ml of oral solution contains 400mg ethanol (alcohol), equivalent to equivalent to 10.13ml of beer or 4.05ml of wine per dose. It is harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women and high-risk groups such as patients with liver disease or epilepsy.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended

Alcohol - Temazepam should not be used together with alcohol (enhanced sedative effects: effect the ability to drive or operate machinery).

Sodium oxybate - avoid concomitant use (enhanced effects of sodium oxybate).

Take into account

Centrally acting drugs: Enhancement of the central depressive effect may occur if temazepam is combined with drugs such as neuroleptics, antipsychotics, tranquillisers, anxiolytics/sedatives, anti-epileptic products, narcotic analgesics, antidepressants, MAOIs, hypnotics, analgesics, anaesthetics, barbiturates and sedative antihistamines. The elderly may require special supervision.

Antiepileptic drugs: When used concurrently, side effects and toxicity may be more evident, particularly with hydantoins (e.g. phenytoin) and/or barbiturates. This requires extra care in adjusting dosage in the initial stages of treatment.

Narcotic analgesics: Enhancement of the euphoria may lead to increased psychological dependence.

Other drugs enhancing the sedative effect of chlordiazepoxide: cisapride, lofexidine, nabilone, disulfiram and the muscle-relaxants baclofen and tizanidine.

Compounds that affect hepatic enzymes (particularly cytochrome P450):
- inhibitors (e.g. cimetidine; ritonavir; fluvoxamine) reduce clearance and may potentiate the action of benzodiazepines
- inducers (e.g. rifampicin) may increase clearance of benzodiazepines.

Antihypertensives, vasodilators & diuretics: enhanced hypotensive effects with ACE-inhibitors, alpha blockers, angiotensin-II receptor antagonists, calcium channel blockers adrenergic neurone blockers, beta-blockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics.

Dopaminergics: possible antagonism of the effects of levodopa.

Theophylline: possible reduced effects of temazepam.

Antivirals: concurrent use of zidovudine with benzodiazepines may decrease zidovudine clearance. Ritonavir may inhibit benzodiazepine hepatic metabolism.

Clozapine: reports of cardiorespiratory collapse. Also increase in hypersalivation with both drugs.

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

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

4.6 Fertility, pregnancy and lactation

Insufficient data are available on temazepam to assess its safety during pregnancy and lactation. If the product is prescribed to a woman of child bearing age, she should be warned to contact her physician about stopping the product if she intends to become, or suspects that she is, pregnant. If for compelling medical reasons, temazepam is administered during the late phase of pregnancy, or during labour, effects on the neonate, such as hypothermia, hypotonia, and moderate respiratory depression, can be expected due to the pharmacological action of the product. Moreover, infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Since benzodiazepines are found in breast milk, temazepam should not be administered to breast feeding mothers.

4.7 Effects on ability to drive and use machines

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. 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 (called 'statutory defence') 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.

Patients should be advised that sedation, amnesia, impaired concentration, dizziness, blurred vision and impaired muscular function may occur and that, if affected, they should not drive or use machines, or take part in other activities where this would put themselves or other at risk. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. Concurrent medication may increase these effects (see section 4.5).

4.8 Undesirable effects

At the start of treatment patients may suffer from drowsiness, light-headedness the next day; confusion and ataxia (especially in the elderly); amnesia may occur and

dependence. Reduced alertness, dizziness, muscle weakness, fatigue, numbed emotions, double vision, unsteadiness, respiratory depression or slurred speech. These will normally disappear with continued treatment.

More rarely, headache, vertigo, hypotension, salivation changes, visual disturbances, dysarthria, tremor, incontinence, urinary retention, blood disorders, jaundice, vivid dreams/nightmares, restless sleep, palpitations, change in libido, skin reactions, sedation, impaired muscular function, dry mouth and gastro-intestinal disturbances may occur.

Severe anaphylactic and anaphylactoid reactions, including rare cases of fatal anaphylaxis, have been reported in patients receiving temazepam.

Pre-existing depression may be unmasked during treatment with temazepam.

Blood dyscrasias and increased liver enzymes have also been reported to occur occasionally. If any of these effects do occur, treatment should be discontinued.

Other effects, including delusions, psychoses, hallucinations, psychoses, irritability and restlessness, agitation, aggressiveness, nightmares and rages or other inappropriate behaviour and other adverse behavioural effects have also been reported to occur. They are more likely to occur in children and in the elderly. If any of these effects occur, treatment should be discontinued.

Dependence: Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of therapy may result in withdrawal of rebound phenomena (See warnings and precautions).

Psychological dependence may occur. Abuse of benzodiazepines has been reported.

Withdrawal effects on abrupt cessation of treatment: Depression, anxiety, headache, dizziness, impaired concentration, tinnitus, loss of appetite, tremor, perceptual disturbances, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, orthostatic hypotension, photophobia, hyperacusis, confusion, tension, nervousness, rebound insomnia, irritability, sweating and diarrhoea have been reported following abrupt cessation of treatment. In rare cases, withdrawal following excessive dosages may produce confusional states, psychotic manifestations and convulsions. Broken sleep with vivid dreams may persist for some weeks after withdrawal.

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 the Yellow Card Scheme Website at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Benzodiazepines commonly cause drowsiness, ataxia, dysarthria, mental confusion and nystagmus. Coma, hypotension, hypotonia and respiratory depression occasionally occur but are seldom serious if these drugs are taken alone. Coma usually lasts only a few hours but in elderly people it may be more protracted and cyclical. Benzodiazepine respiratory depressant effects are more serious in patients with severe chronic respiratory disease. Benzodiazepines potentiate the effects of other central nervous system depressants, including alcohol.

Management

Consider activated charcoal in adults or children who have taken more than 1mg/kg within 1 hour, provided they are not too drowsy. The benefit of gastric decontamination is uncertain. Gastric lavage is unnecessary if these drugs have been taken alone. The value of dialysis has not been determined for temazepam. Patients who are asymptomatic at four hours are unlikely to develop symptoms. Institute supportive measures as indicated by the patient's clinical state. If CNS depression is severe consider the use of flumazenil (Anexate), a benzodiazepine antagonist. This should rarely be required. It has a short half-life (about an hour) and should NOT TO BE USED IN MIXED OVERDOSE OR AS A "DIAGNOSTIC" TEST. It is contraindicated in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Temazepam has a similar pharmacological action to Oxazepam and Diazepam, that is, central nervous system sedation, anxiolysis and muscle relaxation. Animal studies show anticonvulsant activity. These effects are likely to be due to potentiation of gamma-aminobutyric acid (GABA) although other neurotransmitters may also be affected. Evidence suggests a close molecular association between the sites and action for GABA and the benzodiazepines.

5.2 Pharmacokinetic properties

Reported elimination half-life values for Temazepam after night time administration in young volunteers vary from 5.3 - 11.5 hours. There is, however, an approximately 30% increase in the half-life of Temazepam when taken in the morning. The mean

elimination half-life values in young volunteers after morning administration vary from 8.3 - 13.6 hours. In the elderly the half-life may be longer with a mean value of about 15 hours. The half-life in elderly women may be longer than in elderly men.

5.3 Preclinical safety data

None

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol

Propylene glycol (E1520)

Trometamol

Citric acid monohydrate

Liquid sorbitol (non-crystallising) (E420)

Purified water

Peppermint oil

Patent Blue V (E131)

Caramel (E150)

Glycerol (E422)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

21 months.

Discard 90 days after first opening.

6.4 Special precautions for storage

Do not store above 25^{o}C.

Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container

Bottle: Ph. Eur. Type III amber glass bottle

Closure: Tamper evident, child resistant plastic cap with polypropylene inner, polyethylene outer, and expanded polyethylene (EPE) liner.

Dosing Device: 10ml oral syringe with 0.5 ml graduations with an adaptor

Pack size: 300 ml

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/10/2017

10 DATE OF REVISION OF THE TEXT

30/07/2020