IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1332/025/002
Case No: 2050275

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Transferred from PA0022/026/004.

Meda Health Sales Ireland Limited

Office 10, Dunboyne Business Park, **Dunboyne**, **Co. Meath**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Normison 20 mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **29/08/2008**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Normison 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of temazepam.
Excipient: Lactose monohydrate 120 mg per tablet

For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White, to off-white, flat, bevel-edged tablets imprinted with “Wyeth” on one side and “WY” breakbar “041” on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Insomnia:
The short term treatment of insomnia only when it is severe, disabling or subjecting the individual to extreme distress.

Temazepam may be used as a pre- medicant prior to minor surgery or other related procedures.

4.2 Posology and method of administration

Dosage and duration of therapy should be individualised. The lowest effective dose should be prescribed for the shortest duration possible. This may vary from a few days to two weeks with a maximum (including tapering off) of four weeks. The risk of withdrawal and rebound phenomena is greater after abrupt discontinuation; therefore the drug should be discontinued gradually. The dose reduction process should be tailored to the individual.

The maximum dose should not be exceeded.

In certain cases extension beyond the maximum treatment period may be necessary; if this is the case it should not take place without re-evaluation of the patient’s status.

The product should be taken on retiring or up to 30 minutes before going to bed.

Dosage**:**
Insomnia:
Adults: 10-20 mg. In exceptional circumstances, the dose may be increased to 30-40 mg.

Elderly: 10mg. In exceptional circumstances the dose may be increased to 20mg.

Pre-medication: The usual dose is 20-40mg 30-60 minutes before the procedure.

Children: Not recommended for use in children.

Use in patients with hepatic impairment:
Normison is contraindicated in severe hepatic insufficiency. Dosage for patients with mild to moderate hepatic insufficiency should be reduced and adjusted carefully according to patient response.

Use in patients with renal impairment:
A reduced dose is recommended in patients with renal impairment.

4.3 Contraindications

Myasthenia gravis.

Hypersensitivity to benzodiazepines - including Normison tablets or their components.

Severe respiratory insufficiency.

Sleep apnoea syndrome.

Severe hepatic insufficiency.

4.4 Special warnings and precautions for use

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

Dependence
Use of benzodiazepines may lead to the development of physical and psychic 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 drug and alcohol abuse.

Dependence may lead to withdrawal symptoms, especially if treatment is discontinued abruptly. Therefore, the drug should always be discontinued gradually.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, extreme anxiety, tension, depression, insomnia, restlessness, confusion irritability, sweating, rebound phenomena, dysphoria, dizziness, derealisation, depersonalisation, hyperacusis, numbness/tingling of extremities, hypersensitivity to light, noise and physical contact/perceptual changes, involuntary movements, nausea, vomiting, diarrhoea, loss of appetite, hallucinations/delirium, convulsions/seizures, tremor, abdominal cramps, myalgia, agitation, palpitations, tachycardia, panic attacks, vertigo, hyperreflexia, short-term memory loss, and hyperthermia. Convulsions/seizures may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

Rebound Insomnia and anxiety
A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, and may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety, sleep disturbances and restlessness. Since the risk of withdrawal/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 depending on the indication. Treatment should not exceed 4 weeks including the tapering off period. 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 be aware of the possibility of rebound phenomena, thereby minimising anxiety while the product is being discontinued.

There are indications that, in the case of benzodiazepines with a short elimination half-life, withdrawal phenomena can become manifest within the dosage interval especially when the dosage is high.

Amnesia
Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk of this occurring, patients should ensure that they will be able to have uninterrupted sleep for 7-8 hours.

Psychiatric and 'paradoxical' reactions
Reactions like restlessness, agitation, irritability, aggressiveness, delusions, rages, hallucinations, psychoses, inappropriate behaviour are known to occur when using benzodiazepines. Should this occur, use of the drug should be discontinued. These are more likely to occur in children and the elderly.

Specific patient groups
Use of benzodiazepines, including temazepam, may lead to potentially fatal respiratory depression. A lower dose is recommended for patients with chronic respiratory insufficiency.

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as it may precipitate encephalopathy. Benzodiazepines are not indicated 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). Benzodiazepines should also be used with extreme caution in patients with a history of alcohol or drug abuse.

Caution should be used in the treatment of patients with acute narrow-angled glaucoma.

Elderly or debilitated patients may be more susceptible to the effects of temazepam; therefore, these patients should be monitored frequently and have their dosage adjusted carefully according to patient response.

Caution should be used in patients in whom a drop in blood pressure might lead to cardiovascular or cerebrovascular complications. This is particularly important in elderly patients.

Elderly patients should be warned of the risk of falls due to the myorelaxant effect of Normison Tablets, particularly if they get up at night.

Some patients taking benzodiazepines have developed a blood dyscrasia, and some have had elevations in liver enzymes. Periodic haematologic and liver function assessments are recommended where repeated courses of treatment are considered clinically necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended: Concomitant intake of alcohol. The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.
Take into account: Combination with CNS depressants. Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressants, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines. In the case of narcotic analgesics, potentiation of the euphoria may also occur leading to an increase in psychic dependence.

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.

Administration of theophylline or aminophylline may reduce the sedative effects of benzodiazepines, including temazepam.

4.6 Pregnancy and lactation

Temazepam should not be used during pregnancy.

An increased risk of congenital malformations associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested in several studies. In humans, umbilical cord blood samples indicate placental transfer of benzodiazepines and their glucuronide metabolites. Infants of mothers who ingested benzodiazepines for several weeks or more preceding delivery have been reported to have withdrawal symptoms during the postnatal period. Symptoms such as hypoactivity, hypotonia, hypothermia, respiratory depression, apnea, feeding problems, and impaired metabolic response to cold stress have been reported in neonates born of mothers who have received benzodiazepines during the late phase of pregnancy or at delivery.

If the product is prescribed to a woman of child bearing potential, she should be warned to contact her physician regarding discontinuance of treatment if she intends to become or suspects that she is pregnant.

It is unknown if temazepam is excreted in breast milk. However, 3-OH-benzodiazepines (such as temazepam) a expected to be secreted in small amounts into breast milk, therefore, temazepam should not be administered to breas feeding women, unless the expected benefit to the woman outweighs the potential risk to the infant.

Sedation and inability to suckle have occurred in neonates of lactating mothers taking benzodiazepines. Infants lactating mothers should be observed for pharmacological effects (including sedation and irritability).

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration, and impaired muscular function may adversely affect the ability to drive use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. Patients shou be warned not to operate dangerous machinery or motor vehicles if any of these effects occur.

4.8 Undesirable effects

Adverse reactions are listed in the following table in CIOMS frequency categories:

Very common ≥ 10%

Common ≥ 1%

Uncommon ≥ 0.1% and < 1%

Rare ≥ 0.01% and < 0.1%

Very rare < 0.01%

<u>Body as a whole</u>:	
Frequency undetermined:	hypersensitivity reactions, anaphylactic/anaphylactoid reactions, SIADH, hyponatraemia, hypothermia
Common:	muscle weakness, asthenia
<u>Cardiovascular:</u>	
Frequency undetermined:	hypotension, lowering in blood pressure
<u>Digestive:</u>	
Uncommon:	nausea
Frequency undetermined:	constipation, increase in bilirubin, jaundice, increase in liver transaminases, increase in alkaline phosphatase

Haematological/lymphatic:	
Frequency undetermined:	thrombocytopenia, agranulocytosis, pancytopenia
Nervous system and special senses:	
Frequency undetermined:	benzodiazepine effects on the CNS are dose dependent, with more severe CNS depression occurring with high doses
	extrapyramidal symptoms, tremor, vertigo, visual disturbances (including diplopia and blurred vision), dysarthria/slurred speech, headache, convulsions/seizures, amnesia, disinhibition, euphoria, coma, suicidal ideation/attempt
	paradoxical reactions including anxiety, agitation, excitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual arousal, hallucinations
Very common:	sedation, fatigue, drowsiness
Common:	ataxia, confusion, depression, unmasking of depression, dizziness
Uncommon:	change in libido, impotence, decreased orgasm
Respiratory:	
Frequency undetermined:	respiratory depression, apnoea, worsening of sleep apnoea (the extent of respiratory depression with benzodiazepines is dose dependent, with more severe depression occurring with high doses) Worsening of obstructive pulmonary disease
Skin:	
Frequency undetermined:	allergic skin reactions, alopecia

Amnesia
Anterograde amnesia may occur using therapeutic doses, the risk increasing at higher doses. Amnesia may be associated with inappropriate behaviour.

Depression
Pre-existing depression may be unmasked during benzodiazepine use.

Psychiatric and ‘paradoxical’ reactions
See Section 4.4 Special Warnings and Precautions for Use.

Dependence
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 Special Warnings and Precautions for Use). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

4.9 Overdose

As with other benzodiazepines, overdose 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. In postmarketing experience, overdose with temazepam has occurred predominantly in combination with alcohol and/or other drugs.

Following overdose with oral benzodiazepines, general supportive and symptomatic measures are recommended; vital signs must be monitored.

Vomiting should be induced (within one hour) if the patient is conscious, or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

When there is a risk of aspiration, induction of emesis is not recommended.

Temazepam is poorly dialysable.

The benzodiazepine antagonist, flumazenil may be useful in hospitalised patients as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. The physician should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma.

In mild cases, symptoms may include drowsiness, mental confusion and lethargy. In some serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

5 PHARMACOLOGICAL PROPERTIES

Temazepam is a 1, 4 benzodiazepine. Benzodiazepines have anxiolytic, hypnotic, sedative, anticonvulsant and muscle relaxing properties.

Temazepam hastens the onset of sleep, increases the duration of sleep, improves its quality and decreases awakenings.

5.1 Pharmacodynamic properties

The exact mechanism of action of benzodiazepines has not yet been elucidated; however, they appear to work through several mechanisms. Benzodiazepines presumably exert their effects by binding to specific receptors at several sites within the central nervous system either by potentiating the effects of synaptic or presynaptic inhibition mediated by gamma-aminobutyric acid (increased opening of postsynaptic chloride channels) or by directly affecting the action potential generating mechanisms.

5.2 Pharmacokinetic properties

Absorption
Pharmacokinetic studies have shown that temazepam is well-absorbed (90-100% and the first pass effect is slight (about 5%). The time to reach peak plasma levels is usually about 50 minutes when given orally. Maximum plasma levels observed after doses of 20 mg are 660-1100 ng/ml. With multiple dosing steady state is obtained by the third day and there is little or no accumulation of parent drug or metabolites.

Distribution
Volume of distribution: The volume of distribution volume is 1.3 to 1.5 L/kg bodyweight; for the unbound fraction, 43-68 L/kg. Approximately 96% of unchanged drug is bound to plasma proteins.

Metabolism
Temazepam is metabolised principally in the liver where most of the unchanged drug is directly conjugated to the glucuronide and excreted in the urine. Less than 5% of drug is demethylated to oxazepam and eliminated as the glucuronide. The glucoronides of temazepam have no demonstrable CNS activity.

Elimination
Temazepam is rapidly eliminated; most studies showing an elimination half life in the range of 7 - 11 hours (mean 8 hours).

Following a single dose, 80% of the dose appears in the urine, mostly as the conjugates and 12% of the dose appears in the faeces. Less than 2% of the dose is excreted unchanged in the urine

Elimination in reduced renal function
In established renal insufficiency the metabolic clearance of temazepam as well as the plasma level of the non-protein bound temazepam, remain within the normal range. The elimination half-life for temazepam glucuronide is however increased by which this inactive metabolite accumulates. As stated under “Overdose” it is unlikely that temazepam may be significantly removed by dialysis.

5.3 Preclinical safety data

- Toxicology

  Temazepam has demonstrated a low acute toxicity with an oral LD50 of:

  Mouse > 800 mg/kg
  Rat > 2800 mg/kg

  Chronic toxicity tests have been performed for six months on rats with doses of 60 and 120 mg/kg/day and on dogs with doses of up to 120 mg/kg/day without manifestations of significant toxic effects.

- Teratogenesis

  Studies conducted on rats at the doses of 5 and 10 mg/kg/day to verify the effects of temazepam on offspring have not shown teratogenic effects connected to the drug. Similar results were obtained in studies conducted on rabbits at doses of 5 and 10 mg/kg/day.

- Carcinogenesis, metagenesis

  Long term studies on mice and rats did not demonstrate carcinogenic potential. The Ames test has been performed on Saccharomyces cerevisiae and Schizosaccharomyces pombe without showing mutagenicity potential.

- Fertility studies

  Fertility in male and female rats has not been influenced negatively by temazepam.

- Perinatal studies

  An increase in perinatal death rate in rabbits has been observed from animal studies following the concomitant administration of temazepam and diphenhydramine in the last phases of pregnancy compared with rabbits receiving the drugs separately.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Lactose monohydrate
Macrogol 1540
Crospovidone
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Blisters – Do not store above 25°C. Store in the original package. Keep container in the outer carton.
Bottles – Do not store above 25°C. Keep the container tightly closed. Store in the original container.

6.5 Nature and contents of container

Polypropylene tubular container with an open end equipped to accept a polyethylene closure with a tamper-evident tear strip.

High density polyethylene tubular container with an open end equipped to accept a high density polyethylene closure with a tamper evident tear strip.

The containers are of sufficient volume to hold tablet quantities of either 50, 100, 250, 500 or 1000 tablets.

PVDC/Aluminium foil blister pack strips consisting of 250 µm PVDC and 20 µm Aluminium foil with a capacity to hold a total of 14 tablets. The strips are then carton packed.

Polypropylene Blister pack strips consisting of 300 µm transparent polypropylene and 16 µm Aluminium foil with a capacity to hold a total of 14 tablets. The strips are then carton packed.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Meda Health Sales Ireland Limited
Office 10, Dunboyne Business Park
Dunboyne
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8 MARKETING AUTHORISATION NUMBER

PA 1332/25/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th March 1997

Date of last renewal: 7th March 2007

10 DATE OF REVISION OF THE TEXT

August 2008