New Zealand Data Sheet

1. NORMISON (temazepam) 10 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of temazepam.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

NORMISON 10 mg are white to off-white, round, biconvex tablets with a stylised "S" on one side and plain on the other side.

Do not halve the tablet. Dose equivalence when the tablet is divided has not been established.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NORMISON is indicated for use as a hypnotic or night-time sedative. As a hypnotic, NORMISON is indicated for severe or disabling insomnia characterised by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening.

NORMISON is indicated for use as a premedicant taken 30-60 minutes prior to surgical or other procedures.

4.2 Dose and method of administration

For use as a hypnotic, the usual adult dose is 20 mg taken one-half hour before retiring. In elderly or debilitated patients, 10 mg NORMISON is the initial recommended dosage.

The recommended dosage range in adults is 10 to 30 mg but dosage should be individualised to the lowest effective dose.

For use as a premedicant, the recommended adult dose is 20-30 mg taken 30-60 minutes prior to surgical or other procedures.

Since insomnia is often transient and intermittent, the prolonged administration of NORMISON is generally not necessary or recommended. In general, hypnotics should be prescribed for short periods only (not more than 2-4 weeks) unless the patient is already reliant on regular hypnotic use. Continuous long term use of NORMISON is not recommended, but intermittent use may be appropriate.

For patients already receiving long-term NORMISON, it is recommended that the need for continued therapy be reviewed periodically.

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

NORMISON is not recommended for children.

4.3 Contraindications

NORMISON is contraindicated in:

- Patients with a known hypersensitivity to benzodiazepines.
- Patients with chronic obstructive airways disease with incipient respiratory failure.
- Patients with sleep apnoea.

Temazepam should not be used as monotherapy to treat depression, or symptoms of anxiety associated with depression, due to a risk of suicide (see Section 4.4).

4.4 Special warnings and precautions for use

Although hypotension has occurred rarely, NORMISON should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in elderly patients.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

NORMISON could increase the muscle weakness in myasthenia gravis and should be used with caution in this condition.

Caution should be used in the treatment of patients with acute narrow-angle glaucoma (because of atropine-like side effects).

Impaired renal/liver function and blood dyscrasias
Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances some patients taking benzodiazepines have developed blood dyscrasias, and some have had elevations of liver enzymes. As with other benzodiazepines, periodic blood counts and liver function tests are recommended. The use of temazepam may worsen hepatic encephalopathy; therefore, temazepam should be used with caution in patients with severe hepatic insufficiency and/or encephalopathy.

Depression, psychosis and schizophrenia
NORMISON is not recommended as primary therapy in patients with depression and psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated. Benzodiazepines may increase depression in some patients, and may contribute to deterioration in severely disturbed schizophrenics with confusion and

withdrawal. Suicidal tendencies may be present or uncovered and protective measures may be required.

Psychiatric and/or paradoxical reactions
As with other benzodiazepines and CNS active drugs, three idiosyncratic symptom clusters, which may overlap, have been described.

- Amnestic symptoms: anterograde amnesia with appropriate or inappropriate behaviour;
- Confusional states: disorientation, derealisation, depersonalisation and/or clouding of consciousness; and
- Agitational states: sleep disturbances, restlessness, acute rage, irritability, aggression and excitation.

Temazepam should be discontinued if confusion or agitation occurs.

Paradoxical reactions such as acute rage, stimulation or excitement may occur; should such reactions occur, NORMISON should be discontinued. Such reactions may be more likely to occur in children and the elderly.

Geriatric or debilitated patients
Such patients may be particularly susceptible to the sedative effects of benzodiazepines and associated giddiness, ataxia and confusion, which may increase the possibility of a fall. NORMISON 10 mg is the recommended starting dose for these patients.

Impaired respiratory function
Use of benzodiazepines, including temazepam, may lead to potentially fatal respiratory depression. Caution in the use of NORMISON is recommended in patients with respiratory depression. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased arterial oxygen tension.

Epilepsy
Abrupt withdrawal of benzodiazepines in patients with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures.

Abuse
Abuse of benzodiazepines has been reported. Benzodiazepines should be used in caution in patients with a history of alcohol or drug abuse, dependence on CNS depressants, individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

Before prescribing and throughout treatment, assess each patient's risk for abuse, misuse, and addiction. Use of benzodiazepines, particularly in patients at elevated risk, necessitates counselling about the risks and proper use.

Dependence
The use of benzodiazepines, including temazepam, may lead to physical and psychological dependence as defined by the presence of a withdrawal syndrome on discontinuation of the drug. The risk of dependence increases with higher doses and longer term use and is further increased in patients with

a history of alcoholism or drug abuse or in patients with significant personality disorders. Temazepam may have abuse potential, especially in patients with a history of drug and/or alcohol abuse. Regular monitoring in such patients is essential.

Duration of treatment
In general, benzodiazepines should be prescribed for short periods only (e.g. 2-4 weeks). Continuous long-term use of NORMISON is not recommended. There is evidence that tolerance develops to the sedative effects of benzodiazepines. After as little as one week of therapy withdrawal symptoms can appear following the cessation of recommended doses (e.g. rebound insomnia following cessation of a hypnotic benzodiazepine).

Tolerance
Tolerance as defined by a need to increase the dose in order to achieve the same therapeutic effect seldom occurs in patients receiving recommended doses under medical supervision. Tolerance to benzodiazepines may develop from continued therapy. Tolerance to sedation may occur with benzodiazepines especially in those with drug seeking behaviour.

Withdrawal
Abrupt discontinuation or rapid dosage reduction of benzodiazepines after continued use may precipitate acute withdrawal reactions. The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency. Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepines. These symptoms can range from headache, nausea, diarrhoea, loss of appetite, insomnia, anxiety, tensions, depression, restlessness, irritability, rebound phenomena, dysphoria, dizziness, abdominal cramps, agitation, palpitations, tachycardia, panic attacks, vertigo, myoclonus akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feelings of motion, metallic taste), depersonalisation, derealisation, hyperacusis, delusional beliefs, hyperreflexia, numbness/tingling extremities and loss of short term memory, to a major syndrome which may include convulsions/seizures, tremor, abdominal and muscle cramps, confusional states, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating. Convulsions/seizures may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the seizure threshold such as antidepressants. Particular care should be taken in patients with epilepsy, and other patients who have had a history of seizures, alcohol or drug dependence. Such manifestations of withdrawal, especially the more serious ones, are more common in those patients who have received excessive doses over a prolonged period, or in patients who have been dependent on alcohol or other narcotic drugs in the past. However, withdrawal symptoms have also been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly, Normison should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication.

Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia and anxiety mean an increase in the severity of these symptoms beyond pre-treatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-existing symptoms combined with withdrawal symptoms described earlier. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 to 4 hours) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses taken for relatively short periods. In some cases, patients taking benzodiazepines have developed protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months.

As with all patients taking CNS-depressant medications, patients receiving NORMISON should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from NORMISON therapy. Abilities may be impaired on the day following use. In sleep laboratory studies in volunteers, doses of 10 and 20 mg did not significantly affect morning performance, however the 30 mg dose produced impairment of psychomotor behaviour on the morning following night time administration.

Dose tapering
Following the prolonged use of NORMISON at therapeutic doses withdrawal from the medication should be gradual. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Periods from four weeks to four months have been suggested. As with other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase of sleep disturbance can occur after use of NORMISON (see Section 4.4 Dependence).

Concomitant use with alcohol/CNS depressants
The concomitant use of temazepam with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of temazepam which may include severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see Section 4.5).

Risks from concomitant use with opioids
Concomitant use of benzodiazepines, including temazepam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe NORMISON concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when NORMISON is used with opioids (see Section 4.5).

Paediatric use
The safety and effectiveness of temazepam has not been established in children less than 16 years of age.

Paediatric neurotoxicity
Published juvenile animal studies demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive defects when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans.

Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anaesthetic agents early in life and may result in adverse cognitive or behavioural effects. These studies have substantial limitations and it is not clear if the observed effects are due to the anaesthetic/sedative agent administration or other factors such as the surgery or underlying illness.

Anaesthetic and sedative agents can be part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks (see also Section 4.6).

4.5 Interaction with other medicines and other forms of interaction

The benzodiazepines, including NORMISON, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression, e.g. barbiturates, alcohol, sedatives, tricyclic antidepressants, non-selective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines or narcotic analgesics and anaesthetics.

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABAA sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

The cytochrome P450 system has not been shown to be involved in the disposition of NORMISON and, unlike many benzodiazepines, pharmacokinetic interactions involving the P450 system have not been observed with NORMISON.

The anticholinergic effects of other drugs including atropine and similar drugs, antihistamines and antidepressants may be potentiated.

Interactions have been reported between some benzodiazepines and anticonvulsants, with changes in the serum concentration of the benzodiazepine or anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together, and that serum level monitoring of the anticonvulsant be performed more frequently.

Minor EEG changes, usually low voltage fast activity, of no known clinical significance, have been reported with benzodiazepine administration.

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

No interference with laboratory tests have been identified or reported with the use of temazepam.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Data from observational studies suggest that there is an increased risk of miscarriage from benzodiazepine exposure during pregnancy. When treating women of childbearing potential, the benefits of treatment should be weighed against the risks and the patient should be informed of the increased risk of miscarriage.

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

Use during pregnancy: category C
Temazepam should not be used during pregnancy. Data from observational studies suggest that there is an increased risk of miscarriage from benzodiazepine exposure during pregnancy.

Benzodiazepines cross the placenta and may cause hypoactivity, hypotonia, reduced respiratory function, apnoea, feeding problems, hypothermia and impaired metabolic response to cold stress in the newborn infant of mothers who have received benzodiazepines during the late phase of pregnancy or at delivery. Continuous treatment during pregnancy and administration of high doses in connection with delivery should be avoided. Withdrawal symptoms in newborn infants have been reported with this class of drugs.

The use of benzodiazepines during the first trimester of pregnancy should almost always be avoided. 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.

Risk summary statement
Anaesthetic and sedative agents can be part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any

other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

Preclinical data
Published studies in pregnant primates demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see also Section 5.3).

Non-teratogenic effects
The use of benzodiazepines during the last phase of pregnancy or at delivery may require ventilation of the infant at birth.

In animal studies an increased perinatal mortality has been seen following concomitant administration of temazepam and diphenhydramine to rabbits in the later stages of gestation compared with rabbits that received either drug alone. It is recommended that the use of temazepam be avoided in pregnant women receiving antihistamines.

Impairment of fertility
Fertility in male and female rats was not adversely affected by temazepam.

Use in lactation
Caution should be exercised when NORMISON is given to breast feeding women.

NORMISON is believed to be excreted in human breast milk and may cause drowsiness and feeding difficulties in the infant.

4.7 Effects on ability to drive and use machines

As with all patients taking CNS-depressant medications, patients receiving NORMISON should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from NORMISON therapy. Abilities may be impaired on the day following use.

Somnambulism and associated behaviours
Complex behaviours such as “sleep-driving” (i.e. driving while not fully awake after taking a sedative-hypnotics, with amnesia for the event) have been reported with sedative hypnotics. These events can occur in sedative-hypnotics naïve as well as in sedative hypnotic experienced persons. These events can occur at normal therapeutic doses, and the risk appears to be increased when sedative-hypnotics are combined with alcohol or other CNS depressants or used 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 a “sleep-driving” episode. Other complex behaviours (e.g. preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with “sleep-driving”,

patients usually do not remember these events.

Angioedema
Angioedema involving the tongue, glottis and larynx has been reported in some patients after taking the first or subsequent doses of sedative-hypnotics. These cases of angioedema may cause airway obstruction and be fatal; this has required medical therapy in emergency departments for some patients. Additional symptoms have been reported in some patients including dyspnea, throat closing, or nausea and vomiting suggesting anaphylaxis.

4.8 Undesirable effects

All adverse reactions reported with temazepam are common with other benzodiazepine compounds.

More common reactions
Nervous System: dizziness, headache, vertigo, sedation, fatigue, drowsiness, ataxia.

Less common reactions
Body as a whole: asthenia.

Biochemical: elevated SAP, AST, BUN, bilirubin; proteinuria, neutrophil leucocytosis.

Cardiovascular: palpitation, tachycardia.

Dermatological: allergic skin reactions including macular rash and pruritus.

Gastrointestinal: dry mouth, nausea, vomiting, gastrointestinal upset.

Miscellaneous: loss of taste.

Musculo-Skeletal: leg cramps, weakness.

Nervous System: confusion, disorientation, muzziness, sciatica, tremor, faintness, change in libido, impotence, decreased orgasm.

Ocular: blurred vision.

Pulmonary: breathlessness.

Psychiatric: unmasking of depression, irritability, vivid dreams.

Frequency undetermined
Body as a whole: hypersensitivity reactions, anaphylactic/oid reactions, SIADH, hyponatraemia, hypothermia.

Cardiovascular: hypotension, lowering in blood pressure.

Digestive: constipation, jaundice.

Haemotological/Lymphatic: thrombocytopaenia, agranulocytosis, pancytopaenia.

Nervous system and special senses: extrapyramidal symptoms, visual disturbance (including diplopia), dysarthria/slurred speech, convulsions/seizures, amnesia, disinhibition, euphoria, coma, suicidal ideation/attempt (benzodiazepine effects on the CNS are dose dependent, with more severe CNS depression occurring with higher doses).

Respiratory: respiratory depression, apnoea, worsening of sleep apnoea (the extent of respiratory depression with benzodiazepines is dose dependent, with more severe depression occurring with higher doses), worsening of obstructive pulmonary disease.
Dermatological: alopecia

Paradoxical reactions such as anxiety, agitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual arousal, hallucinations, stimulation and excitement rarely occur (see Section 4.4).

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Symptoms
Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, lethargy, dysarthria and paradoxical reactions. In more serious cases, symptoms may include ataxia, CNS depression, hypotonia, hypotension, respiratory depression, cardiovascular depression, coma, and very rarely proves fatal.

Treatment
In the management of overdosage with any medication, it should be borne in mind that multiple agents may have been taken.

Following overdosage with oral benzodiazepines, activated charcoal should be given to reduce absorption. Hypotension and respiratory depression should be managed according to general principles.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication. The benzodiazepine antagonist flumazenil may be used in hospitalised patients for the reversal of acute benzodiazepine effects. Please consult the flumazenil product information prior to usage.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

NORMISON hastens the onset of sleep and increases total sleeping time in short term use.

The exact mechanism of action of benzodiazepines has not yet been elucidated; however, benzodiazepines 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 pre-synaptic inhibition mediated by gamma-aminobutyric acid or by directly affecting the action potential generating mechanisms.

5.2 Pharmacokinetic properties

Pharmacokinetic studies have shown that NORMISON is well absorbed and has a relatively short elimination half-life of approximately 10 hours (range 5 - 15 hours). Peak plasma levels of the drug occur 35 to 65 minutes after administration of the capsules. With multiple dosing, steady state is obtained by the third day, and there is little or no accumulation of parent drug or metabolites.

NORMISON is metabolised principally in the liver where most drug is directly conjugated to the glucuronide and excreted in the urine. Some drug is demethylated to oxazepam and eliminated as the glucuronide. The glucuronides of NORMISON have no demonstrable CNS activity. Following a single oral 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. Approximately 96% of unchanged drug is bound to plasma proteins.

5.3 Preclinical safety data

Animal toxicology and/or pharmacology

Published studies in animals demonstrate that the use of anaesthetic and sedative agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory.

In a published study conducted on rhesus monkeys, administration of an anaesthetic dose of ketamine for 24 hours on Gestation Day 122 increased

neuronal apoptosis in the developing brain of the foetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring of rhesus macaques. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits. Healthcare providers should balance the benefits of appropriate anaesthesia in pregnant women, neonates and young children who require procedures with the potential risks suggested by the nonclinical data.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, microcrystalline cellulose, maize starch and magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store below 30°C. Protect from moisture.

6.5 Nature and contents of container

Blisters of 25 tablets

6.6 Special precautions for disposal <and other handling>

Not applicable.

7. MEDICINE SCHEDULE

Controlled Drug C5

8. SPONSOR

Pharmacy Retailing (NZ) Limited
Trading as Healthcare Logistics
58 Richard Pearce Drive
Airport Oaks
Auckland
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9. DATE OF FIRST APPROVAL

2 September 2010

10. DATE OF REVISION OF THE TEXT

14 January 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	At the request of Medsafe, additional safety information regarding risks of misuse, addiction, dependence and withdrawal reactions.
3	Update colour
4.6	Addition of safety information about benzodiazepines and the risk of miscarriage.