

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

NOCTAMID® lormetazepam 1.0 mg tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NOCTAMID® lormetazepam 1.0 mg tablet.

For the full list of Excipients, see List of excipients.

3 PHARMACEUTICAL FORM

Each round, biconvex, white tablet, diameter 7 mm, with a score on one side and “CF” in a hexagon on the other, contains 1.0 mg lormetazepam.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term treatment of insomnia (characterised by difficulty in falling asleep and frequent nocturnal awakenings).

Noctamid is only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Dose and method of administration

In adults, treatment should be started with 1 mg lormetazepam as a single dose. Patients of advanced age should take 0.5 mg lormetazepam as a single dose. For patients with chronic respiratory insufficiency or hepatic insufficiency, a dose reduction should be considered.

It is possible to double the dose in individual cases.

The duration of treatment should be as short as possible. Generally it varies from a few days to two weeks with a maximum of four weeks, including gradual reduction of dose.

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 situation (see Special warnings and precautions for use, Duration of Treatment).

Noctamid is to be taken with some liquid shortly before going to bed.

Noctamid should not be given to patients under 18 years of age for insomnia without careful assessment of the need to do so. The single dose for patients under 18 years of age depends on the age, weight and general condition of the patient. The duration of treatment must be kept to a minimum

4.3 Contraindications

Myasthenia gravis, hypersensitivity to benzodiazepines or to any of the excipients of Noctamid, severe respiratory insufficiency (e.g. severe chronic obstructive pulmonary disease) and sleep apnoea syndrome.

Acute intoxication with alcohol, hypnotics, analgesics or psychotropic medicines (neuroleptics, antidepressants, lithium).

4.4 Special warnings and precautions for use

Duration of Treatment

The duration of treatment should be as short as possible. Generally it varies from a few days to two weeks with a maximum of four weeks, including gradual reduction of dose.

The patient should be informed when treatment is started that it will be of limited duration and it should be precisely explained how the dosage will be progressively decreased.

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 situation.

For more information concerning patients under 18 years of age, see the Dose and method of administration.

Tolerance

Some loss of efficacy to the hypnotic effects of Noctamid may develop after repeated use for a few weeks.

Dependence

Use of Noctamid and other benzodiazepines may lead to the development of physical and psychological 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 alcohol or drug abuse. Therefore, Noctamid should be used with extreme caution in patients with a history of alcohol or drug abuse.

Abuse of benzodiazepines has been reported.

Withdrawal symptoms

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 and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, paraesthesia of the limbs, hypersensitivity to light, noise and physical contact, hallucinations and epileptic seizures.

There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can manifest within the dosage interval, especially when the dosage is high. This is unlikely to happen with Noctamid because its elimination half-life is about 10 hours.

However, switching to Noctamid after long and/or high-dose use of a benzodiazepine with a significantly longer duration of action may result in the development of withdrawal symptoms.

Rebound insomnia

Rebound insomnia, a transient syndrome whereby the insomnia that led to treatment with a benzodiazepine recurs in enhanced form, may occur on withdrawal of treatment.

Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is gradually decreased. It is important that the

patient should be made aware of the possibility of rebound phenomena thereby minimising anxiety over such symptoms, should they occur while Noctamid is being discontinued.

Amnesia

Noctamid may induce anterograde amnesia. This condition occurs most often in the first few hours after ingesting the product. In order to reduce the risk of anterograde amnesia, patients should ensure that they will be able to sleep, uninterrupted, for 7 - 8 hours.

Psychiatric and Paradoxical Reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate, abnormal behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the product should be discontinued.

These reactions are more likely to occur in children and the elderly, as well as patients with organic brain syndrome.

Noctamid is not recommended for the primary treatment of psychotic illness. It should not be used alone for the treatment of sleep disorder associated with depression.

The presence of depression must always be ruled out particularly in first-time and early morning sleep disorders, since pre-existing depression may be unmasked during benzodiazepine use, including Noctamid. Suicide may be precipitated in such patients. Noctamid should be used with caution in these patients with depression.

Concomitant Use with Alcohol/CNS Depressants

Enhancement of the clinical effects of lormetazepam may occur when concomitantly used with alcohol and/or CNS depressants (see Interaction with other medicines and other forms of interaction).

SPECIFIC PATIENT GROUPS

Paediatric Use

Noctamid should not be given to patients under 18 years of age without careful assessment of the need to do so; the duration of treatment must be kept to a minimum (see Dose and method of administration).

Use in the Elderly

Benzodiazepines, including Noctamid, may be associated with an increased risk of falling due to adverse effects including ataxia,

Noctamid should be administered with caution to patients with spinal and cerebellar ataxia (see Undesirable effects). muscle weakness, dizziness, somnolence/ sleepiness and fatigue, and therefore it is recommended to treat elderly patients with caution.

Elderly patients should be given a reduced dose (see Dose and method of administration).

Patients with Spinal and Cerebellar Ataxia

Patients with Chronic Respiratory Insufficiency

A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression (see Dose and method of administration and Contraindications).

Patients with Hepatic Impairment

It is recommended to treat patients with severe hepatic insufficiency with caution, as benzodiazepines may enhance symptoms of encephalopathy. In hepatic impaired patients, elevated systemic exposure has been observed. A dose reduction should be considered (see Dose and method of administration and Pharmacokinetic properties)

Patients with Renal Impairment

Noctamid should be administered with caution to patients with severe renal insufficiency.

4.5 Interaction with other medicines and other forms of interaction

CNS Depressants

Enhancement of the depressive effect on the central nervous system may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic products, anaesthetics and sedative antihistamines.

Narcotic analgesics

In the case of narcotic analgesics, enhancement of euphoria may also occur, leading to an increased risk in psychological dependence.

Alcohol

Concomitant intake with alcohol should be avoided. The sedative effect may be enhanced when Noctamid is used in combination with alcohol.

Other Interactions

The following interactions have been observed for lormetazepam:

- cardiac glycosides: concurrent use may increase plasma levels of cardiac glycosides
- beta-blocking agents: concurrent use may increase the clinical effects of lormetazepam

The following drug interactions have been described for benzodiazepines similarly metabolised as lormetazepam:

- methylxanthines: concurrent use may reduce sedative effect
- oestrogen-containing medicinal products: concurrent use may decrease plasma levels of benzodiazepines
- rifampicin: concurrent use may reduce sedative effect

4.6 Fertility, pregnancy and lactation

Use in Pregnancy

Pregnancy Category C: “Medicines which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible”.

As a precaution, Noctamid should not be used during pregnancy, delivery and lactation. If Noctamid is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of Noctamid if she intends to become or suspects that she is pregnant.

If, for compelling medical reasons, Noctamid is administered during the late phase of pregnancy, or during labour and delivery, effects on the neonate, such as hypothermia, hypotonia, hypotension, moderate respiratory depression and sucking difficulties can be expected due to the pharmacological action of the compound.

Infants born to mothers who took Noctamid or other 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.

Use in Lactation

Since small amounts of the medicine may enter the breast-milk, Noctamid should not be administered to breast-feeding mothers. By calculation, 0.35 % of the daily dose of a breast feeding mother could reach the newborn.

4.7 Effects on ability to drive and use machines

Noctamid has a major influence on the ability to drive and use machines, or to perform tasks requiring alertness, as it causes sedation, amnesia, impaired concentration and impaired muscular function. Reactions can be particularly impaired depending on the time of ingestion, insufficient sleep duration, individual sensitivity and dosage. This applies to an increased extent in association with alcohol.

4.8 Undesirable effects

At the beginning of treatment, somnolence during the day, emotional disorder, depressed consciousness, confusion, fatigue, headache, dizziness, muscular weakness, ataxia, or double vision may occur; these reactions usually disappear with repeated administration.

The most frequently observed adverse drug reactions (ADRs) in patient receiving Noctamid are headache, sedation and anxiety.

The most serious ADRs in patients receiving Noctamid are angioedema, completed suicide or suicide attempt in association with unmasking of pre-existing depression.

The ADRs observed with Noctamid are represented in the table below. They are classified according to System Organ Class (MedDRA version 13.1). The most appropriate MedDRA terminology is used to describe a certain reaction and its synonyms and related conditions.

ADRs from clinical trials (in 852 patients, administered dose: 0.5 mg to 3 mg lormetazepam) are classified according to their frequencies. Frequencies are defined as:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

The ADRs identified only during post marketing surveillance, and for which a frequency could not be estimated, are listed under “not known”.

Within each frequency grouping, adverse effects are presented in order of decreasing seriousness.

Table 1. ADRs reported in clinical trials or during post-marketing surveillance in patients treated with Noctamid

System Organ Class	Very Common	Common	Not Known
Immune System Disorders		Angioedema*	
Psychiatric Disorders		Anxiety Decreased libido	Completed suicide (unmasking of pre-existing depression)* Suicide attempt (unmasking of pre-existing depression)* Acute psychosis# Hallucination# Dependence# Depression (unmasking of pre-existing depression)# Delusion# Withdrawal syndrome (rebound insomnia)# Agitation# Aggression# Irritability# Restlessness# Anger# Nightmare# Abnormal behaviour# Emotional disorder
Nervous System Disorders	Headache	Dizziness Sedation Somnolence Disturbance in attention Amnesia Visual impairment Speech disorder Dysgeusia Bradyphrenia	Confusional state Depressed level of consciousness Ataxia# Muscular weakness#
Cardiac Disorders		Tachycardia	
Gastrointestinal Disorders		Vomiting Nausea Upper abdominal pain Constipation Dry mouth	

System Organ Class	Very Common	Common	Not Known
Skin and Subcutaneous Tissue Disorders		Pruritus	Urticaria Rash
Renal and Urinary Disorders		Micturition disorder	
General Disorders and Administration Site Conditions		Asthenia Hyperhidrosis	Fatigue#
Injury, Poisoning and Procedural Complications			Fall

* Life threatening and/or fatal cases have been reported

See Special warnings and precautions for use

Dependence

Use of Noctamid and other benzodiazepines (even with therapeutic doses) may lead to the development of physical and psychological 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 alcohol or drug abuse. Therefore, Noctamid should be used with extreme caution in patients with a history of alcohol or drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of extreme anxiety, tension, restlessness, confusion, irritability, headaches and muscle pain. In severe cases the following symptoms may occur: derealisation, depersonalisation, hallucinations, paraesthesia of the limbs, hypersensitivity to light, noise and physical contact, hyperacusis and epileptic seizures.

There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can manifest within the dosage interval, especially when the dosage is high. This is unlikely to happen with Noctamid because its elimination half-life is about 10 hours (see Pharmacokinetic properties).

For more information concerning dependence/withdrawal phenomena, see Special warnings and precautions for use.

Psychiatric disorders

Rebound insomnia: a transient syndrome whereby the insomnia that led to treatment with a benzodiazepine recurs in enhanced form, may occur on withdrawal of treatment.

Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is gradually decreased, and the patient should be made aware of the possibility of rebound phenomena thereby minimising anxiety over such symptoms, should they occur while Noctamid is being discontinued.

Psychiatric and paradoxical reactions: Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate, abnormal behaviour and other adverse behavioural disorders are known to occur when using Noctamid. Should this occur, use of the product should be discontinued.

These reactions are more likely to occur in children and in elderly patients as well as in patients with organic brain syndrome.

Noctamid is not recommended for the primary treatment of psychotic illness. It should not be used alone for the treatment of sleep disorder associated with depression. Pre-existing depression may be unmasked during benzodiazepine use, including Noctamid. Suicide may be precipitated in such patients. Noctamid should be used in caution in these patients with depression.

Nervous system disorders

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. The condition occurs most often in the first few hours after ingesting the product. In order to reduce the risk of anterograde amnesia, patients should ensure that sufficient uninterrupted sleep of 7 - 8 hours is possible.

Reporting of suspected adverse reactions

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://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

As with other benzodiazepines, overdose of Noctamid 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 and that respiratory depression, rarely coma and very rarely death may occur. Special attention must be paid to respiratory and cardiovascular functions in intensive care.

Symptoms

The symptoms of mild lorazepam intoxication are drowsiness, tiredness, ataxic symptoms, and disturbed vision.

Oral intake of higher doses (e.g. a package with 20 tablets of 2 mg medicine substance) may result in deep sleep ranging to unconsciousness, respiratory depression and hypotension.

Treatment

Patients with milder symptoms of intoxication should be allowed to sleep them off under observation. On oral intake of larger amounts, 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.

Flumazenil may be useful as an antidote.

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

Noctamid has a high affinity for specific binding sites in the central nervous system. These benzodiazepine receptors display a close functional relationship to the receptors of the inhibitory neurotransmitter γ -aminobutyric acid (GABA). As a benzodiazepine receptor agonist, Noctamid

reinforces the GABA-ergic inhibition of the activity of distal neurons. This effect pharmacologically manifests in the form of anxiolytic, anticonvulsive, muscle relaxing and sedative-hypnotic effects.

Noctamid shortens sleep latency, reduces the frequency of nocturnal arousals and prolongs sleep duration without contributing to undesired sedation or reduced performance on the day after its use. The anxiolytic and muscle relaxing effects can be exploited pre- and post-operatively.

5.2 Pharmacokinetic properties

Lormetazepam is completely absorbed from the Noctamid tablet. Absorption proceeds with a half-life of 0.5 - 0.9 hours.

Maximum plasma levels of about 6 ng/mL are reached 1.5 hours after ingestion of Noctamid 1 mg. Postmaximal decrease of medicine plasma levels is in two phases characterised by half-lives of 2 - 2.5 hours and about 10 hours. During absorption and first-pass through the liver, about 20 % of the dose is inactivated presystemically. Thus, the absolute bioavailability is about 80 % of the dose.

Lormetazepam is extensively bound to plasma albumin. Independent of the concentration, 8.6 % of total plasma levels are present as free portions. The metabolic clearance rate accounts for 3.6 mL/min/kg. Lormetazepam is almost exclusively metabolised by glucuronidation. Lormetazepam glucuronide does not bind to the benzodiazepine-receptor. It is the main metabolite and the only one found in plasma and is almost exclusively excreted with urine. Less than 6 % of the dose was found as N-demethylated lormetazepam glucuronide, exclusively in urine. The excretion rate was in one phase, for which a half-life of 13.6 hours was calculated. In urine 86 % of the dose was recovered. The renal clearance of lormetazepam glucuronide was about 0.65 mL/min/kg.

The pharmacokinetics of lormetazepam are dose linear within the range of 1 - 3 mg.

No sex differences in pharmacokinetics were found. Small differences in terms of lower metabolic clearance rate, longer half-life of the terminal disposition phase in plasma and higher steady-state medicine levels in plasma were found in elderly volunteers as compared to young test subjects. The elimination of lormetazepam glucuronide from plasma is significantly slower in the elderly population ($t_{1/2} = 20$ hours) than in a group of young subjects ($t_{1/2} = 12$ hours).

Multiple (daily) dose pharmacokinetics of lormetazepam is predictable from single dose parameters. Steady-state conditions are reached within 3 days at the latest and respective steady-state medicine plasma levels increased by a factor of 1.3 (young) or 1.6 (elderly).

No medicine/medicine interactions are expected at the level of protein binding. At the level of phase I biotransformation no interaction was expected or found with cimetidine.

Terminal renal failure did not affect lormetazepam pharmacokinetics. The medicine's glucuronide showed a dialysate clearance of 20 mL/min and inactive glucuronide levels decreased with a half-life of about 80 hours due to the forced biliary (instead of renal) elimination.

In patients with liver cirrhosis, the reduced plasma clearance leads to an average 2-fold increase of maximum concentration and systemic exposure (AUC) after single dose administration of lormetazepam.

No enterohepatic recirculation of lormetazepam or its glucuronide was found.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

In studies on toxicity after repeated oral administration no findings were noted that are predictive of intolerance reactions related to the therapeutic use of Noctamid.

In tumourigenicity studies, no indication of a tumourigenic effect of the product was observed.

Studies on genotoxic effects in vitro and in vivo did not indicate a mutagenic potential for somatic or germ cells in humans.

Animal experiments on the influence on fertility, embryonal development, delivery and lactation as well as on development and reproductive capacity of the offspring did not indicate that undesirable effects, in particular teratogenic effects, are to be expected in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, maize starch, polyvidone 25 000, magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 25°C.

Store all medicines properly and keep them out of reach of children.

6.5 Nature and contents of container

Noctamid tablets are contained in PVC/Alu blister packs.

Pack of 30 tablets. Each tablet contains lormetazepam 1 mg.

6.6 Special precautions for disposal

No special requirements.

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

7 MEDICINE SCHEDULE

Class C5 Controlled Drug

8 SPONSOR

Bayer New Zealand Limited
3 Argus Place
Hillcrest
North Shore
Auckland 0627

Free Phone 0800 233 988

www.bayer.co.nz

9 DATE OF FIRST APPROVAL

16 August 2013

10 DATE OF REVISION OF THE TEXT

10 February 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
Whole document	Data sheet reformatted with minor editorial changes- update to the SPC-style format only.

® Registered Trademark of the Bayer Group, Germany