

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Noctamid Tablets 1 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains lormetazepam 1mg

Excipient: Contains 70.3mg lactose (as monohydrate)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Round, white, flat tablets with a beveled edge, imprinted 'CF' in a regular hexagon on one face and a breakline on the reverse. The tablet can be divided into equal halves.

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 Posology and method of administration

Posology

In adults, treatment should be started with 1 mg lormetazepam as a single dose.

Patients of advanced age should get 0.5 mg lormetazepam as a single dose.

For patients with mild to moderate chronic respiratory insufficiency or hepatic insufficiency a dose reduction should be considered.

The dose may be doubled 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 section 4.4 'Special warnings and precautions for use').

Paediatric population

Noctamid should not be given to patients under 18 years of age 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.

Method of administration

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

4.3 Contraindications

Myasthenia gravis.

Severe respiratory insufficiency (e.g. severe chronic obstructive pulmonary disease)

Sleep apnea syndrome.

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

Hypersensitivity to benzodiazepines or to any of the excipients of Noctamid listed in section 6.1.

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 section 4.2 'Posology 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 psychic dependence upon these products. Abuse of benzodiazepines has been reported. 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 reactions. 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, sensory disturbance 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 become 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 section 5.2 'Pharmacokinetic properties').

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, 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. 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. Abuse of benzodiazepines has been reported.

Amnesia:

Noctamid may induce anterograde amnesia. 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.

Psychiatric and "paradoxical" reactions:

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate, abnormal behaviour and other adverse behaviour disorders 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 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 disorders 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 with caution in these patients with depression.

Specific patient groups:

Paediatric population

For insomnia, 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 section 4.2 'Posology and method of administration').

Elderly

Benzodiazepines, including Noctamid, may be associated with an increased risk of falling due to adverse effects including ataxia, muscle weakness, dizziness, somnolence/sleepiness, fatigue and therefore it is recommended to treat elderly patients with particular caution.

Elderly patients should be given a reduced dose (see section 4.2 'Posology and method of administration').

Patients with spinal and cerebellar ataxia

Noctamid should be administered with caution to patients with spinal and cerebellar ataxia (see section 4.8 'Undesirable effects').

Patients with chronic respiratory insufficiency

A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression (see also sections 4.2 'Dosage and method of administration' and 4.3 'Contraindications').

Patients with hepatic insufficiency

There are limited pharmacokinetic data concerning single dosing of Noctamid in patients with mild to moderate hepatic insufficiency. The reduced plasma clearance in these patients leads to an average 2-fold increase of maximum concentration and systemic exposure (AUC). However, no pharmacokinetic data from clinical trials are available regarding repeated dosing of Noctamid in this patient population.

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 sections 4.2 'Dosage and method of administration' and 5.2 'Pharmacokinetic properties').

Patients with severe renal insufficiency

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

Concomitant use with opioids and/or CNS depressants

Concomitant use of Noctamid with opioids and/or CNS depressants may result in sedation, respiratory depression, coma and death. Because of these risks, such combinations should be reserved for patients with no alternative treatment options. If a decision is made to prescribe Noctamid concomitantly with opioids and/or CNS depressants, the lowest effective dose should be used and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. It is recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Excipients

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interactions

Benzodiazepines produce an additive effect when co-administered with alcohol or other CNS depressants.

Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol. Special care should be made with drugs depressing respiratory function such as opioids (analgesics, antitussives, substitutive treatments), notably in the elderly people. Enhancement of the euphoria with opioids may also occur leading to an increased risk in psychic dependence.

Lormetazepam should be used with caution when combined with other CNS depressants. Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics (opioids), anticonvulsants, anaesthetics and sedative antihistamines. The dosage and the duration of concomitant use should be limited (see section 'Concomitant use with opioids and/or CNS depressants').

The following drug interactions have been observed for lormetazepam:

- Cardiac glycosides: concurrent use may increase plasma levels of cardiac glycosides
- Beta-blocking agents: concurrent use may increase clinical effects of lormetazepam
- The following drug interactions have been described for benzodiazepines similarly metabolized as lormetazepam:
- Methylxanthines: concurrent use may reduce sedative effect
- Estrogen-containing medicinal products: concurrent use may decrease plasma levels of benzodiazepines
- Rifampicin: concurrent use may reduce sedative effect.

4.6 Fertility, pregnancy and lactation

As a precaution, Noctamid should not be used during pregnancy, delivery or lactation.

Women of childbearing potential

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.

Pregnancy

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, moderate respiratory depression and sucking difficulties can be expected due to the pharmacological action of the compound.

Moreover, infants born to mothers who took Noctamid or other benzodiazepines chronically during the late phase of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the post-natal period.

Breast-feeding

Since small amounts of the drug may enter the breast-milk, Noctamid should not be administered to breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Noctamid has a major influence on the ability to drive and use machines, as it causes sedation, amnesia, impaired concentration and impaired muscular function. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.

Reactions can be particularly impaired due to insufficient sleep duration, individual sensitivity and dosage. This applies to an increased extent in association with alcohol.

4.8 Undesirable effects

Summary of the safety profile

At the beginning of the 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 patients receiving Noctamid are headache, sedation and anxiety.

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

Tabulated list of adverse reactions

The adverse drugs reactions 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.

Adverse drug reactions from clinical trials (in 852 patients; administered dose: 0.5mg to 3mg lorazepam) 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 not listed under "not known".

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

Table 1: Adverse drug reactions reported in clinical trials or during post-marketing surveillance in patients treated with Noctamid

System Organ Class (MedDRA v. 8.0)	Very common	Common	Not known (cannot be estimated from the available data)
Immune system disorders		Angioedema *	
Psychiatric disorders		Anxiety Libido decreased	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	Confusional state Depressed level of consciousness Ataxia [§] Muscular weakness [§]

		Bradyphrenia	
Cardiac disorders		Tachycardia	
Gastrointestinal disorders		Vomiting Nausea Abdominal pain, upper Constipation Dry mouth	
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 complaints			Fall

*Life threatening and/or fatal cases have been reported

[§] see section 4.4 'Special warnings and precautions for use'

Description of selected adverse reactions

Dependence:

Use of Noctamid and other 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 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 reactions. These may consist of extreme anxiety, tension, restlessness, confusion, irritability, headaches and muscle pain. In severe cases the following symptoms may occur: derealization, depersonalization, hallucinations, paraesthesia of the limbs, sensory disturbance 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 become 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 section 5.2 'Pharmacokinetic properties').

For more information concerning dependence/withdrawal phenomena see section 4.4 '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.

The patient should be made aware of the possibility of rebound phenomena, thereby minimizing 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 behaviour 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 the elderly, 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 disorders 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 with caution in these patients with depression.

Nervous system disorders

Amnesia: Noctamid may induce anterograde amnesia. 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 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 lormetazepam intoxication are drowsiness, tiredness, ataxic symptoms, disturbed vision.

Oral intake of higher doses may result in deep sleep ranging to unconsciousness, respiratory depression, hypotension.

Therapy

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 further information concerning the safe use of flumazenil please refer to the SmPC for products containing flumazenil.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives/Benzodiazepine derivatives

ATC Code: N05CD06

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 becomes pharmacologically manifest in the form of anxiolytic, anticonvulsive, muscle relaxing and sedative-hypnotic effects.

Noctamid shortens sleep latency, reduces the frequency of nocturnal arousal and prolongs sleep duration without contributing to undesired sedation or reduced performance on the day after its use.

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 drug plasma levels is in two phases characterized 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, is the main metabolite and the only one found in plasma and is almost exclusively excreted with urine. Less than 6% of the dose is found as N-demethylated lormetazepam glucuronide, exclusively in urine. Excretion is in one phase, for which a half-life of 13.6 hours is calculated. In urine 86% of the dose is recovered. Renal clearance of lormetazepam glucuronide is 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 drug 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 drug plasma levels increased by a factor of 1.3 (young) or 1.6 (elderly).

No drug-drug interactions are expected at the level of protein binding. At the level of phase I biotransformation no interaction is expected and found with cimetidine.

Terminal renal failure does not affect lormetazepam pharmacokinetics. The drug's glucuronide shows a dialysate clearance of 20 ml/min and inactive glucuronide levels decrease 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.

Lormetazepam is not detectable in breast milk. By calculation at most 0.35% of the daily dose of a breast-feeding mother could reach the newborn.

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 tumorigenicity studies no indication of a tumorigenic 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
Magnesium stearate
Maize starch
Povidone 25000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/Al blister strips, 10 tablets/strip, in a cardboard carton.

Pack size: 30 and 100 tablets.

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

Bayer Limited
The Atrium
Blackthorn Road
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1410/009/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st November 1982

Date of last renewal: 1st November 2007

10 DATE OF REVISION OF THE TEXT

August 2019