AUSTRALIAN PRODUCT INFORMATION

HYPNODORM™

(flunitrazepam) tablets

1 NAME OF THE MEDICINE

Flunitrazepam

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each HYPNODORM tablet contains 1 mg flunitrazepam as the active ingredient.

Excipients with known effect: sugars as lactose, and trace amounts of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Flunitrazepam 1 mg tablets: 12.6 x 6 mm, oval, convex, green film-coated tablet. Debossed "FM/1" on one side and an alpha symbol on the other

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Severe cases of insomnia.

4.2 DOSE AND METHOD OF ADMINISTRATION

In most patients, HYPNODORM need only be administered for a few nights. Treatment should be discontinued gradually by decreasing the dosage.

Dosage should be selected carefully, due consideration being given to the patient's age and general condition, as well as the type of sleep disturbance.

The drug should be taken immediately before going to bed. In general, the following dosages are recommended.

Adults

1 to 2 mg on going to bed.

Elderly patients

0.5 to 1 mg.

In impaired renal or hepatic function

Elimination of metabolites will be impaired. For these patients, commence treatment with small doses which are increased slowly until the desired response is attained.

4.3 CONTRAINDICATIONS

HYPNODORM is contraindicated in:

- Patients with known hypersensitivity to flunitrazepam or to any other components of HYPNODORM
- Patients with known hypersensitivity to benzodiazepines
- Patients with chronic obstructive airways disease with incipient respiratory failure
- Myasthenia gravis
- Sleep apnoea
- Children

- Severe hepatic insufficiency.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Severe allergic reactions

Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics. Some patients have had additional symptoms such as dyspnea, throat closing, or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal.

Withdrawal Reactions

Following the prolonged use of HYPNODORM 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 HYPNODORM (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Dependence).

Tolerance

In general, benzodiazepines should be prescribed for short periods only (e.g. 2 to 4 weeks). Continuous long-term use of HYPNODORM 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).

Hypotension

Although hypotension has occurred only rarely, HYPNODORM 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.

Memory Impairment

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines. On rare occasions, especially when flunitrazepam was taken with alcohol or CNS active drugs, patients developed unusual or disturbed behaviour of which they had no recollection.

Myasthenia gravis

HYPNODORM could increase the muscle weakness in myasthenia gravis and is therefore contraindicated in this condition.

Glaucoma

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

Blood Dyscrasias

In rare instances, some patients taking benzodiazepines have developed blood dyscrasias. As with other benzodiazepines, periodic blood counts are recommended.

Depression, Psychosis and Schizophrenia

HYPNODORM is not recommended as primary therapy in patients with depression and/or 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.

Paradoxical Reactions

HYPNODORM should be discontinued if paradoxical reactions such as acute rage, stimulation or excitement occur. These reactions are more common in the elderly.

Impaired respiratory function

Caution in the use of HYPNODORM 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

Caution must be exercised in administering HYPNODORM to 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.

Dependence

The use of benzodiazepines may lead to dependence, as defined by the presence of a withdrawal syndrome on discontinuation of the drug. Tolerance, as defined by a need to increase the dose in order to achieve the same therapeutic effect, seldom occurs in patients receiving the recommended doses under medical supervision. Tolerance to sedation may occur with benzodiazepines, especially in those with drug seeking behaviour.

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, tension, muscle pain, restlessness, irritability, insomnia, anxiety, dysphoria, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feelings of motion, metallic taste), numbness and tingling of the extremities, depersonalisation, derealisation, delusional beliefs, hyperreflexia and loss of short term memory, to a major syndrome which may include convulsions, tremor, abdominal and muscle cramps, confusional states, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating. Such manifestations of withdrawal, especially the more serious ones, are more common in those patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have also been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly, HYPNODORM 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.

It is important to warn against changing to a benzodiazepine with a short duration of action when benzodiazepines with a long half-life are used, as withdrawal symptoms may develop.

Use in Hepatic Impairment

Patients with impaired hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances some patients have had elevation of liver enzymes. As with other benzodiazepines, periodic liver function tests are recommended.

Use in Renal Impairment

Patients with impaired renal function should use benzodiazepine medication with caution and dosage reduction may be advisable.

Use in the Elderly

Geriatric or debilitated 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.

Paediatric Use

Contraindicated in children.

Effects on Laboratory Tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

CNS Depressant Drugs. The benzodiazepines, including flunitrazepam, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression, e.g. barbiturates, alcohol, sedatives, antidepressants, nonselective MAO inhibitors, phenothiazines and other antipsychotics, antiepilectic drugs, hypnotics, skeletal muscle relaxants, antihistamines or narcotic analgesics and anaesthetics (see Section 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES).

Disulfiram and Cimetidine. Flunitrazepam undergoes oxidative metabolism, and consequently may interact with disulfiram or cimetidine, resulting in increased plasma levels of flunitrazepam. Patients should be observed closely for evidence of enhanced benzodiazepine response during concomitant treatment with either disulfiram or cimetidine; some patients may require a reduction in benzodiazepine dosage.

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

Anticonvulsants. 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.

Alcohol. The mutual potentiation between alcohol and flunitrazepam may produce unforeseeable reactions in certain patients. Alcoholic drinks should therefore be avoided while under the influence of this drug.

Cisapride. Cisapride may lead to a temporary increase in the serum levels, and thus sedative effects, of orally administered benzodiazepines due to faster absorption.

Narcotic Analgesics. In the case of narcotic analgesics, enhancement of euphoria may also occur, leading to an increase in psychological dependence.

Anticoagulants and Antidiabetics. There appears to be no interaction with coumarin anticoagulants or oral diabetic agents.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Studies have not been performed to assess the potential of flunitrazepam to impair fertility.

Use in Pregnancy (Category C)

Benzodiazepines cross the placenta and may cause hypotonia, respiratory depression and hypothermia in the newborn infant if used in high doses during labour. 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 prolonged use of this class of drugs.

Use in Lactation

Flunitrazepam is excreted in human breast milk and therefore should not be used when breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Complex behaviours such as "sleep-driving" (i.e. driving while not fully awake after taking a sedative-hypnotic, with amnesia for the event) have been reported with sedative hypnotics. These events can occur in sedative-hypnotic naive 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 (eg. 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.

As with all patients taking CNS-depressant medications, patients receiving HYPNODORM should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from HYPNODORM therapy. Abilities may be impaired on the day following use. Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of HYPNODORM.

Due to the slight accumulation of flunitrazepam in the plasma, a 2 mg dose of flunitrazepam should not be administered on a daily basis to patients involved in activities requiring concentration during the early part of the day.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Note: Percentages indicate the incidence of adverse reactions in clinical trials.

About 13% of patients experience adverse effects, usually due to the persistence or accentuation of the pharmacological effects of the drug. They are more frequent at higher doses (over 4 mg) and in sensitive or elderly persons.

Body as a whole

Common: headache, falling.

Uncommon: asthenia, malaise, collapse, unsteadiness.

Cardiovascular

Common: hypotension.

Uncommon: tachycardia, orthostatic hypotension.

Gastrointestinal

Common: gastrointestinal upsets, dry mouth.

Uncommon: hiccups

Musculoskeletal

Uncommon: muscle weakness

Nervous system

Common: hangover, tiredness, drowsiness, sleepiness, dizziness, ataxia, confusion, tremor, amnesia, excitation.

Uncommon: daytime sedation, disorientation, slurred speech.

Rare: anxiety, hallucinations, agitation, sleep disturbances, unusual dreams.

Dermatological

Uncommon: skin reactions, sweating, rash, angioedema.

In rare cases, paradoxical reactions such as acute excitation, confusion, agitation, sleep disturbances including unusual dreams, anxiety and hallucinations may occur. If this happens, treatment must be stopped. These reactions may be quite severe with flunitrazepam, and are more likely to occur in the elderly.

Daytime sedative effects, particularly in elderly people, may cause serious domestic accidents.

Post-marketing experience

Paradoxical reactions

Restlessness, irritability, nightmares, inappropriate behaviour, delusions, aggressiveness and psychoses.

Special senses

Double vision.

Urogenital system

Changes in libido.

Central nervous system

Pre-existing depression may be unmasked during benzodiazepine use.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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 and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, coma, and very rarely death.

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 flunitrazepam tablets, activated charcoal should be given to reduce absorption. General symptomatic and supportive measures are recommended. 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.

If excitation occurs in patients following overdosage, barbiturates should **not** be used.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Flunitrazepam is a member of the benzodiazepine group of drugs and is closely related to nitrazepam, flurazepam and clonazepam. It has marked sedative and hypnotic properties with a rapid onset of action. In experimental animals, flunitrazepam has also been shown to possess anticonvulsant, anxiolytic and muscle-relaxant properties.

Given orally, flunitrazepam induces sleep and maintains and deepens it. The intensity of the effect depends both on the dose taken and on the aetiology of the sleep disturbance.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, flunitrazepam is almost completely absorbed. Peak blood levels of flunitrazepam occur usually 45 minutes after ingestion. 10% to 15% is metabolised by a liver first-pass effect, resulting in bioavailability of 64-77%.

Chronic oral administration of flunitrazepam leads to slight accumulation of flunitrazepam in the plasma. The accumulation ratio of flunitrazepam given once daily is approximately 2. Steady-state concentrations are reached after 3 to 5 days for flunitrazepam, and after 5 to 7 days for N-desmethyl-flunitrazepam. Subsequently, the minimum and maximum concentrations remain constant, even on prolonged administration.

Distribution

The distribution of flunitrazepam is rapid and extensive. About 77 to 80% of absorbed flunitrazepam is bound to plasma proteins over a concentration range of 1 to 20 ng/mL.

Metabolism

Flunitrazepam is extensively metabolised, and both the major metabolites, 7-amino-flunitrazepam and N-desmethyl-flunitrazepam, are pharmacologically active in humans but less so than the parent drug. Both metabolites are eliminated as glucuronides, largely through the kidneys.

Excretion

Following intravenous administration, the elimination half-life for flunitrazepam is 20 to 30 hours, 10 to 16 hours for 7-amino-flunitrazepam and 23 to 33 hours for N-desmethyl-flunitrazepam. However, due to

extensive distribution of the drug and metabolites out of the plasma into body tissues, the long elimination half-lives are not reflected in the duration of clinical effect.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Studies have not been performed to assess the mutagenic potential of flunitrazepam.

Carcinogenicity

Studies have not been performed to assess the carcinogenic potential of flunitrazepam.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain the following excipients: lactose monohydrate, maize starch, pregelatinised maize starch, magnesium stearate, indigo carmine and Opadry Green OY-LS-21051 Green CHN (ARTG PI No. 4346).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: HDPE bottle with PP child resistant closure.

Pack size: 30 tablets

Australian Register of Therapeutic Goods (ARTG)

AUST R 78344 - HYPNODORM flunitrazepam 1mg tablet bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

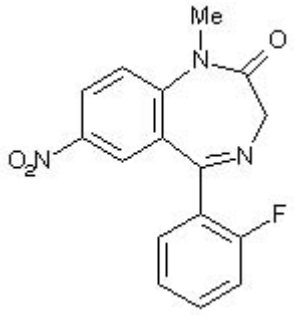
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name : 5-(2-fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2H-1,4-benzodiazepin 2 one

Structural formula :



Molecular formula : $C_{16}H_{12}FN_3O_3$

Molecular weight : 313.3

Flunitrazepam is a pale yellow crystalline solid, sparingly soluble in water, slightly soluble in alcohol.

CAS Number

1622-62-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S8 (Controlled Drug)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

04/10/2001

10 DATE OF REVISION

02/04/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
2, 6.1	Minor editorial change to update excipient details
3	Minor editorial changes
6.5	Minor editorial changes, Added AUST R details
9	Update to Sponsor details

HYPNODORM™ is a Viatris company trade mark

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