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HYPNODORM®

TABLETS

Composition

Each tablet contains:

Active Ingredient

Flunitrazepam	2 mg

Other Ingredients

Microcrystalline cellulose, lactose, talc, magnesium stearate

Lactrose content: 63.8 mg per tablet.

Action

Hypnodorm contains flunitrazepam, a benzodiazepine hypnotic.

Hypnodorm induces sleep within 15-20 minutes, which lasts for 6-8 hours.

Hypnodorm enjoys a wide therapeutic margin, is well tolerated and during prolonged use, tolerance has practically not been observed.

Indications

Insomnia of various etiology.

Contraindications

Known hypersensitivity to benzodiazepines or to any other ingredient of the preparation.

First trimester of pregnancy and in breastfeeding.

Acute pulmonary insufficiency; respiratory depression, chronic psychoses, phobic or obsessional states.

Acute narrow-angle glaucoma because of atropine-like side effects. Benzodiazepines may be used in patients with open-angle glaucoma who are receiving appropriate therapy).

Myasthenia gravis.

Severe hepatic insufficiency

Sleep apnea syndrome.

Use in children.

Warnings

(See also Precautions)

Effect on Ability to Drive and/or Operate Machinery

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 (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.

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

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.

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 flunitrazepam at therapeutic doses, withdrawal from the medication should be gradual. An individualized withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Periods from 4 weeks to 4 months have been suggested. As with other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase of sleep disturbance can occur after use of flunitrazepam.

Tolerance

In general, benzodiazepines should be prescribed for short periods only (e.g.2 to 4 weeks). Continuous long-term use of flunitrazepam is not recommended. There is evidence that tolerance/some loss of efficacy develops to the sedative/hypnotic 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, flunitrazepam 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

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

Glaucoma

See Contraindications

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.

Depression, Psychosis and Schizophrenia

(see also Contraindications)

Flunitrazepam 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

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

Reactions like paradoxical aggressive outbursts, excitement, confusion, restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucination, psychoses, inappropriate behaviour, the uncovering of suicidal tendencies and other adverse behavioural effects are known to occur when using benzodiazepines. Extreme caution should therefore be used in prescribing benzodiazepines to patients with personality disorders. Should this occur, use of the drug should be discontinued. These reactions may be quite severe and are more likely to occur in the elderly.

Concomitant use of alcohol and/or CNS depressants

The concomitant use of flunitrazepam with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of flunitrazepam, possibly including severe sedation and clinically relevant respiratory and/or cardiovascular depression.

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. Also, due to the myorelaxant effect of benzodiazepines, there is a risk of falls and consequently of hip fractures, particularly in the elderly when they get up at night.

Impaired respiratory function

Caution in the use of flunitrazepam 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 flunitrazepam 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. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse.

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 behavior.

Regular monitoring of such patients is essential; routine repeat prescriptions should be avoided and treatment should be withdrawn gradually. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms.

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, depression, nervousness, mood changes, diarrhea, rebound insomnia, restlessness, irritability, insomnia, extreme anxiety, dysphoria, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feelings of motion, metallic taste), hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact and hallucinations or epileptic seizures, depersonalisation, derealization, 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, flunitrazepam 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; It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. 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.

Abuse of flunitrazepam had been reported.

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.

Duration of treatment

The duration of treatment should be as short as possible (see Dosage and Administration) should not exceed four weeks for insomnia, including tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued.

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. When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Other warnings

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression, (suicide may be precipitated in such patients).

This drug should be used with extreme caution in patients with a history of alcohol or drug abuse.

In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.

Use in Pregnancy

Benzodiazepines have the potential to cause fetal harm when administered to pregnant women. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, she should be informed of the potential hazard to the fetus.

Benzodiazepines are assumed to be capable of causing an increased risk of congenital abnormalities when administered to pregnant women during the first trimester. Since use of these drugs is rarely a matter of urgency, their use during the first trimester of pregnancy should almost always be avoided (see Contraindications).

The possibility that women of child-bearing potential may be pregnant when therapy is instituted should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant, they should refer to their physician about the desirability of discontinuing the drug.

Administration of benzodiazepines in the last trimester of pregnancy or during labour has been reported to produce irregularities in the foetal heart rate, and hypotonia, poor sucking, hypothermia and moderate respiratory depression in the neonate.

Infants born to mothers who took benzodiazepines chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Use in Breastfeeding

Benzodiazepines are excreted in breast milk. Since neonates metabolize this drug more slowly than adults, and accumulation of the drug and its metabolites to toxic levels is possible, it should not be administered to nursing mothers (see Contraindications). Flunitrazepam has been detected in breast milk.

Adverse Reactions

Adverse reactions with different benzodiazepines vary in type and frequency. Some are dose-related, while others involve individual patient sensitivity. Although not all of the following adverse reactions have been attributed specifically to each benzodiazepine drug, the potential for their occurrence exists. This should be borne in mind when drugs of this class are administered.

Side effects most commonly reported have been drowsiness, fatigue and ataxia, especially in elderly or debilitated patients.

Infrequently reported side effects are as follows:

Central Nervous System

Sedation and sleepiness, hangover, tiredness, drowsiness during the day, ataxia, tremor, amnesia, excitation, daytime sedation, disorientation, hallucinations, agitation, anxiety, depression, lethargy, apathy, hypoactivity, lightheadedness, disorientation, restlessness, confusion, delirium, headache, slurred speech, dysarthria, syncope, vertigo, dizziness, nervousness, vivid dreams, psychomotor retardation.

Occasionally, prolonged use with this medicine may cause behavioral changes and paranoid symptoms.

Gastrointestinal

Constipation, diarrhea, dry mouth, nausea, vomiting, increased salivation, hiccups.

Genitourinary

Incontinence, dysuria, enuresis, changes in libido, urinary retention, menstrual irregularities.

Cardiovascular

Bradycardia, tachycardia, hypertension, hypotension, palpitations, cardiac failure including cardiac arrest .

Ophthalmological

Visual disturbances, diplopia.

Dermatological

Urticaria, pruritus, skin rash, dermatitis, sweating, angioedema.

Musculoskeletal and Connective Tissue Disorders

Muscle weakness. This phenomenon occurs predominantly at the start of therapy and usually disappears with prolonged administration.

Immune System Disorders:

Hypersensitivity reactions, including rash, angioedema and hypotension, may occur.

Respiratory Disorders

Respiratory depression.

Other

Hepatic dysfunction (including hepatitis and jaundice), blood dyscrasias including agranulocytosis, anemia, thrombocytopenia, eosinophilia.

More frequent adverse reactions indicative of possible withdrawal synptoms following abrupt discontinuation, and necessitating medical attention (if they occur within 2-3 days with short to intermediate half-life benzodiazepines, and 10-20 days with long half-life benzodiazepines) include: irritability, nervousness, and trouble in sleeping.

Other adverse reactions: falling, asthenia, collapse, unsteadiness, muscle weakness.

Injury, Poisoning and Procedural Complications: An increased risk for falls and fractures has been reported in elderly benzodiazepine users

Postmarketing 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.

Precautions

In elderly or debilitated patients and in children, the initial dose should be low and dosage increments made gradually, in accordance with the response of the patient, to preclude ataxia or excessive sedation.

Although hypotension has rarely occurred, administer with caution to patients in whom a drop in blood pressure might lead to cardiac complications.

Caution should be exercised in patients with chronic pulmonary insufficiency, and in patients with impaired renal or hepatic function.

Flunitrazepam clearance is increased in cigarette smokers, probably due to enzyme induction.

Patients who experience drowsiness during treatment should be warned that their ability to perform potentially-hazardous tasks requiring mental alertness or physical coordination , such as driving a vehicle or operating machinery, may be impaired.

Because of a possible muscular relaxant effect, caution should be exercised when administering this drug in patients with myasthenia gravis.

Liver and kidney function tests and blood counts should be performed regularly during long-term therapy.

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

Drug Interactions

Flunitrazepam/Estrogen-Containing Oral Contraceptives/Cimetidine/Disulfiram: Concurrent administration of estrogen-containing oral contraceptives, disulfiram or cimetidine with flunitrazepam, which is metabolized primarily by nitro-reduction, may result in inhibition of hepatic metabolism of the benzodiazepine leading to delayed elimination and increased plasma concentrations of the benzodiazepine. Dosage reduction of fllunitrazepam may be required in some patients.

Benzodiazepines/Centrally-Acting Drugs/Alcohol: Benzodiazepines may have a potentiating effect on centrally-acting drugs such as barbiturates, neuroleptics, tranquilizers, antidepressants, nonselective MAO inhibitors, phenothiazines and other antipsychotics, hypnotics, antiepileptics, sedatives, analgesics (including narcotic analgesics), skeletal muscle relaxants, antihistamines, and anesthetics. When these drugs are administered concomitantly with benzodiazepines, their dosage should be reduced.
In case of narcotic analgesics, enhancement of euphoria may also occur, leading to an increase in psychological dependence.
Benzodiazepines may also intensify the response to alcohol. Patients should be advised to avoid drinking alcoholic beverages while under treatment with this drug.
Benzodiazepines/Anticholinergics: The anticholinergic effects of other drugs, including atropine and similar drugs, antihistamines and antidepressants may be potentiated.
Benzodiazepines/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.
Benzodiazepines/Cisapride: Cisapride may lead to a temporary increase in the serum levels, and thus sedative effects, of orally administered benzodiazepines due to faster absorption.
Benzodiazepines/Anticoagulants/Antidiabetics: There appears to be no interaction with coumarin anticoagulants or oral diabetic agents.
Benzodiazepines/Levodopa*:* Rare reports indicate that patients treated with levodopa experienced diminished control of parkinsonian symptoms when chlordiazepoxide or diazepam was added to their therapeutic regimen, For this reason, benzodiazepines should be administered with caution to patients receiving levodopa.
Benzodiazepines/Digoxin: Limited evidence suggests that some benzodiazepines, namely diazepam and alprazolam, may reduce the renal excretion of digoxin, resulting in an increased plasma half-life of the cardiac glycoside and possibe digoxin toxicity.
Although the exact mechanism for the effect of benzodiazepines on the renal excretion of digoxin has not been clearly elucidated, serum digoxin concentrations should be monitored and patients should be carefully observed for signs and/or symptoms of digoxin toxicity during concomitant therapy. Dosage reduction of digoxin may be necessary in some patients receiving concomitant therapy.
Benzodiazepines/Rifampin/Isoniazid*:* Concurrent use may enhance the elimination of diazepam, resulting in decreased plasma concentrations; dosage adjustment of the benzodiazepine may be necessary. Data as to whether this effect applies to other benzodiazepines are not available.

Known Inhibitors of Hepatic Enzymes: e.g. cimetidine, have been shown to reduce the clearance of benzodiazepines and may potentiate their action, and known inducers of hepatic enzymes, e.g. rifampicin, may increase the clearance of benzodiazepines

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

Information for Patients

(see also Dosage and Administration)

Treatment is usually intended for short periods only. Patients should be instructed to consult their physician after 2-4 weeks of the treatment.
Since benzodiazepines may produce psychologic and physical dependence, patients should be advised to consult their physician before increasing the dose of, or abruptly discontinuing, benzodiazepine therapy.

Patients should be advised to exercise caution if drowsiness, dizziness, lightheadedness, or clumsiness or unsteadiness occurs, especially in the elderly, who are more sensitive to the CNS effects of benzodiazepines.

Dosage and Administration

Treatment should be as short as possible and should be started with the lowest recommended dose. The maximum dose should not be exceeded. Generally the duration of treatment varies from a few days to two weeks with a maximum of four weeks, including the tapering off process. Patients who have taken benzodiazepines for a prolonged time may require a longer period during which doses are reduced. Specialist help may be appropriate. Little is known regarding the efficacy or safety of benzodiazepines in long-term use.

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 status. Long-term chronic use is not recommended.

The product should be taken just before going to bed.

The dosage should be carefully adapted to the age and the general condition of the patient and to the nosological classification of the sleep disturbance.
Adults: Half a tablet at bedtime. In severe insomnia, 1 tablet at bedtime.
Elderly Patients: One quarter of a tablet at bedtime. In severe insomnia, half a tablet at bedtime.

Overdosage

Manifestations

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. Coma may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol. When combined with other CNS depressants, the effects of overdosage are likely to be severe and may prove fatal.

Treatment

In managing overdosage the possibility of multiple drug involvement may be considered.

The patient’s vital signs should be monitored and supportive measures should be instituted as indicated by the patient’s clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

If the patient is conscious, vomiting should be induced either mechanically or with emetics. Also, activated charcoal may be administered orally (within 1-2 hours) to increase clearance, as well as decrease absorption of the benzodiazepine

If the patient is unconscious, immediate gastric lavage utilizing a cuffed endotracheal tube, to prevent aspiration and pulmonary complications, should be employed.

General supportive measures should be employed along with intravenous fluids. An adequate airway should be maintained.

Hypotension may be combated by the administration of noradrenaline or metaraminol

If excitation occurs, barbiturates should not be used.

Hemoperfusion and hemodialysis are of limited value.

If CNS depression is severe the use of Flumazenil injection (Anexate), a specific benzodiazepine-receptor antagonist, should be considered for the complete or partial reversal of the sedative effects of benzodiazepines, and may be used in situations when an overdose with a benzodiazepine is known or suspected.

The following should be kept in mind when flumazenil is used in the treatment of benzodiazepine overdosage:

- Flumazenil should only be administered under closely monitored conditions. In view of the short half life (about 1 hour) and duration of action of flumazenil, and the possible need for repeat doses, the patient should be closely monitored until all possible central benzodiazepine effects (e.g., resedation) have subsided.
- Particular caution is necessary when using flumazenil in cases of multiple drug overdosage, since the toxic effects (cardiac arrhythmias and/or convulsions) of other psychotropic drugs, especially cyclic antidepressants, may increase as the effects of benzodiazepines subside. Flumazenil is contraindicated in patients who are showing signs of serious cyclic antidepressant overdose.

Warning: The benzodiazepine receptor antagonist flumazenil is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures.

Prior to the administration of flumazenil, the complete package insert of the product should be consulted, and necessary measures should be instituted to secure airway, ventilation, and intravenous access.

Flumazenil is intended as an adjunct to, not a substitute for, proper management of benzodiazepine overdosage. Patients treated with flumazenil should be monitored for resedation, respiratory depression, and other residual benzodiazepine effects, for an appropriate period after treatment. **Awareness is required regarding a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.**

Storage

Store below 25°C.

Drug Registration Number:
032 33 22417 00.

Manufacturer

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