Rohypnol®

Flunitrazepam

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1. Description

1.1 Therapeutic/Pharmacologic Class of Drug

Sleep-inducing agent

ATC code: N05CD03

1.2 Type of Dosage Form

Film-coated tablets.

Grey green oval, biconvex film-coated tablet; with a score line on one side and embossed "542" on the other side.

Tablet can be divided into equal doses.

1.3 Route of Administration

Oral use.

1.4 Sterile/Radioactive Statement

Not applicable.

1.5 Qualitative and Quantitative Composition

Active ingredient: flunitrazepam.
1 film-coated tablet contains 1 mg flunitrazepam.

Excipients: lactose, microcrystalline cellulose, povidone K 90, hypromellose, sodium starch glycolate, indigotine (E132), magnesium stearate (Ph. Eur.), ethyl cellulose, triacetin, titanium dioxide (E171), talc iron oxide yellow (E172),.

2. Clinical Particulars

2.1 Therapeutic Indications

Short-term treatment of sleep disorders.

Benzodiazepines are indicated only when the disorder is severe or disabling or subjects the individual to extreme stress.

2.2 Dosage and Administration

Standard dosage

Treatment should be started at the lowest recommended dose. The maximum dose stated should not be exceeded.

The recommended dosage for adult patients is 0.5 - 1 mg/day. In exceptional circumstances the dose may be increased to 2 mg.

Method of administration

The product should be taken just before going to bed.

Treatment should be as short as possible. Generally, the duration of treatment varies from a few days to 2 weeks, with a maximum of 4 weeks, including a tapering-off process.

In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without a re-evaluation of the patient's status.

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 be made 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 (see 2.4.1 General [Warnings and Precautions] and 2.4.2 Drug Abuse and Dependence).

2.2.1 Special Dosage Instructions

Elderly

The recommended dosage for elderly patients is 0.5 mg. In exceptional circumstances the dose may be increased to 1 mg.

Patients with renal impairment

Patients with impaired renal function should receive a lower, individually adjusted dose.

Patients with hepatic impairment

Patients with impaired liver function should receive a reduced dose.

Patients with respiratory insufficiency

Patients with chronic respiratory insufficiency should receive a reduced dose (see 2.4 Warnings and Precautions).

Paediatric population

Rohypnol is contraindicated in children (see 2.3 Contraindications).

2.3 Contraindications

- Hypersensitivity to benzodiazepines or to any of the excipients listed in 1.5 Qualitative and Quantitative Composition
- Myasthenia gravis
- Severe respiratory insufficiency
- Sleep apnoea syndrome
- Severe hepatic insufficiency

- Children

2.4 Warnings and Precautions

2.4.1 General

Benzodiazepines are not recommended for the primary treatment of psychotic illness. In certain circumstances it is possible that depressive symptoms may be enhanced if no suitable treatment of the underlying disease with antidepressants occurs and the risk of suicide is increased.

Concomitant use of alcohol/CNS depressants

The concomitant use of Rohypnol with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Rohypnol possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression (see 2.4.5 Drug Interactions).

Medical history of alcohol or drug abuse

Rohypnol should be used with extreme caution in patients with a history of alcohol or drug abuse (see 2.4.5 Drug Interactions).

Risk from concomitant use of opioids

Concomitant use of Rohypnol and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Rohypnol with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Rohypnol concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see 2.2 Dosage and Administration).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see 2.4.5 Drug Interactions).

Hypersensitivity

Hypersensitivity reactions such as rash, angioedema or hypotension may occur in susceptible individuals.

Tolerance

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

Rebound insomnia

A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine or benzodiazepine-like agent recur in an enhanced form, rebound insomnia may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions, including mood changes, anxiety and restlessness.

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

Amnesia

Benzodiazepines may induce anterograde amnesia. The condition most often occurs within the first few hours after ingesting the product, and therefore, to reduce the risk, patients should ensure that they will be able to sleep undisturbed for 7 - 8 hours (see 2.6 Adverse Reactions).

Psychiatric and 'paradoxical' reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur with benzodiazepines. Should these occur, the use of the drug should be discontinued. These reactions may be quite severe with this product and are more likely to occur in the elderly.

2.4.2 Drug Abuse and Dependence

Dependence

The chronic use of benzodiazepines and benzodiazepine-like agents even in therapeutic doses may lead to the development of physical and psychic dependence on these products (see 2.6 Adverse Reactions). The risk of dependence increases with dose and duration of treatment. The risk is also higher in patients with a medical history of alcohol and/or drug abuse.

To minimise the risk of dependence, benzodiazepines should be prescribed only after careful evaluation of the indication and for a time as short as possible. The need for further treatment should be evaluated properly.

Withdrawal

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal and rebound symptoms. These may consist of headache, muscle pain, extreme anxiety, tension, restlessness, tremor, confusion, irritability and rebound insomnia.

In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

2.4.3 Ability to Drive and Use Machines

Sedation (see 2.4.5 Drug Interactions), amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or operate machinery. Insufficient sleep may increase the likelihood of impaired alertness.

2.4.4 Excipients with known effects

Contains Lactose.

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

2.4.5 Drug Interactions

Combination with CNS depressants may lead to enhancement of the central depressive effect (antipsychotics, neuroleptics, hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, anesthetics and sedative antihistamines).

Enhanced effects on sedation, respiration and hemodynamics may occur when Rohypnol is co-administered with any centrally acting depressants including alcohol.
Alcohol should be avoided in patients receiving Rohypnol (see 2.4.1 General [Warnings and Precautions]).
See section 2.7 Overdose for warnings of other central nervous system depressants, including alcohol.

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Rohypnol with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see 2.4 Warnings and Precautions).

In the case of narcotic analgesics, enhancement of euphoria may also occur, leading to an increase in psychic drug dependence.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines and benzodiazepine-like agents. A possible interaction with potent CYP3A4 inhibitors (including, but not limited to, those listed below) cannot be excluded.

- Azolantimycotics: Fluconazole, Ketoconazole, Itraconazole
- Cimetidine
- HIV-Protease Inhibitors
- Gemfibrozil (PPAR-α-Agonist)
- Macrolide antibiotics: Erythromycin, Clarithromycin, Telithromycin
- Nefazodone (SNRI)
- Statins
- Verapamil (Ca^{2+}-Antagonist)
- Grapefruit juice

Rohypnol may be given in conjunction with oral antidiabetic agents and anticoagulants.

2.5 Use in Specific Populations

2.5.1 Children and adolescents

See 2.3 Contraindications.

2.5.2 Fertility

Studies in rats revealed no adverse effects on fertility and early embryonic development.

2.5.3 Pregnancy

Insufficient data are available on flunitrazepam to assess its safety during pregnancy. The risk for malformations after administration of therapeutic doses of benzodiazepines during early pregnancy appears to be low, but some epidemiological studies have shown evidence of an increased risk of cleft palate.

If the product is prescribed to a woman of childbearing potential, she should be advised to contact her physician regarding discontinuance of the product if she intends to become pregnant or suspects that she is pregnant. Although the placental transfer of flunitrazepam is small after a single dose, prolonged administration should be avoided in the last trimester of pregnancy. If, for compelling medical reasons, flunitrazepam is administered during the late phase of pregnancy or during labour, effects on the neonate such as hypothermia, hypotonia and moderate respiratory depression can be expected due to the pharmacological action of the product.

Moreover, 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 (see 2.4.2 Drug Abuse and Dependence).

2.5.4 Breastfeeding

Since benzodiazepines pass into breast milk, flunitrazepam should not be administered to breast-feeding mothers (see 3.2.2 Distribution [Pharmacokinetic Properties]).

2.5.5 Impaired hepatic function

Caution is recommended when treating patients with impaired hepatic function. Patients with severe hepatic insufficiency should not be treated with benzodiazepines because of the risk of encephalopathy (see 2.2. Dose and Administration and 2.3. Contraindications).

2.5.6 Impaired renal function

See 3.2.5 Pharmacokinetics in Special Populations.

2.5.7 Impaired respiratory function

A lower dose is recommended for patients with chronic respiratory insufficiency, due to the risk of respiratory depression.

2.5.8 Elderly

Benzodiazepines should be used with caution in the elderly, due to the risk of sedation and/or muscle relaxant effect that may lead to falls, with consequences often serious in this population. The risk of falls and fractures is also increased, regardless of age, in patients taking sedative drugs or alcohol at the same time.

In elderly patients with organic cerebral changes and in debilitated patients the dose should be chosen with caution because of their increased sensitivity to drugs.

2.6 Adverse Reactions

Undesirable Effects

2.6.1 Post Marketing

Immune System Disorders:
Hypersensitivity reactions, including rash and angioedema, may occur.

Psychiatric Disorders:
Confusional state, emotional disorder, these undesirable effects are reported most commonly and occur predominantly at the start of therapy and usually disappear with prolonged administration. Libido disorders have been reported occasionally.

Depression:
Pre-existing depression may be unmasked during benzodiazepine use.

Psychiatric and Paradoxical Reactions:
Paradoxical reactions such as restlessness, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, psychosis, inappropriate behaviour and other adverse behavioural effects are known to occur with benzodiazepines or benzodiazepine-like agents. These reactions may be quite severe with this product, and are more likely to occur in the elderly.

Dependence:
Chronic use (even at therapeutic doses) may lead to the development of physical dependence: abrupt discontinuation of the therapy may result in withdrawal or rebound phenomena (see 2.4.1 General [Warnings and Precautions] and 2.4.2. Drug Abuse and Dependence). Abuse has been reported.

Nervous System Disorders:
Drowsiness during the day, headache, dizziness, decreased alertness, ataxia. These undesirable effects are reported most commonly and occur predominantly at the start of therapy and usually disappear with prolonged administration.

Anterograde amnesia may occur with therapeutic doses, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see 2.4.1 General [Warnings and Precautions]).

Cardiac Disorders:
Cardiac failure including cardiac arrest.

Vascular Disorders:
Hypotension.
Respiratory Disorders:
Respiratory depression.

Eye Disorders:
Diplopia, this undesirable effect is reported most commonly and occurs predominantly at the start of therapy and usually disappears with prolonged administration.

Gastrointestinal Disorders:
Gastrointestinal disorders, have been reported occasionally.

S*kin and Subcutaneous Tissue Disorders:*
Skin reactions have been reported occasionally.

Musculoskeletal and Connective Tissue Disorders:
Muscle weakness, this phenomenon occurs predominantly at the start of therapy and usually disappears with prolonged administration.

Renal and urinary disorders:
Urinary retention, urinary incontinence and dysuria.

General Disorders and Administration Site Conditions:
Fatigue, this phenomenon occurs predominantly at the start of therapy and usually disappears with prolonged administration.

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

2.7 Overdose

Symptoms of intoxication

Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of Rohypnol is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and coma. Coma, if it occurs, usually lasts a few hours but it 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.

Treatment of intoxication

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

Further absorption should be prevented using an appropriate method, e.g. treatment within 1 - 2 hours with activated charcoal. If activated charcoal is used, airway protection is imperative for drowsy patients. In case of mixed ingestion gastric lavage may be considered, however, not as a routine measure.

If CNS depression is severe, consider the use of flumazenil (Anexate®), a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer

to the prescribing information for flumazenil (Anexate®), for further information on the correct use of this drug.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Flunitrazepam is a full benzodiazepine agonist with a high affinity for the benzodiazepine central site.

It has anxiolytic, anticonvulsant and sedative effects, and induces slowing of psychomotor performance, amnesia, muscle relaxation and sleep.

3.2 Pharmacokinetic Properties

3.2.1 Absorption

Following oral administration, flunitrazepam is almost entirely absorbed. 10 - 15% undergoes first-pass metabolism in the liver, resulting in an absolute (vs. i.v. solution) bioavailability of 70 - 90%. The maximum plasma concentrations of flunitrazepam are 6 - 11 ng/ml and occur 0.75 - 2 hours after administration of a single oral dose of 1 mg on an empty stomach.

Food reduces the rate and extent of flunitrazepam absorption.

The pharmacokinetics of flunitrazepam are linear in the 0.5 - 4 mg dose range.

Repetitive daily oral administrations lead to a moderate accumulation of flunitrazepam in plasma (accumulation ratio 1.6 - 1.7). The steady state plasma concentration of flunitrazepam is reached after 5 days. The minimum plasma concentration of flunitrazepam at steady state is 3 - 4 ng/ml following multiple oral doses of 2 mg. The steady state plasma concentration of the pharmacologically active N-desmethyl metabolite is almost identical to that of the parent compound.

3.2.2 Distribution

The distribution of flunitrazepam is rapid and extensive. The volume of distribution at steady state is 3 - 5 litres/kg.

Flunitrazepam is 78% bound to plasma proteins.

There is a rapid uptake of flunitrazepam into human cerebrospinal fluid. Flunitrazepam crosses the human placenta and blood-milk barrier slowly and to a minor extent after a single dose.

3.2.3 Metabolism

Flunitrazepam is almost completely metabolised. About 80% and 10% of the radiolabel are found in urine and feces, respectively. The principal plasma metabolites are 7-amino-flunitrazepam and N-desmethyl-flunitrazepam. The major urinary metabolite is 7-amino-flunitrazepam. Less than 2% of a dose is excreted renally as unchanged drug and as N-desmethyl-flunitrazepam. The N-desmethyl-flunitrazepam is pharmacologically active in

man, though less so than flunitrazepam, and plasma levels at steady state resulting from daily doses of 2 mg flunitrazepam are below the minimum effective concentration of the metabolite.

3.2.4 Elimination

The elimination half-life of flunitrazepam is between 16 and 35 hours. The half-life of the active N-desmethyl-flunitrazepam is 28 hours. The total plasma clearance is 120 - 140 ml/min.

3.2.5 Pharmacokinetics in Special Populations

Elderly

There are no age-related changes in the pharmacokinetics of flunitrazepam.

Patients with renal impairment

Accumulation of metabolites after repeated administration is somewhat greater in patients with renal failure than in patients with normal renal function. Therefore, the dose must be reduced.

Patients with hepatic impairment

The pharmacokinetics of flunitrazepam and N-desmethyl-flunitrazepam in patients with hepatic disease are similar to those in healthy volunteers.

3.3 Preclinical Safety

3.3.1 Carcinogenicity

Carcinogenicity studies of two years duration were conducted in mice and rats with doses of up to 25 and 50 mg/kg/d, respectively, administered orally. Histopathological examinations of the various tissues in both studies did not reveal any obvious signs of carcinogenicity of flunitrazepam.

3.3.2 Mutagenicity

Flunitrazepam has been investigated for mutagenic activity in a series of bacterial and mammalian genotoxicity tests. While mutagenic activity was observed in bacteria, the tests with mammalian cells in vitro and in vivo yielded no indication for a genotoxic activity. The effect in bacteria is not considered to be of relevance for human exposure conditions.

3.3.3 Impairment of Fertility

Studies in rats at doses of up to 25 mg/kg revealed no adverse effects on fertility and early embryonic development.

3.3.4 Teratogenicity

Studies in rats (up to 25 mg/kg/d), rabbits (up to 5 mg/kg/d) and mice (up to 100 mg/kg/d) revealed no teratogenic action of flunitrazepam even at hypnotic doses.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

This medicinal product does not require any special storage conditions.

This medicine should not be used after the expiry date (EXP) shown on the pack.

4.2 Packs

PVC/PVDC and aluminium blister with 10 film-coated tablets.

4.3 Special Instructions for Use, Handling and Disposal

No special requirements.

4.4 Shelf-Life

3 years.

Medicine: keep out of reach of children

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