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

2.5.4 Pediatric Use
See 2.3 Contraindications

2.5.5 Geriatric Use
See 2.2.1 Special Dosage Instructions

2.5.6 Renal Impairment
See 3.2.5 Pharmacokinetics in Special Populations

2.5.7 Hepatic Impairment
See 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations

2.6 Undesirable Effects
2.6.1 Post Marketing
The most commonly reported undesirable effects are drowsiness during the day, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia and double vision. These phenomena occur predominantly at the start of therapy and usually disappear with prolonged administration.
Other undesirable effects, including gastrointestinal disturbances, changes in libido and skin reactions, have been reported occasionally.
Hypersensitivity reactions, including rash, angioedema and hypotension, may occur.
Anterograde amnesia may occur with therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behavior (see 2.4.1 General [Warnings and Precautions]).
Pre-existing depression may be unmasked during benzodiazepine use.

Psychiatric and 'paradoxical' reactions
Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behavior and other adverse behavioral effects are known to occur with benzodiazepines and benzodiazepine-like agents. These reactions may be quite severe with this product, and are more likely to occur in the elderly.
Chronic use (even at therapeutic doses) may lead to the development of physical dependence: abrupt discontinuation of 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.
An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.

2.7 Overdose
Symptoms
Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Coma, hypotension and respiratory depression occasionally occur but are seldom serious if these drugs are taken alone. Coma, if it occurs, usually lasts only 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
Monitor the patient's vital signs and institute 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 contraindicated 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 liters/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 metabolized. About 80% and 10% of the radiolabel are found in urine and feces, repectively. 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
The pharmacokinetics of the active moieties of flumitrazepam are similar in patients with renal impairment compared to healthy subjects.
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/day), rabbits (up to 5 mg/kg/day) and mice (up to 100 mg/kg/day) revealed no teratogenic action of flunitrazepam even at hypnotic doses.

4. PHARMACEUTICAL PARTICULARS
4.1 Storage
This medicine should not be used after the expiry date (EXP) shown on the pack.
Do not store above 30 °C.

4.2 Packs
Film-coated tablets (scored) 1 mg 30

Medicine: keep out of reach of children

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