PRODUCT MONOGRAPH

T\C pms-FLURAZEPAM

(Flurazepam Hydrochloride Capsules USP)
15 mg

Hypnotic

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PRODUCT MONOGRAPH

T\C pms-FLURAZEPAM

(Flurazepam Hydrochloride Capsules USP)

15 mg

THERAPEUTIC CLASSIFICATION

Hypnotic

ACTIONS AND CLINICAL PHARMACOLOGY

pms-FLURAZEPAM (flurazepam hydrochloride), a benzodiazepine derivative, is a hypnotic agent which does not appear to decrease dream time as measured by rapid eye movements (REM). pms-FLURAZEPAM decreases sleep latency and number of awakenings for a consequent increase in total sleep time.

The duration of hypnotic effect and the profile of unwanted effects may be influenced by the alpha (distribution) and beta (elimination) half-lives of the administered drug and any active metabolites formed. When half-lives are long, the drug or metabolite may accumulate during periods of nightly administration and be associated with impairments of cognitive and motor performance during waking hours. If half-lives are short, the drug and metabolites will be cleared before the next dose is ingested, and carry-over effects related to sedation or CNS depression should be minimal or absent. However, during nightly use and for an extended period, pharmacodynamic tolerance or adaptation to some effects of benzodiazepine hypnotics may develop. If the drug has a very short elimination half-life, it is possible that a relative deficiency (i.e., in relation to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepine hypnotics: 1) increased wakefulness during the last third of the night; and 2) the appearance of increased daytime anxiety (see WARNINGS).

Flurazepam is a benzodiazepine with a long half-life.

Rebound Insomnia

A transient syndrome, whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of hypnotic treatment.

Pharmacokinetics

Following oral administration of 15 mg flurazepam hydrochloride to male and female volunteers, measurable concentrations for the parent compound were not detectable. Flurazepam undergoes rapid and pronounced metabolism to two pharmacologically active metabolites, namely hydroxyethyl flurazepam and flurazepam aldehyde. In healthy volunteers, C_{max} values for the two metabolites were 8.6 and 2.5 ng/mL, respectively. They were reached in an average of 1.0 and 1.2 hours, respectively. The mean elimination half-lives for these two metabolites were less than 2.5 hours.

The final active and principal metabolite, desalkyl flurazepam (DAFLZ), appears in the systemic circulation more slowly, with a mean C_{max} of 14 ng/mL attained an average of 10.6 hours after dosing. The mean elimination half-life of DAFLZ is approximately 75 hours (range 50 to 100 hours). Therefore, multiple-dose therapy with flurazepam leads to the accumulation of DAFLZ. The half-life of DAFLZ was found to be longer in elderly males than in young males (160 versus 74 hours, $p<0.05$), but was similar in elderly and young females (120 versus 90 hours, p=N.S.). DAFLZ was extensively bound to plasma protein. The unbound fraction increased with age regardless of sex.

Following 15 days treatment with 15 mg flurazepam once daily, mean steady-state plasma levels of DAFLZ were higher in elderly than in young men (81 and 53 ng/mL, $p<0.05$), but were similar in elderly and young women (86 and 85 ng/mL).

More than 50% of the total dose of flurazepam appears in the urine in 24 hours, with eventual urinary excretion accounting for 80% or more of the total dose. The major urinary metabolite is conjugated hydroxyethyl flurazepam. Less than 1% of the dose is excreted in the urine as DAFLZ. Approximately 10% of the total dose of flurazepam appears in the feces.

INDICATIONS AND CLINICAL USE

Sleep disturbance may be the presenting manifestation of a physical and/or psychiatric disorder. Consequently, a decision to initiate symptomatic treatment of insomnia should only be made

after the patient has been carefully evaluated.

pms-FLURAZEPAM (flurazepam hydrochloride) is indicated for the short-term treatment and symptomatic relief of transient and short-term insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening.

Treatment with pms-FLURAZEPAM should usually not exceed 7 to 10 consecutive days. Use for more than 2 to 3 consecutive weeks requires complete re-evaluation of the patient. Prescriptions for pms-FLURAZEPAM should be written for short-term use (7 to10 days) and it should not be prescribed in quantities exceeding a one-month supply.

The use of hypnotics should be restricted for insomnia where disturbed sleep results in impaired daytime functioning.

CONTRAINDICATIONS

pms-FLURAZEPAM (flurazepam hydrochloride) is contraindicated in patients with known hypersensitivity to benzodiazepines, or any component of its formulation, and in those with severe impairment of respiratory function, e.g., significant sleep apnea syndrome.

pms-FLURAZEPAM is contraindicated in patients who have myasthenia gravis or severe hepatic
insufficiency.

WARNINGS

General

Benzodiazepines should be used with extreme caution in patients with a history of substance or alcohol abuse.

The smallest possible effective dose should be prescribed for elderly patients. Inappropriate, heavy sedation in the elderly, may result in accidental events/falls.

The failure of insomnia to remit after 7-10 days of treatment may indicate the presence of a

primary psychiatric and/or medical illness or the presence of sleep-state misperception. Worsening of insomnia or the emergence of new abnormalities of thinking or behaviour may be the consequence of an unrecognized psychiatric or physical disorder. These have also been reported to occur in association with the use of drugs that act at the benzodiazepine receptors.

pms-FLURAZEPAM (flurazepam hydrochloride) should be used with caution in patients who in the past manifested paradoxical reactions to alcohol and/or sedative medications.

Pregnancy: The use of pms-FLURAZEPAM during pregnancy is not recommended. Benzodiazepines may cause fetal damage when administered during pregnancy. During the first trimester of pregnancy, several studies have suggested an increased risk of congenital malformations associated with the use of benzodiazepines. During the last weeks of pregnancy, ingestion of therapeutic doses of a benzodiazepine hypnotic has resulted in neonatal CNS depression due to transplacental distribution. If pms-FLURAZEPAM is prescribed to women of childbearing potential, the patient should be warned of the potential risk to a fetus and advised to consult her physician regarding the discontinuation of the drug if she intends to become pregnant or suspects that she might be pregnant.

Memory disturbance: Anterograde amnesia of varying severity has been reported following therapeutic doses of benzodiazepines. The event is rare with pms-FLURAZEPAM. Anterograde amnesia is a dose-related phenomenon and elderly subjects may be at particular risk.

Cases of transient global amnesia and “traveller's amnesia” have also been reported in association with benzodiazepines, the latter in individuals who have taken benzodiazepines, often in the middle of the night, to induce sleep while travelling. Transient global amnesia and traveller's amnesia are unpredictable and not necessarily dose-related phenomena. Patients should be warned not to take pms-FLURAZEPAM under circumstances in which a full night's sleep and clearance of the drug from the body are not possible before they need again to resume full activity.

Abnormal thinking and psychotic behavioural changes have been reported to occur in association with the use of benzodiazepines including pms-FLURAZEPAM, although rarely. Some of the changes may be characterized by decreased inhibition, e.g., aggressiveness or extroversion that seem excessive, similar to that seen with alcohol and other CNS depressants (e.g.,

sedative/hypnotics). Particular caution is warranted in patients with a history of violent behaviour and a history of unusual reactions to sedatives including alcohol and the benzodiazepines. Psychotic behavioural changes that have been reported with benzodiazepines include bizarre behaviour, hallucinations, and depersonalization. Abnormal behaviours associated with the use of benzodiazepines have been reported more with chronic use and/or high doses but they may occur during the acute, maintenance or withdrawal phases of treatment.

It can rarely be determined with certainty whether a particular instance of abnormal behaviours listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric disorder. Nevertheless, the emergence of any new behavioural sign or symptom of concern requires careful and immediate evaluation.

Confusion: The benzodiazepines affect mental efficiency, e.g., concentration, attention and vigilance. The risk of confusion is greater in the elderly and in patients with cerebral impairment.

Anxiety, Restlessness: An increase in daytime anxiety and/or restlessness has been observed during treatment with short half-life benzodiazepines although the syndrome can apply on occasion to drugs with longer elimination half-lives as well. Flurazepam has a long half-life.

Depression: Caution should be exercised if pms-FLURAZEPAM is prescribed to patients with signs or symptoms of depression that could be intensified by hypnotic drugs. The potential for self-harm (e.g., intentional overdose) is high in patients with depression and thus, the least amount of drug that is feasible should be available to them at any one time.

Complex Sleep-related Behaviours: Complex sleep-related behaviours such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in patients who have taken flurazepam. Other potentially dangerous behaviours have been reported in patients who got out of bed after taking a sedative-hypnotic and were not fully awake, including preparing and eating food, making phone calls, leaving the house, etc. As with “sleep-driving”, patients usually do not remember these events. The use of alcohol and other CNS-depressants with flurazepam appears to increase the risk of such behaviours, as does the use of flurazepam at doses exceeding the maximum recommended dose. pms-FLURAZEPAM is not to be taken with alcohol. Caution is needed with concomitant use of other CNS depressant drugs. Due to the risk to the patient and the community, discontinuation of flurazepam should be strongly considered for patients who report any such sleep-related

behaviours.

Severe Anaphylactic and Anaphylactoid 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, including flurazepam. 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 throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with flurazepam should not be rechallenged with the drug.

PRECAUTIONS

Drug interactions: pms-FLURAZEPAM (flurazepam hydrochloride) may produce additive CNS depressant effects when co-administered with alcohol, sedative antihistamines, narcotic analgesics, anticonvulsants, or psychotropic medications which themselves can produce CNS depression.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. Examples include cimetidine or erythromycin.

Drug abuse, Dependence and Withdrawal: Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting, sweating, dysphoria, perceptual disturbances and insomnia) have occurred following abrupt discontinuations of benzodiazepines, and may follow the discontinuation of pms-FLURAZEPAM. The more severe symptoms are usually associated with higher dosages and longer usage, although patients given therapeutic dosages for as few as 1 to 2 weeks can also have withdrawal symptoms including daytime anxiety between nightly doses. Consequently, abrupt discontinuation should be avoided and a gradual dosage tapering schedule is recommended in any patient taking more than the lowest dose for more than a few weeks. The recommendation for tapering is particularly important in patients with a history of seizures. The risk of dependence is increased in patients with a history of alcoholism, drug abuse, or in patients with marked personality disorders. Caution must be exercised in administering pms-FLURAZEPAM to these individuals.

As with all hypnotics, repeat prescriptions should be limited to those who are under medical

supervision.

Patients with specific conditions: pms-FLURAZEPAM should be given with caution to patients with impaired hepatic or renal function, or severe pulmonary insufficiency. Respiratory depression has been reported in patients with compromised respiratory function.

Patients Requiring Mental Alertness: Because of pms-FLURAZEPAM's CNS depressant effect, patients receiving the drug should be cautioned against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be warned against the concomitant ingestion of pms-FLURAZEPAM and alcohol or CNS-depressant drugs.

Use in Pregnancy: For teratogenic effects see WARNINGS. Non-teratogenic effects: a child born to a mother who is on benzodiazepines may be at risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity has been reported in an infant born to a mother who had been receiving benzodiazepines.

Use in Nursing Mothers: The safety of the use of pms-FLURAZEPAM during lactation has not been established. Therefore, its use during nursing is not recommended.

Use in Children: The safety and effectiveness of pms-FLURAZEPAM in children below the age of 15 have not been established.

Use in the Elderly: Elderly patients are especially susceptible to dose-related adverse effects, such as drowsiness, dizziness, or impaired coordination. Inappropriate, heavy sedation may result in accidental events/falls. Therefore, the lowest possible dose (15 mg) should be used in these subjects.

Laboratory Tests: Should pms-FLURAZEPAM be used repeatedly, periodic blood counts, liver, and kidney function tests should be performed.

ADVERSE EFFECTS

The most common adverse reactions reported with pms-FLURAZEPAM (flurazepam hydrochloride) are dizziness, drowsiness, lightheadedness, and ataxia. These adverse effects are

particularly common in elderly and debilitated patients (See PRECAUTIONS). Severe sedation, lethargy, disorientation, and coma, probably indicative of drug intolerance or overdosage, have been reported.

Isolated instances of headache, heartburn, upset stomach, nausea, vomiting, amnesia, constipation, diarrhea, gastrointestinal pain, nervousness, apprehension, irritability, weakness, palpitations, chest pains, and genito-urinary complaints have been reported. However, in controlled studies, these appeared as often or more often with placebo than with the active drug.

There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, nightmares, numbed emotions, reduced alertness, changes in libido, inappropriate behaviour and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase. Paradoxical reactions such as excitement, stimulation, agitation, aggressiveness, rages, psychoses and hyperactivity have also been reported in rare instances when using drugs that act at the benzodiazepine receptors.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Manifestatins of pms-FLURAZEPAM (flurazepam hydrochloride) overdosage include somnolence, confusion and coma. Respiration, pulse and blood pressure should be monitored as in all cases of drug overdosage. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension and CNS depression may be combated by judicious use of appropriate therapeutic agents. The value of dialysis has not been determined. If excitation occurs in patients following pms-FLURAZEPAM overdosage, barbiturates should not be used.

As with the management of intentional overdosage with any drug, it should be borne in mind that multiple agents may have been ingested. The benzodiazepine antagonist, flumazenil (ANEXATE), is a specific antidote in known or suspected benzodiazepine overdose. (For conditions of use see ANEXATE Product Monograph).

DOSAGE AND ADMINISTRATION

The lowest effective dose of pms-FLURAZEPAM (flurazepam hydrochloride) should be used. Treatment with pms-FLURAZEPAM should be as short as possible, and should usually not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient.

Dosage should be individualized for maximal beneficial effects.

Adults: The usual adult dosage is 30 mg before retiring. In some patients, 15 mg may suffice.

Elderly and/or Debilitated Patients: It is recommended that therapy be initiated with 15 mg until individual responses are determined.

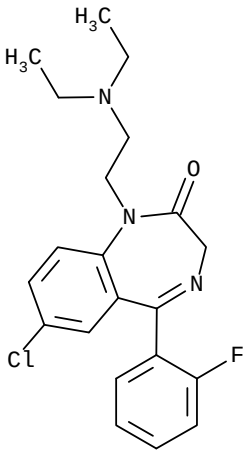
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Flurazepam Hydrochloride

Chemical Name: 7-Chloro-1-[2-(diethylamino)ethyl]-5-(O-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one dihydrochloride.

Structural Formula:



Molecular Formula: $C_{21}H_{23}ClFN_3O.2HCl$

Molecular Weight: 460.8

Description: Off white to yellow odourless or almost odorless crystalline powder.

Melting Point: 190–220°C

Solubility: Very soluble in water. Freely soluble in alcohol. Slightly soluble in chloroform and acetone. Practically insoluble in benzene and ether.

Composition

pms-FLURAZEPAM capsules contain 15 mg flurazepam hydrochloride. Non-medicinal ingredients: Cornstarch, Lactose. Capsule also contains: D&C Yellow No. 10, FD&C Red No. 40, FD&C Yellow No. 6, Gelatin, and Titanium Dioxide.

Stability and Storage Recommendations

Store at 15° – 30°C in tight, light-resistant containers.

AVAILABILITY OF DOSAGE FORMS

pms-FLURAZEPAM 15 mg: Each orange/ivory, capsule imprinted “P” and “15” contains 15 mg flurazepam hydrochloride. Available in bottles of 100, 500 and 1000.

PHARMACOLOGY

In animals, flurazepam hydrochloride has been demonstrated to produce sedative, anticonvulsant, taming, and muscle relaxant effects. At high doses, flurazepam hydrochloride exhibited sedative effects in rats (36 mg/kg), as well as a depressant effect on behaviour in squirrel monkeys (40 mg/kg). Some cardiovascular depressant effects were also observed, but were largely attributed to the central nervous system depressant effects of high doses.

Flurazepam and its metabolites bind with high affinity to mouse brain membranes. In vitro specific binding affinities (K_i) for flurazepam, hydroxyethyl-flurazepam, flurazepam aldehyde and desalkyl-flurazepam were 10.7, 16.2, 10.6, and 0.85 nM, respectively. Flurazepam hydrochloride is rapidly absorbed from the gastrointestinal tract and is rapidly metabolized. Studies in rats with ^{14}C-labelled flurazepam hydrochloride indicated that the drug is widely distributed throughout body tissues with no excessive accumulation of drug or metabolite in any one tissue.

TOXICOLOGY

The oral LD_{50} was 870 mg/kg in mice, 1,232 mg/kg in rats and 568 mg/kg in rabbits. Chronic toxicity studies for one year indicated that the tolerated dose is 80 mg/kg/day in the rat and 10 mg/kg/day in the dog.

Effects on Reproduction: A two-cycle reproductive study in rats was carried out at doses of 5 and 50 mg/kg/day of flurazepam hydrochloride. There were no significant teratogenic or other adverse effects related to the drug. In the second series of rat reproductive studies, doses of 3 and 20 mg/kg/day of flurazepam hydrochloride did not induce changes in fertility and general reproductive performance. There were no significant teratogenic effects related to the drug or adverse effects in the perinatal and postnatal study. In another reproductive study in rats at doses

of 10, 20, 40 and 80 mg/kg/day, no adverse effects on reproduction and no significant teratological changes were noted.

In rabbits, two sets of teratogenic studies were done. In the first, flurazepam hydrochloride was administered in doses of 5 and 20 mg/kg/day. Twenty-three live litters were obtained in this study. One animal which received 20 mg/kg/day had a litter of nine viable but deformed fetuses. In the second study, the dose of flurazepam hydrochloride was increased to 40 mg/kg/day without the occurrence of abnormalities in all eleven litters. In both studies, there were no significant differences between the control and treated groups in maternal weight, body weight of
viable fetuses, fetal body weight and litter size.

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27. Product Monograph - Dalmane, Valeant Canada Ltd., dated June 29, 2009, control number 127818

PART III: CONSUMER INFORMATION

pms-FLURAZEPAM
Flurazepam Hydrochloride capsules

This leaflet is part III of a three-part "Product Monograph" published when pms-FLURAZEPAM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-FLURAZEPAM. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
pms-FLURAZEPAM is intended to help you sleep if you have transient and short-term insomnia. Symptoms of insomnia include difficulty falling asleep and/or waking up often during the night or too early in the morning.

Treatment with pms-FLURAZEPAM should usually not go on for more than 7-10 days and should be restricted for insomnia where disturbed sleep results in impaired daytime functioning. pms-FLURAZEPAM does not treat the underlying cause of your insomnia.

What it does:
pms-FLURAZEPAM is one of several benzodiazepine sleeping pills that have generally similar properties such as a calming effect.

If you are prescribed one of these medications, you should consider both their benefits and risks. Important risks and limitations include the following:
- you may become dependent on the medication,
- the medication may affect your mental alertness or memory, particularly when not taken as prescribed.

(see "WARNINGS AND PRECAUTIONS")

When it should not be used:
Do not take pms-FLURAZEPAM if you have:
- known allergy to flurazepam or other benzodiazepines, or any of the ingredients pms-FLURAZEPAM contains (see "What the nonmedicinal ingredients are")
- severe lung or respiratory disease, including sleep apnea
- myasthenia gravis, a chronic disease characterized by weakness of the skeletal muscles
- a severe liver condition

What the medicinal ingredient is:
Flurazepam hydrochloride

What the nonmedicinal ingredients are:
Cornstarch, D&C Yellow No. 10, FD&C Red No. 40, FD&C Yellow No. 6, Gelatin, Lactose, and Titanium Dioxide.

What dosage forms it comes in:
15 mg Capsules

WARNINGS AND PRECAUTIONS

Complex sleep-related behaviours
There have been reports of people getting out of bed while not fully awake after taking pms-FLURAZEPAM and doing activities that they did not know they were doing. The next morning, they did not remember doing those activities. This unusual behaviour is more likely to occur when pms-FLURAZEPAM is taken with alcohol or other drugs that can make you sleepy such as those for the treatment of depression or anxiety. The activities you may do in these situations can put you and people around you in danger. Reported activities included driving a car ("sleep-driving"), leaving the house, making and eating food, talking on the phone, etc.

Important:
1. Do not take more pms-FLURAZEPAM than prescribed.
2. Do not take pms-FLURAZEPAM if you drink alcohol.
3. Talk to your doctor about all of your medicines, including over-the-counter medicines and herbal products. Your doctor will tell you if you can take pms-FLURAZEPAM with your other medicines.
4. You and people close to you should watch for the type of unusual behaviour described above. If you find out that you have done any such activities for which you have no memory you should call your doctor immediately.

Mental Alertness: pms-FLURAZEPAM may affect your ability to be alert. DO NOT DRIVE A CAR or operate potentially dangerous machinery until you experience how this drug will affect you.

Memory Problems: All benzodiazepine sleeping pills can cause a special type of memory loss (amnesia); you may not recall events that occurred during some period of time, usually several hours, after taking the drug. This lapse is usually not a problem, because the person taking the sleeping pill intends to be asleep during this critical period of time. But it can be a problem if you take the medication to induce sleep while travelling, such as during an airplane flight, because you may wake up before the effect of the

drug is gone. This has been called “traveller's amnesia”. DO NOT TAKE pms-FLURAZEPAM when a full night's sleep is not possible before you would again need to be active and functional; e.g., an overnight flight of less than 8 hours. Memory lapses may occur in such situations. Your body needs time to eliminate the medication from your system.

Tolerance/Withdrawal Symptoms: After nightly use for more than a few weeks benzodiazepines may lose some of their effectiveness. You may also develop a degree of dependence.

“Withdrawal” effects can occur when patients stop taking benzodiazepine sleeping pills. The effects may occur following use for only a week or two but may be more common and severe after long periods of continuous use. For example, you may experience an increase in sleep difficulties (rebound insomnia) and/or increased daytime anxiety (rebound anxiety) for one or two days after discontinuing pms-FLURAZEPAM.

Other withdrawal symptoms following abrupt stopping of sleeping pills may range from unpleasant feelings to a major withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremor, and rarely, convulsions. The severe symptoms are uncommon.

Dependence/Abuse: All benzodiazepine sleeping pills can cause dependence (addiction) especially when used regularly for more than a few weeks, or at higher doses. Some people develop a need to continue taking these drugs, either at the prescribed dose or at higher doses not only for continued therapeutic effect, but also to avoid withdrawal symptoms or to achieve non-therapeutic effects.

Individuals who depend, or have depended at any time in the past, on alcohol or other drugs may be at particular risk of becoming dependent on drugs of this class. But ALL PEOPLE ARE AT SOME RISK. Consider this matter before you take these medications beyond a few weeks.

Mental and Behavioural Changes: A variety of abnormal thinking and behaviour changes may occur when you use benzodiazepine sleeping pills. Some of these changes include aggressiveness and extroversion which seem out of character. Other changes, although rare, can be more unusual and extreme such as confusion, strange behaviour, restlessness, illusions, hallucinations, feeling like you are not yourself, worsening insomnia and worsening depression, including suicidal thinking.

It is rarely clear whether such symptoms are caused by the medication, or by an illness that was present before the medication was used, or are simply spontaneous happenings. If you develop any unusual disturbing thoughts or behaviour while using pms-FLURAZEPAM, discuss the matter immediately with your doctor.

Worsening of Side Effects
DO NOT CONSUME ALCOHOL WHILE TAKING pms-FLURAZEPAM. Some medicines may also worsen side effects that some patients experience with pms-FLURAZEPAM (see “INTERACTIONS WITH THIS MEDICATION”).

Elderly: An increased risk of falls and fractures has been reported in elderly people who take benzodiazepines such as pms-FLURAZEPAM.

Effects on Pregnancy: Certain benzodiazepine sleeping pills have been linked to birth defects when taken during the early months of pregnancy. In addition, benzodiazepine sleeping pills taken during the last weeks of pregnancy have been known to sedate the baby and may also cause withdrawal symptoms after birth. DO NOT TAKE pms-FLURAZEPAM at any time during pregnancy.

BEFORE you use pms-FLURAZEPAM talk to your doctor or pharmacist if:

- You have a lung disease or breathing problems.
- You have liver or kidney condition.
- You have a history of depression and/or suicide thoughts or attempts.
- You have had unexpected reactions to alcohol or sedative medications in the past, such as irritability, aggression, hallucinations, etc.
- You have a history of drug or alcohol abuse or addiction.
- You are planning to become pregnant, you are pregnant, or you become pregnant while taking this medication.
- You are breastfeeding.
- You consume alcohol.
- You are taking other medicines, including drugs you can buy without a prescription.
- You have lactose intolerance.

INTERACTIONS WITH THIS MEDICATION

pms-FLURAZEPAM may produce more pronounced side effects when coadministered with alcohol, other tranquilizers or sleeping pills, sedative antihistamines, narcotic analgesics, anticonvulsants, antipsychotics and antidepressants or other psychotropic medications which themselves can make you sleepy.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. Examples include cimetidine or erythromycin.

Do not take pms-FLURAZEPAM if you drink alcohol. DO NOT USE pms-FLURAZEPAM along with other medications without first discussing this with your doctor.

PROPER USE OF THIS MEDICATION

Benzodiazepine sleeping pills are effective medications and are relatively free of serious problems when used for the short-term management of insomnia. Insomnia may last only for a short time and may respond to brief treatment. The risks and benefits of prolonged use should be discussed with your doctor.

Usual dose:
pms-FLURAZEPAM is a prescription medication intended to help you sleep. Follow your doctor's advice about how to take pms-FLURAZEPAM, when to take it, and how long to take it.

Adults: The recommended dose is 30 mg just before bedtime, although some patients may require only 15 mg.

Elderly and/or Debilitated Patients should start with 15 mg just before bedtime.

DO NOT TAKE pms-FLURAZEPAM if it is not prescribed for you.

DO NOT TAKE pms-FLURAZEPAM for more than 7 to 10 days without first consulting your doctor. If you still have problems sleeping after you finish your capsules, contact your doctor again.

The lowest effective dose should be used.

DO NOT INCREASE THE PRESCRIBED DOSE.

Do not take pms-FLURAZEPAM if you drink alcohol.

Do not take pms-FLURAZEPAM when a full night's sleep is not possible before you would again need to be active and functional.

Do not drive a car or operate potentially dangerous machinery until you experience how pms-FLURAZEPAM will affect you the next day.

pms-FLURAZEPAM is not for use in children under 18 years of age.

Overdose:
Manifestations of flurazepam hydrochloride overdosage include somnolence, confusion and coma.

Contact your doctor, regional Poison Control Centre or pharmacist immediately if you suspect you have taken an overdose or someone else accidentally takes your pms-FLURAZEPAM. If you are unable to contact them, go to a hospital emergency department for medical help, even though you may not feel sick. Show your doctor your bottle of capsules.

Missed Dose:
If you forget to take pms-FLURAZEPAM capsules, do not take a double dose to make up for the forgotten individual dose. Take the next dose at the usual time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common Side Effects
Benzodiazepine sleeping pills may cause drowsiness, dizziness, light-headedness, and difficulty with coordination. Users must be cautious about engaging in hazardous activities requiring complete mental alertness, e.g., operating machinery or driving a motor vehicle.

DO NOT drink alcohol while using pms-FLURAZEPAM. DO NOT USE benzodiazepine sleeping pills along with other medications without first discussing this with your doctor.

How sleepy you are the day after you use one of these sleeping pills depends on your individual response and on how quickly your body gets rid of the medication. The larger the dose, the more likely that you will experience drowsiness, etc., the next day. For this reason, it is important that you use the lowest dose possible that will still help you sleep at night. Benzodiazepines which are eliminated rapidly tend to cause less drowsiness the next day, but may cause withdrawal problems the day after use.

Elderly patients are especially susceptible to side effects. Excessive drowsiness in the elderly may result in falls and fractures.

Rare cases of severe allergic reactions have been reported. Symptoms may include swelling of the tongue or throat, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking 'Dalmane'.

Withdrawal-related side effects: See "WARNINGS AND PRECAUTIONS, **Tolerance/Withdrawal Symptoms"**.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	Unexpected reactions such as excitement, agitation, hyperactivity, hallucination, worsened insomnia, aggressiveness, irritability, rages, psychoses, and violent behaviour		✓	
	Severe allergic reactions (swelling of the tongue or throat, trouble breathing, nausea and vomiting)			✓
	Depressed mood; thoughts of death or suicide		✓	
Very rare	Somnambulism (sleepwalking) – getting out of bed while not fully awake and do activities you do not remember the day after		✓	

This is not a complete list of side effects. For any unexpected effects while taking pms-FLURAZEPAM, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature (15-30°C) in tightly closed, light resistant container.

Keep out of reach of children.

REPORTING SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect .

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Pharmascience Inc. at, 1-888-550-6060.

This leaflet was prepared by
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