PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

SOM-PAM

Flurazepam Hydrochloride Capsules

Capsules, 15 mg and 30 mg, Oral

Hypnotic

Biomed Pharma
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Saint-Leonard, QC
H1P 3H8

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RECENT MAJOR LABEL CHANGES

1 Indications, 1.2 Geriatrics	08/2022
3 Serious Warnings and Precautions Box	08/2022
4 Dosage and Administration	08/2022
7 Warnings and Precautions	08/2022
7 Warnings and Precautions, 7.1.4 Geriatrics	08/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SOM-PAM (flurazepam hydrochloride) is indicated for:

- the symptomatic relief of transient and short-term insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening.

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

1.1 Pediatrics

Pediatrics (< 18 years of age):
The safety and efficacy of SOM-PAM in children below the age of 18 have not been established. Therefore, Health Canada has not authorized an indication for use in this pediatric population.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.
Long-term use of SOM-PAM should be avoided in elderly patients. Enhanced monitoring is recommended (see 7 WARNINGS AND PRECAUTIONS, Falls and fractures; 4.1 Dosing considerations).

2 CONTRAINDICATIONS

SOM-PAM (flurazepam hydrochloride) is contraindicated:

- In patients with known hypersensitivity to this drug or to other benzodiazepines, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- In patients with severe impairment of respiratory function, e.g. significant sleep apnea syndrome
- In patients who have myasthenia gravis
- In patients with severe hepatic insufficiency

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Addiction, Abuse and Misuse

The use of benzodiazepines, including SOM-PAM, can lead to abuse, misuse, addiction, physical dependence and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol or illicit drugs.

- Assess each patient's risk prior to prescribing SOM-PAM
- Monitor all patients regularly for the development of these behaviours or conditions.
- SOM-PAM should be stored securely to avoid theft or misuse.

Withdrawal

Benzodiazepines, like SOM-PAM, can produce severe or life-threatening withdrawal symptoms.

- Avoid abrupt discontinuation or rapid dose reduction of SOM-PAM.
- Terminate treatment with SOM-PAM by gradually tapering the dosage schedule under close monitoring.

(see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

Risks from Concomitant use with Opioids

Concomitant use of SOM-PAM and opioids may result in profound sedation, respiratory depression, coma and death (see 7 WARNINGS AND PRECAUTIONS, General, Concomitant use with opioids).

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- 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.
- The use of hypnotics should be restricted for insomnia where disturbed sleep results in impaired daytime functioning.
- SOM-PAM should always be prescribed at the lowest effective dose for the shortest duration possible.
- Treatment with SOM-PAM 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. Prescriptions for SOM-PAM should be written for short-term use (7 to 10 days) and it should not be prescribed in quantities exceeding a one-month supply.

Discontinuation

- SOM-PAM can produce withdrawal signs and symptoms or rebound phenomena following abrupt discontinuation or rapid dose reduction (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance). Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal signs and symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.

Geriatric
- Geriatric patients in particular may be more sensitive to benzodiazepines (see 7 WARNINGS AND PRECAUTIONS, Falls and Fractures).
- Long-term use of SOM-PAM should be avoided in elderly patients. Enhanced monitoring is recommended.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

Adults: The usual adult dose is 30 mg before retiring, although some patients may require only 15 mg.

Elderly and/or Debilitated Patients: In elderly and/or debilitated patients, it is recommended that therapy be initiated with 15 mg until individual responses are determined.

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric patients under 18 years of age (see 1.1 Pediatrics).

Dosage Adjustment

Dosage should be individualized for maximal beneficial effects.

4.4 Administration

SOM-PAM should be taken orally just before going to bed. The patient should be checked regularly at the start of the treatment in order to decrease, if necessary, the dose or frequency of administration to prevent overdose due to accumulation.

4.5 Missed Dose

If the patient misses a dose, inform the patient to skip the missed dose and take the next dose at the regular dosing schedule.

5 OVERDOSAGE

Manifestations of 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. 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 flurazepam hydrochloride 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, is a specific antidote in known or suspected benzodiazepine overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule 15 mg, 30 mg	Corn starch, gelatin and lactose

SOM-PAM 15 mg: Branded hard gelatin capsules, size #2, with orange opaque body and grey opaque cap containing 15 mg flurazepam hydrochloride. Available in bottles of 100 and 500.

SOM-PAM 30 mg: Branded hard gelatin capsules, size #2 with scarlet opaque body and grey opaque cap containing 30 mg flurazepam hydrochloride. Available in bottles of 100 and 500.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

SOM-PAM should be used with caution in patients who in the past manifested paradoxical reactions to alcohol and/or sedative medications.

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.

Concomitant use with opioids
Concomitant use of benzodiazepines, including SOM-PAM, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant use with Opioids; 9.1 Serious Drug Interactions).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with benzodiazepines.

If a decision is made to prescribe SOM-PAM concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of SOM-PAM than indicated, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking SOM-PAM, prescribe a lower initial dose of the opioid analgesic and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation (see 5 OVERDOSAGE).

Advise both patients and caregivers about the risks of respiratory depression and sedation when SOM-PAM is used with opioids.

Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined.

Dependence/Tolerance

Use of benzodiazepines, such as SOM-PAM, can lead to abuse, misuse, addiction, physical dependence (including tolerance) and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol, or illicit drugs.

The risk of dependence increases with higher doses and longer term use but can occur with short-term use (days to weeks) at recommended therapeutic doses. The risk of dependence is greater in patients with a history of psychiatric disorders and/or substance (including alcohol) use disorder.

- Discuss the risks of treatment with SOM-PAM with the patient, considering alternative (including non-drug) treatment options.
- Carefully evaluate each patient's risk of abuse, misuse and addiction, considering their medical condition and concomitant drug use, prior to prescribing SOM-PAM. In individuals prone to substance use disorder, SOM-PAM should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- SOM-PAM should always be prescribed at the lowest effective dose for the shortest duration possible.
- All patients receiving benzodiazepines should be routinely monitored for signs and symptoms of misuse and abuse. If a substance use disorder is suspected, evaluate the patient and refer them for substance abuse treatment, as appropriate.

Withdrawal

Benzodiazepines, such as SOM-PAM, can produce withdrawal signs and symptoms, ranging from mild to severe and even life threatening, following abrupt discontinuation or rapid dose reduction. Other factors that may precipitate withdrawal are switching from a long-acting to a short-acting benzodiazepine, decreasing blood levels of the drug or administration of an antagonist. The risk of withdrawal is higher

with higher dosages and/or prolonged use, but can occur with short-term use (days to weeks) at recommended therapeutic doses.

The onset of withdrawal signs and symptoms can range from hours to weeks following drug cessation and occur even with tapered dosage. Some symptoms can persist for months. Since symptoms are often similar to those for which the patient is being treated, it may be difficult to distinguish from a relapse of the patient's condition.

Severe or life-threatening signs and symptoms of withdrawal include catatonia, delirium tremens, depression, dissociative effects (e.g. hallucinations), homicidal thoughts, mania, psychosis, seizures (including status epilepticus) and suicidal ideation and behaviour.

Other withdrawal signs and symptoms include abdominal cramps, cognitive impairment, diarrhea, dysphoria, extreme anxiety or panic attacks, headache, hypersensitivity to light, noise and physical contact, insomnia, irritability, muscle pain or stiffness, paresthesia, restlessness, sweating, tension, tremors and vomiting. There is also a possibility of rebound anxiety or rebound insomnia.

- Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Inform patients of risk of discontinuing abruptly, reducing dosage rapidly or switching medications.
- Stress the importance of consulting with their health care professional in order to discontinue safely.
- Patients experiencing withdrawal symptoms should seek immediate medical attention.

(see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal; 4.1 Dosing Considerations)

Driving and Operating Machinery

Because of SOM-PAM'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 SOM-PAM and alcohol or CNS-depressant drugs (see 9.3 Drug-Behavioural Interactions, 9.4 Drug-Drug Interactions).

Falls and fractures

There have been reports of falls and fractures among benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly or debilitated patients.

Hepatic/Biliary/Pancreatic

SOM-PAM is contraindicated in patients with severe hepatic insufficiency (see 2 CONTRAINDICATIONS).

SOM-PAM should be given with caution to patients with impaired hepatic function.

Immune

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 SOM-PAM. 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 SOM-PAM should not be rechallenged with the drug.

Monitoring and Laboratory Tests

Rare cases of elevated bilirubin and liver enzyme levels, leukopenia, and granulocytopenia have been reported with SOM-PAM (see 8.1 Adverse Reaction Overview).
Should SOM-PAM be used repeatedly, periodic blood counts, liver, and kidney function tests should be performed.

Neurologic

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

Cases of transient global amnesia and “traveler'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 traveling. Transient global amnesia and traveler's amnesia are unpredictable and not necessarily dose-related phenomena. Patients should be warned not to take SOM-PAM 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.

Psychiatric

Abnormal thinking and psychotic behavioural changes: Abnormal thinking and psychotic behavioural changes have been reported to occur in association with the use of benzodiazepines including SOM-PAM, 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 have 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 SOM-PAM 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 SOM-PAM. 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 SOM-PAM appears to increase the risk of such behaviours, as does the use of SOM-PAM at doses exceeding the maximum recommended dose. SOM-PAM 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 SOM-PAM should be strongly considered for patients who report any such sleep- related behaviours.

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.

Renal

SOM-PAM should be given with caution to patients with impaired renal function.

Reproductive Health: Female and Male Potential

- **Fertility**
  No effect of flurazepam hydrochloride on fertility was observed in animal studies (see 16 NON-CLINICAL TOXICOLOGY).

- **Teratogenic Risk**
  Teratogenic and non-teratogenic effects have been reported in association to use of benzodiazepines during pregnancy. The use of SOM-PAM during pregnancy is not recommended (see 7.1.1 Pregnant Women).

Respiratory

Respiratory depression has been reported in patients with compromised respiratory function. SOM-PAM is contraindicated in patients with severe impairment of respiratory function (see 2 CONTRAINDICATIONS).

7.1 Special Populations

7.1.1 Pregnant Women

The use of SOM-PAM (flurazepam hydrochloride) during pregnancy is not recommended. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies have suggested an increased risk of congenital malformations associated with the use of the benzodiazepines during the first trimester of pregnancy. 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 SOM-PAM is prescribed to a woman of child-bearing potential, the patient should be warned of potential risk to a fetus and advised to consult her physician regarding the discontinuation of the drug if she intends to become or suspects that she might be pregnant.
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.

7.1.2 Breast-feeding

The safety of SOM-PAM during lactation has not been established. Therefore, its use during nursing is not recommended.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of SOM-PAM in children below the age of 18 have not been established. Therefore, Health Canada has not authorized an indication for use in this pediatric population.

7.1.4 Geriatrics

Long-term use of SOM-PAM should be avoided in elderly or debilitated patients who may be more sensitive to benzodiazepines. There is an increased risk of cognitive impairment, delirium, falls, fractures, hospitalizations and motor vehicle accidents in these users. Enhanced monitoring is recommended in this population.

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 (see 4.2 Recommended Dose and Dosage Adjustment).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions reported with SOM-PAM (flurazepam hydrochloride) are dizziness, drowsiness, light-headedness, and ataxia. These adverse effects are particularly common in elderly and debilitated patients (See 7.1.4 Geriatrics). 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, diarrhea, constipation, gastrointestinal pain, nervousness, apprehension, irritability, weakness, palpitations, chest pains, and genitourinary 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 focussing, 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, change in libido, inappropriate behaviour, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase. Paradoxical reactions, e.g. excitement, stimulation, agitation, aggressiveness, rages, psychoses, and hyperactivity also have been reported in rare instances when using drugs that act at the benzodiazepine receptors.

8.5 Post-Market Adverse Reactions

Injury, Poisoning and Procedural Complications: There have been reports of falls and fractures in benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly and debilitated patients.

Dependence/Withdrawal: Development of physical dependence and withdrawal following discontinuation of therapy has been observed with benzodiazepines such as SOM-PAM. Severe and life-threatening symptoms have been reported. (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse; 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

Concomitant use of SOM-PAM and opioids may result in profound sedation, respiratory depression, coma and death.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation. (see 7 WARNING AND PRECAUTIONS, General, Concomitant use with opioids)

9.2 Drug Interactions Overview

SOM-PAM 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.

9.3 Drug-Behavioural Interactions

SOM-PAM may produce additive CNS depressant effects when co-administered with alcohol.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Sedative antihistamines	T	Co-administration with benzodiazepines may produce additive CNS depressant effects	Caution is warranted and therapeutic concentration monitoring is recommended
Anticonvulsants	T		
Psychotropic medications	T		
Cimetidine	T	Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines	
Erythromycin	T		
Opioids or narcotic analgesics	T	Due to additive CNS depressant effect, the concomitant use of benzodiazepines, including SOM-PAM, and opioids increases the risk of profound sedation, respiratory depression, coma, and death.	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations of concomitant use of benzodiazepines and opioids to the minimum required. Follow patients closely for respiratory depression and sedation.

Legend: T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

10.2 Pharmacodynamics

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 7 WARNINGS AND PRECAUTIONS, Psychiatric).

Flurazepam is a benzodiazepine with a long half-life.

In animals, flurazepam hydrochloride has been shown 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. Metabolic 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.

10.3 Pharmacokinetics

Absorption

Following oral administration of 15 mg flurazepam hydrochloride to male and female volunteers, measurable concentrations for the parent compound were not detectable.

Metabolism
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 final active and principal metabolite, desalkyl flurazepam (DAFLZ), appears in the systemic circulation moreslowly, with a mean C_{max} of 14 ng/mL attained an average of 10.6 hours after dosing.

Elimination
The mean elimination half-lives for hydroxyethyl flurazepam and flurazepam aldehyde were less than 2.5 hours.

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.

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.

Special Populations and Conditions
- **Geriatrics:** Following 15 days of 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). 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.

11 STORAGE, STABILITY AND DISPOSAL

Keep in a tightly closed, light-resistant container. Store at 15-30ºC.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

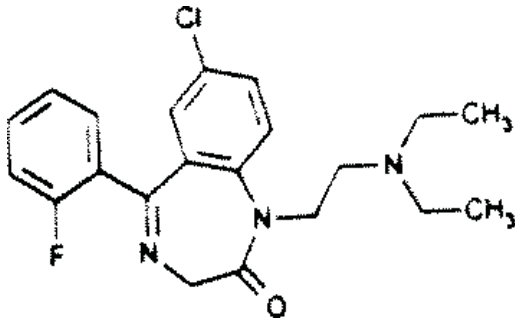
Drug Substance

Proper Name: Flurazepam Hydrochloride

Chemical Name: 7-chloro-1-[2(diethylamino)ethyl]-5-(0-fluorophenyl)-1, 3-dihydro-2H-1, 4-benzodiazepin-2-one-dihydrochloride

Molecular formula and molecular mass: $C_{21}H_{23}ClFN_3O \cdot 2HCl$ and 460.81

Structural Formula:



Physiochemical Properties: Flurazepam hydrochloride is an off-white to yellow, crystalline powder. It is odourless, or has a slight odour, and its solutions are acid to litmus. Melts at about 212°C with decomposition. Freely soluble in water and in alcohol; slightly soluble in isopropyl alcohol and in chloroform.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: The oral LD_{50} values of flurazepam hydrochloride have been reported to be 870 mg/kg in mice, 1232 mg/kg in ratsand 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/dayin the dog.

Reproductive and Developmental Toxicology: A two-cycle reproduction study in rats has been reported 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 reproduction 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 oradverse effects in the perinatal and postnatal study. In another reproduction 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.

Two teratogenic studies of flurazepam hydrochloride in rabbits have been reported. In one study, 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 foetuses. 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 foetuses, foetal body weight and litter size.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

SOM-PAM
Flurazepam hydrochloride capsules

Read this carefully before you start taking **SOM-PAM** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SOM-PAM**.

Serious Warnings and Precautions

Addiction, Abuse and Misuse: Even if you take SOM-PAM exactly as you were told to, you are at risk for abuse, misuse, addiction, physical dependence and withdrawal. Abuse and misuse can result in overdose or death, especially if you take SOM-PAM with:

- **opioids**
- **alcohol or**
- **illicit drugs**

Your healthcare professional should:

- **talk to you about the risks of treatment with SOM-PAM as well as other treatment (including non-drug) options**
- **assess your risk for these behaviours before prescribing SOM-PAM**
- **monitor you while you are taking SOM-PAM for the signs and symptoms of misuse and abuse. If you feel like you are craving SOM-PAM, or not using it as directed, talk to your healthcare professional right away.**

Store SOM-PAM in a secure place to avoid theft or misuse.

Withdrawal: If you suddenly stop taking SOM-PAM, lower your dose too fast, or switch to another medication, you can experience severe or life-threatening withdrawal symptoms (see Other warnings you should know about)

- **Always contact your healthcare professional before stopping, or lowering your dose of SOM-PAM or changing your medicine.**

SOM-PAM with Opioids: Taking SOM-PAM with opioid medicines can cause:

- **severe drowsiness**
- **decreased awareness**
- **breathing problems**
- **coma**
- **death**

What is SOM-PAM used for?

SOM-PAM is used in adults to treat short-term insomnia. This is a sleep disorder that makes it hard to fall asleep, hard to stay asleep, or causes you to wake up too early. SOM-PAM should only be used when

the effects of insomnia affect your daytime activities. Treatment with SOM-PAM is short-term and should usually not exceed 7 to 10 days in a row.

If you are 65 years or older, talk to your healthcare professional before starting SOM-PAM. SOM-PAM may not be an effective treatment for you and you may be more sensitive to experiencing side effects.

How does SOM-PAM work?

SOM-PAM belongs to a group of medicines called benzodiazepine sleeping pills. It works to decrease the time required to fall asleep and the number of times you wake up during sleep.

What are the ingredients in SOM-PAM?

Medicinal ingredients: Flurazepam hydrochloride
Non-medicinal ingredients: cornstarch, gelatin, and lactose.

SOM-PAM comes in the following dosage forms:

Capsules: 15 mg and 30 mg.

Do not use SOM-PAM if:

- you are allergic to flurazepam or other benzodiazepines, or to any of the ingredients in SOM-PAM (see "**What are the ingredients in SOM-PAM?"**)
- you have severe lung or breathing problems (e.g. sleep apnea)
- you have myasthenia gravis (a condition characterized by weakness of your muscles).
- you have a severe liver condition.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SOM-PAM. Talk about any health conditions or problems you may have, including if you:

- have a lung disease or breathing problems.
- have a liver or kidney condition.
- have signs of depression, or a history of depression.
- have a history of suicide thoughts or attempts.
- have a history of violent behaviours.
- have a history of any personality disorder.
- have had unexpected reactions to alcohol or sedative medications in the past (e.g. such as irritability, aggression, hallucinations, etc.).
- are pregnant or planning to become pregnant, SOM-PAM is not recommended for use during pregnancy.
- are breastfeeding or planning to breast-feed, SOM-PAM is not recommended for use during breastfeeding.
- drink or plan to drink alcohol. Do not drink alcohol while you take SOM-PAM.
- are taking other medications, including over-the-counter medications, opioids, sedatives, medications that affect your central nervous system (CNS depressants).
- are taking illicit drugs.
- have lactose intolerance, as SOM-PAM contains lactose.

- are 65 years of age or older.
- have a condition that causes weakness or frailty.
- have impaired thinking, confusion or any other type of brain damage.
- have ever had a problem with:
    - substance use, including prescribed or illegal drugs, or
    - alcohol
- have ever had seizures or convulsions (violent uncontrollable shaking of the body with or without loss of consciousness)

Other warnings you should know about:

Sleep-Related Behaviours: Treatment with SOM-PAM can cause potentially dangerous sleeping-related behaviours such as getting out of bed while not fully awake after taking SOM-PAM and doing activities that you do not know you are doing. If this happens, you may not remember doing these activities when you wake up. These unusual behaviours are more likely to occur when SOM-PAM is taken with alcohol or other drugs that can make you sleepy (e.g. medications used to treat depression or anxiety). If you drink alcohol, do not take SOM-PAM. The activities you may do in these situations can put you and people around you in danger. This can include driving a car ("sleep-driving"), leaving the house, making and eating food, talking on the phone.

You and people close to you should watch for unusual types of behaviour when you are asleep. If you find out that you have done any such activities for which you have no memory, you should call your healthcare professional immediately.

Memory Problems: In rare cases, SOM-PAM can cause a type of memory loss known as amnesia. This is characterized by having difficulty recalling events that recently occurred, usually several hours after taking the medication. If you intend to take SOM-PAM before sleeping, this is usually not a problem. However, if you take SOM-PAM to induce sleep while travelling, such as during an airplane flight, you may wake up to memory lapse caused by the drug. This has been called "traveller's amnesia" and can be a problem. DO NOT TAKE SOM-PAM when a full night's sleep is not possible before you need to be active and functional (e.g., an overnight flight of less than 8 hours). Your body needs time to eliminate the medication from your system.

Withdrawal: If you suddenly stop your treatment, lower your dose too fast, or switch to another medication, you can experience withdrawal symptoms that can range from mild symptoms to severe or life threatening. Some of your withdrawal symptoms can last for months after you stop SOM-PAM.

Your risk of going through withdrawal is higher if you are taking SOM-PAM for a long time or at high doses. However, symptoms can still occur if you are taking SOM-PAM as directed for a short period of time or slowly reducing the dose.

The symptoms of withdrawal often resemble the condition that you are being treated for. After stopping your treatment, it may be hard to tell if you are experiencing withdrawal or a return of your condition (relapse).

Tell your healthcare professional **right away** if you experience any symptoms of withdrawal after changing or stopping your treatment.

Severe symptoms of withdrawal include:

- feeling like you cannot move or respond (catatonia)
- severe confusion, shivering, irregular heartrate and excessive sweating (delirium tremens)
- feeling depressed
- feeling disconnected from reality (dissociation)
- seeing or hearing things that are not there (hallucinations)
- overactive behavior and thoughts (mania)
- believing in things that are not true (psychosis)
- convulsions (seizures), including some that do not stop
- thoughts or actions of suicide

For other symptoms of withdrawal, see the **Serious side effects and what to do about them** table (below).

To reduce your chances of going through withdrawal:

- always contact your healthcare professional before stopping or reducing your dose of SOM-PAM or changing medications
- always follow your healthcare professional's instructions on how to reduce your dose carefully and safely
- tell your healthcare professional **right away** if you experience any unusual symptoms after changing or stopping your treatment

SOM-PAM with Opioids: Taking SOM-PAM with opioid medicines can cause severe drowsiness and breathing problems.

Tell your healthcare professional if you:

- are taking opioid medicines
- are prescribed an opioid medicine after you start taking SOM-PAM

Do NOT drive or operate heavy machinery or do tasks that require special attention until you know how taking an opioid medicine and SOM-PAM affects you.

Falls and Fractures: there have been reports of falls and fractures in people who take benzodiazepines such as SOM-PAM. You have a greater risk of falling, which can cause fractures or other fall related-injuries if you:

- take other sedatives
- consume alcohol
- are elderly or
- have a condition that causes weakness or frailty

Mental and Behavioural Changes: A variety of abnormal thinking and behaviour changes may occur when you take benzodiazepine sleeping pills, including SOM-PAM. Some of these changes include aggressiveness and extroversion, which seem out of character, confusion, strange behaviour, anxiety, restlessness, hallucinations, feeling like you are not yourself, worsening insomnia or depression, including suicidal thinking. It is hard to determine if these symptoms are caused by the medication, by

an illness that was present before the medication was used, or are natural. If you develop any unusual thoughts or behaviour while using SOM-PAM, tell your healthcare professional right away.

Worsening of Side Effects: DO NOT CONSUME ALCOHOL WHILE TAKING SOM-PAM.
Your symptoms of insomnia may worsen with SOM-PAM, especially if you are taking other similar medications.

Severe Allergic Reaction: In rare cases, SOM-PAM has caused severe allergic reactions including anaphylaxis, which can be life-threatening. The symptoms of a severe allergic reaction include angioedema of the tongue or throat (swelling of tissues under the skin), shortness of breath, throat closing, nausea or vomiting. Angioedema can lead to a blocked airway and can be life-threatening. If you develop angioedema or you notice signs of a severe allergic reaction after taking SOM-PAM, you should stop taking SOM-PAM and tell your healthcare professional right away.

Elderly: If you are 65 years of age or older and take benzodiazepines including SOM-PAM, you are at a higher risk of falls and fractures.

Pregnancy: Benzodiazepines, such as SOM-PAM, may cause a risk to your unborn baby (e.g., birth defects) if you are pregnant. This typically occurs more often during the first trimester or last weeks of pregnancy. If you are able to get pregnant, want to be or think you are pregnant, there are specific risks you should discuss with your healthcare professional.

Monitoring and Testing: If you are prescribed SOM-PAM, your healthcare professional may conduct blood tests to assess your health as well as your liver and kidney function. Your healthcare professional will interpret your results and may adjust or stop your dose of SOM-PAM.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SOM-PAM:

Serious Drug Interactions
Taking SOM-PAM and opioids may cause: • **severe drowsiness** • **trouble breathing** • **coma** • **death**

- alcohol, do not take SOM-PAM if you drink alcohol.
- sedative antihistamines that are used to treat allergies but make you drowsy or sleepy after you take them.
- anticonvulsants used to prevent or treat seizures.
- antidepressants used to treat depression.
- medicines used to alter your mental state or mood.
- other benzodiazepines typically used to treat anxiety, insomnia, and seizures (e.g., oxazepam).

- medicines that inhibit certain liver enzymes, particularly cytochrome P450 (e.g., cimetidine and erythromycin). If you are unsure, talk to your healthcare professional.

DO NOT USE SOM-PAM with other medications without first discussing this with your healthcare professional.

How to take SOM-PAM:

- Take SOM-PAM exactly as your healthcare professional has told you to.
- Take SOM-PAM just before bedtime. Do not take SOM-PAM if a full night's sleep is not possible before you need to become active and functional again.
- Do **NOT** consume any alcohol while taking SOM-PAM.
- Do **NOT** suddenly stop taking SOM-PAM or you may experience withdrawal symptoms.

Usual dose:

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

Elderly and/or Debilitated Patients: 15 mg just before bedtime.

Your healthcare professional will slowly decrease your dose and will tell you when to stop taking the medicine. Always follow your healthcare professional's instructions on how to lower your dose carefully and safely to avoid experiencing withdrawal symptoms.

Overdose:

Symptoms of an overdose with SOM-PAM include drowsiness, sleepiness, confusion and coma.

If you think you, or a person you are caring for, have taken too much SOM-PAM, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

If you forget or miss a dose of SOM-PAM, do not take the missed dose. Instead, take the next scheduled dose at the usual time. Do not try to make up for the missed dose by taking a double dose.

What are possible side effects from using SOM-PAM?

These are not all the possible side effects you may have when taking SOM-PAM. If you experience any side effects not listed here, tell your healthcare professional.

Side effects of SOM-PAM may include:

Very common (may affect more than 1 in 10 people):

- drowsiness,
- dizziness,
- light-headedness,
- difficulty with coordination.

Common (may affect up to 1 in 10 people):

- lethargy,
- disorientation (inability to know correct time, place or person),
- apprehension (worry about something or about what might happen),
- nervousness,
- heartburn,
- upset stomach,
- nausea,
- constipation,
- stomach pain,
- weakness,
- chest pains,
- urinary and genital problems,
- palpitations (heartbeats that become more noticeable).

Rare (may affect up to 1 in 10,000 people):

- flushing (redness of skin),
- blurred vision,
- fainting,
- itchiness,
- skin rash,
- dry mouth,
- bitter taste,
- excessive salivation
- anorexia (a weight disorder characterized by low weight).

Unknown:

- falls and fractures

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Severe sedation: reduced awareness, or reduced response to stimulation		✓	
RARE			
Amnesia (a type of memory loss): difficulty recalling events that recently happened		✓	
Depression (sad mood that won't go away): difficulty sleeping, sleeping too much, changes in		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
appetite or weight, feelings of worthlessness, guilt, regret, helplessness, hopelessness, withdrawal from social situations, family, gatherings and activities with friends, thoughts of death or suicide, or reduced libido (sex drive)			
Low white blood cells (e.g., leukopenia or granulocytopenia): infections, fatigue, fever, aches, pains, or flu-like symptoms		✓	
Mental and behavioural changes: difficulty focusing, euphoria, excitement, nightmares, numbed emotions, decreased alertness, agitation, hyperactivity, worsened insomnia, aggressiveness, rages, psychoses, violent behaviour, or inappropriate behaviour		✓	
Severe allergic reactions: swelling of the tongue or throat, trouble breathing, sudden wheeziness, chest pain or tightness, shortness of breath, throat closing, nausea or vomiting			✓
VERY RARE			
Somnambulism (sleepwalking): getting out of bed while not fully awake and do activities you do not remember the day after, or sleep driving		✓	
UNKNOWN FREQUENCY			
Overdose: extreme sleepiness, confusion, slurred speech, slow reflexes, slow shallow breathing, coma, loss of balance and coordination, uncontrolled rolling of the eyes, and low blood pressure.			✓
Respiratory Depression: slow, shallow or weak breathing.			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Withdrawal: **Severe symptoms include:** **Catatonia:** feeling like you cannot move or respond **Delirium Tremens:** severe confusion, shivering, irregular heartrate and excessive sweating **Feeling depressed** **Dissociation:** feeling disconnected from reality **Hallucinations:** seeing or hearing things that are not there **Mania:** overactive behaviour and thoughts **Psychosis:** believing in things that are not true **Convulsions:** (seizures – including some that do not stop): loss of consciousness with uncontrollable shaking **Thoughts or actions of suicide** **Other symptoms include:** Stomach cramps; trouble remembering or concentrating; diarrhea; feeling uneasy or restless; severe anxiety or panic-attacks; headache; sensitivity to light, noise or physical contact; shaking; vomiting; trouble sleeping; feeling irritable; muscle pain or stiffness; a burning or prickling feeling in the hands, arms, legs or feet; sweating.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 15-30°C in tightly closed, light resistant container.

Keep out of reach and sight of children.

If you want more information about SOM-PAM:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/eu/health-canada/services/drugs-health/drug-products/drug-product-database-html or by contacting the manufacturer at: info@biomed-pharma.ca , or by calling 1-888-731-6703.

This leaflet was prepared by Biomed Pharma.

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