PRODUCT MONOGRAPH

T/C Bio-FLURAZEPAM

(Flurazepam Hydrochloride Capsules, USP)

15 and 30 mg

Hypnotic

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THERAPEUTIC CLASSIFICATION

Hypnotic

ACTION AND CLINICAL PHARMACOLOGY

Flurazepam hydrochloride is a benzodiazepine with hypnotic properties which decreases sleep latency and the number of awakenings with a consequent increase in sleep time.

In animal studies flurazepam, hydrochloride reduced the pressor response to electrical stimulation of the hypothalamus and increased the arousal threshold to stimulation of the amygdala and hypothalamus; however, the exact site and mode of action are unknown.

Although flurazepam itself is not detectable in the circulation for more than a few hours, its main active metabolite, N-1-desalkylflurazepam has a half-life of up to 100 hours or more. With multiple dosing, steady state levels of this metabolite are reached after 7 to 10 days or more, and, therefore, a cumulative effect of the drug can be expected.

INDICATIONS AND CLINICAL ACTIONS

Bio-FLURAZEPAM (flurazepam hydrochloride) is a hypnotic agent useful in the short-term management of insomnia. The safety and efficacy of long-term use have not been established.

CONTRAINDICATIONS

Flurazepam hydrochloride is contraindicated in patients with myasthenia gravis, a history of glaucoma, and with known hypersensitivity to the drug. Because of lack of sufficient clinical experience, it is also contraindicated in children under fifteen years of age.

WARNINGS

Since Bio-FLURAZEPAM (flurazepam hydrochloride) is an effective hypnotic, patients should be cautioned against engaging in activities requiring complete mental alertness, such as operating machinery or driving a motor vehicle shortly after ingesting the drug.

Potentiation of drug effects: Careful consideration should be given to Bio-FLURAZEPAM being administered in combination with other drugs having known hypnotic or CNS depressant effects, because the pharmacological action of these agents might potentiate the action of Bio-FLURAZEPAM. Since Bio-FLURAZEPAM has a central nervous system depressant effect, patients should be advised against the simultaneous ingestion of alcohol and other central nervous system depressant drugs during Bio-FLURAZEPAM therapy.

Physical and Psychological Dependence: As with other benzodiazepines, caution should be exercised in administering Bio-FLURAZEPAM to individuals known to be addiction-prone or those whose histories suggest they may increase the dosage on their own initiative. Prescriptions should not be repeated without adequate medical supervision.

Use in Pregnancly: The safety of the use of Bio-FLURAZEPAM in pregnancy has not been established. Therefore, Bio-FLURAZEPAM is not recommended for use during pregnancy or lactation. Several studies have suggested an increased risk of wcongenital malformations associated with the use of the benzodiazepines chlordiazepoxide and diazepam, and with meprobamate, during the first trimester of pregnancy. Since flurazepam is also a benzodiazepine derivative, its administration is rarely justified in women of child-bearing potential.

If the drug is prescribed to a woman of child-bearing potential, she should be warned to consult her

physician regarding the discontinuation of the drug if she intends to become or suspects that she is pregnant.

Use in the Elderly: In elderly and/or debilitated patients, it is recommended that treatment with Bio-FLURAZEPAM be initiated at the lowest possible dose and increased gradually, if necessary, to decrease the possibility of development of oversedation, dizziness or ataxia.

PRECAUTIONS

Bio-FLURAZEPAM (flurazepam hydrochloride) should be used with caution in patients.with symptoms of depression or evidence of latent depression, particularly when suicidal tendencies may be present and protective measures may be necessary.

Bio-FLURAZEPAM should be given with caution to patients with impaired renal or hepatic function. When the drug is used repeatedly, periodic blood counts and liver and kidney function tests should be performed.

Since anterograde amnesia has been reported with other benzo- diazepines, the possibility of this occurring with SOM-PAM should be borne in mind.

ADVERSE REACTIONS

Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling, particularly in elderly or debilitated patients, are the most common adverse reactions reported with flurazepam hydrochloride (See WARNINGS). Severe sedation, lethargy, disorientation and coma (probably indicative of drug intolerance or overdosage) have been reported.

Headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, gastrointestinal pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and genitourinary complaints have also been attributed to flurazepam hydrochloride.

There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focussing, blurred vision, burning eyes, faintness, hypotension, dyspnea, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion,
restlessness, hallucinations and elevated SGOT, SGPT, total and direct bilirubins, and-alkaline phosphatase. Paradoxical reactions, e.g. excitement, stimulation and hyperactivity, also have been reported in rare instances.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

Treatment: 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 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.

DOSAGE AND ADMINISTRATION

Dosage should be individualized to obtain the desired hypnotic effect while avoiding oversedation

and impaired performance the following day.

The usual adult dose is 30 mg before retiring, although some patients may require only 15 mg. In elderly and/or debilitated patients, it is recommended that therapy be initiated with 15 mg or less.

AVAILABILITY OF DOSAGE FORMS

Bio-FLURAZEPAM (flurazepam hydrochloride) is supplied as: Branded hard gelatin capsules, size #2, with orange opaque body and grey opaque cap containing 15 mg flurazepam hydrochloride;

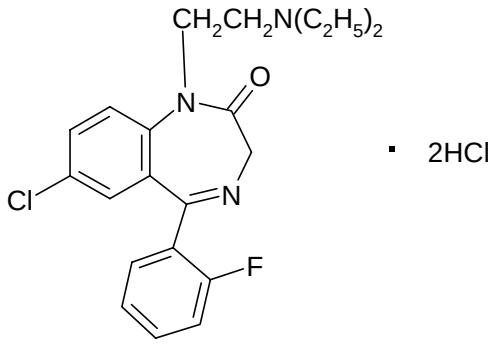
Branded hard gelatin capsules, size #2, with scarlet opaque body and grey opaque cap containing 30 mg flurazepam hydrochloride.

In bottles of 100 and 500.

Bio-FLURAZEPAM is a Schedule F drug and cannot be obtained without a written order from a licenced practitioner.

PHARMACOLOGY

Flurazepam hydrochloride is chemically 7-chloro-l-[2-(diethylamino)ethyl]-5-(o-fluorophenyl) -1,3-dihydro-2H-1, 4-benzodiazepin-2-one dihydrochloride and has the following structural formula:



· 2HCl

In animals flurazepam hydrochloride has been shown to produce sedative, anticonvulsant and muscle relaxant effects, which resemble those of other benzodiazepines. Some cardiovascular depressant effects were also observed, but were largely attributed to the central nervous system depressant effects of high doses.

Metabolic studies in rats with C^{14} -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

Acute and chronic toxicity

The oral LD_{50} values of flurazepam hydrochloride have been reported to be 870 mg/kg in mice, 1232 mg/kg in rats and 568 mg/kg in rabbits.

Administration of flurazepam hydrochloride caused a sudden increase in activity followed by a rapidly developing ataxia and a subsequent decrease in activity. Respiratory depression, loss of grip strength and weak muscle tone were observed. Placing and righting reflexes were greatly reduced or completely absent. At high doses, twitches in rats and clonic convulsions in mice were observed.

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.

Reproductive studies

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 or adverse 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 fetuses. In the second study, the dose of flurazepam hydro- chloride 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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