

# DALMANE<sup>®</sup> C<sup>IV</sup>

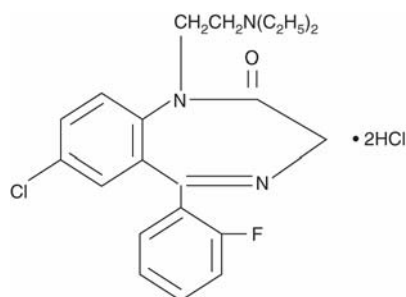
(flurazepam hydrochloride)

## CAPSULES

For Relief of Insomnia

**DESCRIPTION:** Dalmane is available as capsules containing 15 mg or 30 mg flurazepam hydrochloride. Each 15-mg capsule also contains cornstarch, lactose, magnesium stearate and talc; gelatin capsule shells contain the following dye systems: D&C Red No. 28, FD&C Red No. 40, FD&C Yellow No. 6 and D&C Yellow No. 10. Each 30-mg capsule also contains cornstarch, lactose and magnesium stearate; gelatin capsule shells contain the following dye systems: FD&C Blue No. 1, FD&C Yellow No. 6, D&C Yellow No. 10 and either FD&C Red No. 3 or FD&C Red No. 40.

Flurazepam hydrochloride is chemically 7-chloro-1-[2-(diethylamino)ethyl]-5-(*o*-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one dihydrochloride. It is a pale yellow, crystalline compound, freely soluble in USP alcohol and very soluble in water. It has a molecular weight of 460.826 and the following structural formula:



**CLINICAL PHARMACOLOGY:** Flurazepam hydrochloride is rapidly absorbed from the GI tract. Flurazepam is rapidly metabolized and is excreted primarily in the urine. Following a single oral dose, peak flurazepam plasma concentrations ranging from 0.5 to 4.0 ng/mL occur at 30 to 60 minutes post-dosing. The harmonic mean apparent half-life of flurazepam is 2.3 hours. The blood level profile of flurazepam and its major metabolites was determined in man following the oral administration of 30 mg daily for 2 weeks. The N<sub>1</sub>-hydroxyethyl-flurazepam was measurable only during the early hours after a 30-mg dose and was not detectable after 24 hours. The major metabolite in blood was N<sub>1</sub>-desalkyl-flurazepam, which reached steady-state (plateau) levels after 7 to 10 days of dosing, at levels approximately 5- to 6-fold greater than the 24-hour levels observed on Day 1. The half-life of elimination of N<sub>1</sub>-desalkyl-flurazepam ranged from 47 to 100 hours. The major urinary metabolite is conjugated N<sub>1</sub>-hydroxyethyl-flurazepam which accounts for 22% to 55% of the dose. Less than 1% of the dose is excreted in the urine as N<sub>1</sub>-desalkyl-flurazepam.

This pharmacokinetic profile may be responsible for the clinical observation that flurazepam is increasingly effective on the second or third night of consecutive use and

44 that for 1 or 2 nights after the drug is discontinued both sleep latency and total wake time  
45 may still be decreased.

46

47 *Geriatric Pharmacokinetics:* The single dose pharmacokinetics of flurazepam were  
48 studied in 12 healthy geriatric subjects (aged 61 to 85 years). The mean elimination half-  
49 life of desalkyl-flurazepam was longer in elderly male subjects (160 hours) compared  
50 with younger male subjects (74 hours), while mean elimination half-life was similar in  
51 geriatric female subjects (120 hours) and younger female subjects (90 hours). After  
52 multiple dosing, mean steady-state plasma levels of desalkyl-flurazepam were higher in  
53 elderly male subjects (81 ng/ml) compared with younger male subjects (53 ng/ml), while  
54 values were similar between elderly female subjects (85 ng/ml) and younger female  
55 subjects (86 ng/ml). The mean washout half-life of desalkyl-flurazepam was longer in  
56 elderly male and female subjects (126 and 158 hours, respectively) compared with  
57 younger male and female subjects (111 and 113 hours, respectively).<sup>1</sup>

58

59 **INDICATIONS AND USAGE:** Dalmane is a hypnotic agent useful for the treatment of  
60 insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings,  
61 and/or early morning awakening. Dalmane can be used effectively in patients with  
62 recurring insomnia or poor sleeping habits, and in acute or chronic medical situations  
63 requiring restful sleep. Sleep laboratory studies have objectively determined that  
64 Dalmane is effective for at least 28 consecutive nights of drug administration. Since  
65 insomnia is often transient and intermittent, short-term use is usually sufficient.  
66 Prolonged use of hypnotics is usually not indicated and should only be undertaken  
67 concomitantly with appropriate evaluation of the patient.

68

69 **CONTRAINDICATIONS:** Dalmane is contraindicated in patients with known  
70 hypersensitivity to the drug.

71

72 *Usage in Pregnancy:* Benzodiazepines may cause fetal damage when administered  
73 during pregnancy. An increased risk of congenital malformations associated with the use  
74 of diazepam and chlordiazepoxide during the first trimester of pregnancy has been  
75 suggested in several studies.

76

77 Dalmane is contraindicated in pregnant women. Symptoms of neonatal depression have  
78 been reported; a neonate whose mother received 30 mg of Dalmane nightly for insomnia  
79 during the 10 days prior to delivery appeared hypotonic and inactive during the first 4  
80 days of life. Serum levels of N<sub>1</sub>-desalkyl-flurazepam in the infant indicated  
81 transplacental circulation and implicate this long-acting metabolite in this case. If there is  
82 a likelihood of the patient becoming pregnant while receiving flurazepam, she should be  
83 warned of the potential risks to the fetus. Patients should be instructed to discontinue the  
84 drug prior to becoming pregnant. The possibility that a woman of childbearing potential  
85 may be pregnant at the time of institution of therapy should be considered.

86

87 **WARNINGS:** Because sleep disturbances may be the presenting manifestation of a  
88 physical and/or psychiatric disorder, symptomatic treatment of insomnia should be  
89 initiated only after a careful evaluation of the patient. **The failure of insomnia to remit**

90 **after 7 to 10 days of treatment may indicate the presents of a primary psychiatric**  
91 **and/or medical illness that should be evaluated.** Worsening of insomnia or the  
92 emergence of new thinking or behavior abnormalities may be the consequence of an  
93 unrecognized psychiatric or physical disorder. Such findings have emerged during the  
94 course of treatment with sedative-hypnotic drugs. Because some of the important  
95 adverse effects of sedative-hypnotics appear to be dose related (see Precautions and  
96 Dosage and Administration), it is important to use the smallest possible effective dose,  
97 especially in the elderly.

98  
99 Complex behaviors such as “sleep-driving” (i.e., driving while not fully awake after  
100 ingestion of a sedative-hypnotic, with amnesia for the event) have been reported. These  
101 events can occur in sedative-hypnotic-naïve as well as in sedative-hypnotic-experienced  
102 persons. Although behaviors such as sleep-driving may occur with sedative-hypnotics  
103 alone at therapeutic doses, the use of alcohol and other CNS depressants with sedative-  
104 hypnotics appears to increase the risk of such behaviors, as does the use of sedative-  
105 hypnotics at doses exceeding the maximum recommended dose. Due to the risk to the  
106 patients and the community, discontinuation of sedative-hypnotics should be strongly  
107 considered for patients who report a “sleep-driving” episode.

108  
109 Other complex behaviors (e.g., preparing and eating food, making phone calls, or having  
110 sex) have been reported in patients who are not fully awake after taking a sedative-  
111 hypnotic. As with sleep-driving, patients usually do not remember these events.

### 112 **Severe anaphylactic and anaphylactoid reactions**

113  
114  
115 Rare cases of angioedema involving the tongue, glottis or larynx have been reported in  
116 patients after taking the first or subsequent doses of sedative-hypnotics, including  
117 Dalmane. Some patients have had additional symptoms such as dyspnea, throat closing,  
118 or nausea and vomiting that suggest anaphylaxis. Some patients have required medical  
119 therapy in the emergency department. If angioedema involves the tongue, glottis or  
120 larynx, airway obstruction may occur and be fatal. Patients who develop angioedema  
121 after treatment with Dalmane should not be rechallenged with the drug.

122  
123 Patients receiving Dalmane should be cautioned about possible combined effects with  
124 alcohol and other CNS depressants. Also, caution patients that an additive effect may  
125 occur if alcoholic beverages are consumed during the day following the use of Dalmane  
126 for nighttime sedation. The potential for this interaction continues for several days  
127 following discontinuance of flurazepam, until serum levels of psychoactive metabolites  
128 have declined.

129  
130 Patients should also be cautioned about engaging in hazardous occupations requiring  
131 complete mental alertness such as operating machinery or driving a motor vehicle after  
132 ingesting the drug, including potential impairment of the performance of such activities  
133 which may occur the day following ingestion of Dalmane.

135 *Usage in Children:* Clinical investigations of Dalmane have not been carried out in  
136 children. Therefore, the drug is not currently recommended for use in persons under 15  
137 years of age.

138

139 Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of  
140 benzodiazepines. (See DRUG ABUSE AND DEPENDENCE Section.)

141

142 **PRECAUTIONS:** Since the risk of the development of oversedation, dizziness,  
143 confusion and/or ataxia increases substantially with larger doses in elderly and debilitated  
144 patients, it is recommended that in such patients the dosage be limited to 15 mg. If  
145 Dalmane is to be combined with other drugs having known hypnotic properties or CNS-  
146 depressant effects, due consideration should be given to potential additive effects.

147

148 The usual precautions are indicated for severely depressed patients or those in whom  
149 there is any evidence of latent depression; particularly the recognition that suicidal  
150 tendencies may be present and protective measures may be necessary.

151

152 The usual precautions should be observed in patients with impaired renal or hepatic  
153 function and chronic pulmonary insufficiency.

154

155 *Information for Patients:*

156

157 **“Sleep-Driving” and other complex behavior:**

158

159 There have been reports of people getting out of bed after taking a sedative-hypnotic and  
160 driving their cars while not fully awake, often with no memory of the event. If a patient  
161 experiences such an episode, it should be reported to his or her doctor immediately, since  
162 “sleep-driving” can be dangerous. This behavior is more likely to occur when sedative-  
163 hypnotics are taken with alcohol or other central nervous system depressants (see  
164 WARNINGS). Other complex behaviors (e.g., preparing and eating food, making phone  
165 calls, or having sex) have been reported in patients who are not fully awake after taking a  
166 sedative-hypnotic. As with sleep-driving, patients usually do not remember these events.

167

168 To assure the safe and effective use of benzodiazepines, patients should be informed that  
169 since benzodiazepines may produce psychological and physical dependence, it is  
170 advisable that they consult with their physician before either increasing the dose or  
171 abruptly discontinuing this drug.

172

173 *Geriatric Use:* Since the risk of the development of oversedation, dizziness, confusion  
174 and/or ataxia increases substantially with larger doses in elderly and debilitated patients,  
175 it is recommended that in such patients the dosage be limited to 15 mg. Staggering and  
176 falling have also been reported, particularly in geriatric patients.

177

178 Following single-dose administration of flurazepam, the elimination half-life for  
179 desalkyl-flurazepam was longer in elderly male subjects compared with younger male  
180 subjects, while values between elderly and young females were not significantly

181 different. After multiple dosing, elimination half-life of desalkyl-flurazepam was longer  
182 in all elderly subjects compared with younger subjects, and mean steady-state serum  
183 concentrations were higher only in elderly male subjects relative to younger subjects (see  
184 CLINICAL PHARMACOLOGY: *Geriatric Pharmacokinetics*).

185

186 **ADVERSE REACTIONS:** Dizziness, drowsiness, light-headedness, staggering, ataxia  
187 and falling have occurred, particularly in elderly or debilitated persons. Severe sedation,  
188 lethargy, disorientation and coma, probably indicative of drug intolerance or overdose,  
189 have been reported.

190

191 Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea,  
192 constipation, gastrointestinal pain, nervousness, talkativeness, apprehension, irritability,  
193 weakness, palpitations, chest pains, body and joint pains and genitourinary complaints.  
194 There have also been rare occurrences of leukopenia, granulocytopenia, sweating,  
195 flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension,  
196 shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation,  
197 anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations,  
198 and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase.  
199 Paradoxical reactions, eg, excitement, stimulation and hyperactivity, have also been  
200 reported in rare instances.

201

202 **DRUG ABUSE AND DEPENDENCE:** Abuse and addiction are separate and distinct  
203 from physical dependence and tolerance. Abuse is characterized by misuse of the drug  
204 for non-medical purposes, often in combination with other psychoactive substances.  
205 Physical dependence is a state of adaptation that is manifested by a specific withdrawal  
206 syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing  
207 blood level of the drug and/or administration of an antagonist. Tolerance is a state of  
208 adaptation in which exposure to a drug induces changes that result in a diminution of one  
209 or more of the drug's effects over time. Tolerance may occur to both the desired and  
210 undesired effects of the drug and may develop at different rates for different effects.

211

212 Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and  
213 environmental factors influencing its development and manifestations. It is characterized  
214 by behaviors that include one or more of the following: impaired control over drug use,  
215 compulsive use, continued use despite harm, and craving. Drug addiction is a treatable  
216 disease, utilizing a multidisciplinary approach, but relapse is common.

217

218 Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol  
219 (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating), have  
220 occurred following abrupt discontinuance of benzodiazepines. The more severe  
221 withdrawal symptoms have usually been limited to those patients who had received  
222 excessive doses over an extended period of time. Generally milder withdrawal symptoms  
223 (eg, dysphoria and insomnia) have been reported following abrupt discontinuance of  
224 benzodiazepines taken continuously at therapeutic levels for several months.  
225 Consequently, after extended therapy, abrupt discontinuation should generally be avoided  
226 and a gradual dosage tapering schedule followed. Addiction-prone individuals (such as

227 drug addicts or alcoholics) should be under careful surveillance when receiving  
228 flurazepam or other psychotropic agents because of the predisposition of such patients to  
229 habituation and dependence.

230

231 **OVERDOSAGE:** Manifestations of Dalmane overdose include somnolence,  
232 confusion and coma. Respiration, pulse and blood pressure should be monitored as in all  
233 cases of drug overdose. General supportive measures should be employed, along with  
234 immediate gastric lavage. Intravenous fluids should be administered and an adequate  
235 airway maintained. Hypotension and CNS depression may be combated by judicious use  
236 of appropriate therapeutic agents. The value of dialysis has not been determined. If  
237 excitation occurs in patients following Dalmane overdose, barbiturates should not be  
238 used. As with the management of intentional overdose with any drug, it should be  
239 borne in mind that multiple agents may have been ingested.

240

241 Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete  
242 or partial reversal of the sedative effects of benzodiazepines and may be useful in  
243 situations when an overdose with a benzodiazepine is known or suspected. Prior to the  
244 administration of flumazenil, necessary measures should be instituted to secure airway,  
245 ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a  
246 substitute for, proper management of benzodiazepine overdose. Patients treated with  
247 flumazenil should be monitored for re sedation, respiratory depression and other residual  
248 benzodiazepine effects for an appropriate period after treatment. **The prescriber should**  
249 **be aware of a risk of seizure in association with flumazenil treatment, particularly in**  
250 **long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete  
251 flumazenil package insert, including CONTRAINDICATIONS, WARNINGS and  
252 PRECAUTIONS, should be consulted prior to use.

253

254 **DOSAGE AND ADMINISTRATION:** Dosage should be individualized for maximal  
255 beneficial effects. The usual adult dosage is 30 mg before retiring. In some patients, 15  
256 mg may suffice. In elderly and/or debilitated patients, 15 mg is usually sufficient for a  
257 therapeutic response and it is therefore recommended that therapy be initiated with this  
258 dosage.

259

260 **HOW SUPPLIED:** Dalmane (flurazepam hydrochloride) Capsules are available in the  
261 following presentations:

262

263 15 mg hard gelatin capsules in bottles of 100 (NDC 0187-4051-10), with ICN logo  
264 imprinted on the opaque orange cap and Dalmane<sup>®</sup> 15 imprinted on the opaque ivory  
265 body.

266

267 30 mg hard gelatin capsules in bottles of 100 (NDC 0187-4052-10), with ICN logo  
268 imprinted on the opaque red cap and Dalmane<sup>®</sup> 30 imprinted on the opaque ivory body.

269

270 Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

271 [See USP Controlled Room Temperature]

272

273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288

**REFERENCE:**

1. Greenblatt DJ, Divoll M, Harmatz JS, MacLauglin DS, Shader RI: Kinetics and clinical effects of flurazepam in young and elderly noninsomniacs. *Clin Pharmacol Ther* 30:475-486, 1981.

Valeant Pharmaceuticals North America  
Aliso Viejo, CA 92656



Valeant Pharmaceuticals North America  
Aliso Viejo, 92656 U.S.A.

3405197EX06

Rev. April 2007