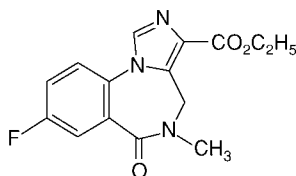


**ROMAZICON®****(flumazenil)****INJECTION****R<sub>x</sub> only****DESCRIPTION**

ROMAZICON® (flumazenil) is a benzodiazepine receptor antagonist. Chemically, flumazenil is ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a](1,4) benzodiazepine-3-carboxylate. Flumazenil has an imidazobenzodiazepine structure, a calculated molecular weight of 303.3, and the following structural formula:



11

Flumazenil is a white to off-white crystalline compound with an octanol:buffer partition coefficient of 14 to 1 at pH 7.4. It is insoluble in water but slightly soluble in acidic aqueous solutions. ROMAZICON is available as a sterile parenteral dosage form for intravenous administration. Each mL contains 0.1 mg of flumazenil compounded with 1.8 mg of methylparaben, 0.2 mg of propylparaben, 0.9% sodium chloride, 0.01% edetate disodium, and 0.01% acetic acid; the pH is adjusted to approximately 4 with hydrochloric acid and/or, if necessary, sodium hydroxide.

**CLINICAL PHARMACOLOGY**

Flumazenil, an imidazobenzodiazepine derivative, antagonizes the actions of benzodiazepines on the central nervous system. Flumazenil competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. Flumazenil is a weak partial agonist in some animal models of activity, but has little or no agonist activity in man.

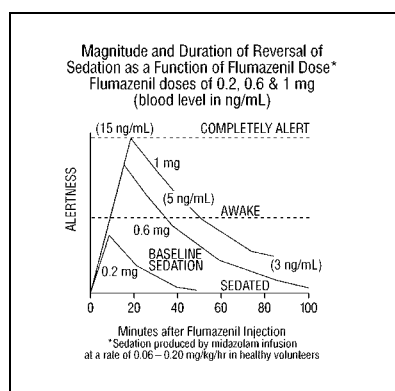
Flumazenil does not antagonize the central nervous system effects of drugs affecting GABA-ergic neurons by means other than the benzodiazepine receptor (including ethanol, barbiturates, or general anesthetics) and does not reverse the effects of opioids.

In animals pretreated with high doses of benzodiazepines over several weeks, ROMAZICON elicited symptoms of benzodiazepine withdrawal, including seizures. A similar effect was seen in adult human subjects.

### 33 Pharmacodynamics

34 Intravenous ROMAZICON has been shown to antagonize sedation,  
35 impairment of recall, psychomotor impairment and ventilatory depression  
36 produced by benzodiazepines in healthy human volunteers.

37 The duration and degree of reversal of sedative benzodiazepine effects are  
38 related to the dose and plasma concentrations of flumazenil as shown in the  
39 following data from a study in normal volunteers.



40

41 Generally, doses of approximately 0.1 mg to 0.2 mg (corresponding to peak  
42 plasma levels of 3 to 6 ng/mL) produce partial antagonism, whereas higher  
43 doses of 0.4 to 1 mg (peak plasma levels of 12 to 28 ng/mL) usually produce  
44 complete antagonism in patients who have received the usual sedating doses  
45 of benzodiazepines. The onset of reversal is usually evident within 1 to 2  
46 minutes after the injection is completed. Eighty percent response will be  
47 reached within 3 minutes, with the peak effect occurring at 6 to 10 minutes.  
48 The duration and degree of reversal are related to the plasma concentration of  
49 the sedating benzodiazepine as well as the dose of ROMAZICON given.

50 In healthy volunteers, ROMAZICON did not alter intraocular pressure when  
51 given alone and reversed the decrease in intraocular pressure seen after  
52 administration of midazolam.

### 53 Pharmacokinetics

54 After IV administration, plasma concentrations of flumazenil follow a two-  
55 exponential decay model. The pharmacokinetics of flumazenil are dose-  
56 proportional up to 100 mg.

### 57 Distribution

58 Flumazenil is extensively distributed in the extravascular space with an initial  
59 distribution half-life of 4 to 11 minutes and a terminal half-life of 40 to 80  
60 minutes. Peak concentrations of flumazenil are proportional to dose, with an  
61 apparent initial volume of distribution of 0.5 L/kg. The volume of distribution  
62 at steady-state is 0.9 to 1.1 L/kg. Flumazenil is a weak lipophilic base. Protein  
63 binding is approximately 50% and the drug shows no preferential partitioning

64 into red blood cells. Albumin accounts for two thirds of plasma protein  
65 binding.

## 66 Metabolism

67 Flumazenil is completely (99%) metabolized. Very little unchanged  
68 flumazenil (<1%) is found in the urine. The major metabolites of flumazenil  
69 identified in urine are the de-ethylated free acid and its glucuronide conjugate.  
70 In preclinical studies there was no evidence of pharmacologic activity  
71 exhibited by the de-ethylated free acid.

## 72 Elimination

73 Elimination of radiolabeled drug is essentially complete within 72 hours, with  
74 90% to 95% of the radioactivity appearing in urine and 5% to 10% in the  
75 feces. Clearance of flumazenil occurs primarily by hepatic metabolism and is  
76 dependent on hepatic blood flow. In pharmacokinetic studies of normal  
77 volunteers, total clearance ranged from 0.8 to 1.0 L/hr/kg.

78 Pharmacokinetic parameters following a 5-minute infusion of a total of 1 mg  
79 of ROMAZICON mean (coefficient of variation, range):

$C_{max}$ (ng/mL)	24	(38%, 11-43)
AUC (ng-hr/mL)	15	(22%, 10-22)
$V_{ss}$ (L/kg)	1	(24%, 0.8-1.6)
Cl (L/hr/kg)	1	(20%, 0.7-1.4)
Half-life (min)	54	(21%, 41-79)

80

## 81 Food Effects:

82 Ingestion of food during an intravenous infusion of the drug results in a 50%  
83 increase in clearance, most likely due to the increased hepatic blood flow that  
84 accompanies a meal.

## 85 Special Populations

### 86 *The Elderly*

87 The pharmacokinetics of flumazenil are not significantly altered in the elderly.

### 88 *Gender*

89 The pharmacokinetics of flumazenil are not different in male and female  
90 subjects.

### 91 *Renal Failure (creatinine clearance <10 mL/min) and Hemodialysis*

92 The pharmacokinetics of flumazenil are not significantly affected.

93 ***Patients With Liver Dysfunction***

94 For patients with moderate liver dysfunction, their mean total clearance is  
95 decreased to 40% to 60% and in patients with severe liver dysfunction, it is  
96 decreased to 25% of normal value, compared with age-matched healthy  
97 subjects. This results in a prolongation of the half-life to 1.3 hours in patients  
98 with moderate hepatic impairment and 2.4 hours in severely impaired patients.  
99 Caution should be exercised with initial and/or repeated dosing to patients  
100 with liver disease.

101 ***Drug-Drug Interaction:***

102 The pharmacokinetic profile of flumazenil is unaltered in the presence of  
103 benzodiazepine agonists and the kinetic profiles of those benzodiazepines  
104 studied (ie, diazepam, flunitrazepam, lormetazepam, and midazolam) are  
105 unaltered by flumazenil. During the 4-hour steady-state and post infusion of  
106 ethanol, there were no pharmacokinetic interactions on ethanol mean plasma  
107 levels as compared to placebo when flumazenil doses were given  
108 intravenously (at 2.5 hours and 6 hours) nor were interactions of ethanol on  
109 the flumazenil elimination half-life found.

110 ***Pharmacokinetics in Pediatric Patients***

111 The pharmacokinetics of flumazenil have been evaluated in 29 pediatric  
112 patients ranging in age from 1 to 17 years who had undergone minor surgical  
113 procedures. The average doses administered were 0.53 mg (0.044 mg/kg) in  
114 patients aged 1 to 5 years, 0.63 mg (0.020 mg/kg) in patients aged 6 to 12  
115 years, and 0.8 mg (0.014 mg/kg) in patients aged 13 to 17 years. Compared to  
116 adults, the elimination half-life in pediatric patients was more variable,  
117 averaging 40 minutes (range: 20 to 75 minutes). Clearance and volume of  
118 distribution, normalized for body weight, were in the same range as those seen  
119 in adults, although more variability was seen in the pediatric patients.

120 **CLINICAL TRIALS**

121 ROMAZICON has been administered in adults to reverse the effects of  
122 benzodiazepines in conscious sedation, general anesthesia, and the  
123 management of suspected benzodiazepine overdose. Limited information from  
124 uncontrolled studies in pediatric patients is available regarding the use of  
125 ROMAZICON to reverse the effects of benzodiazepines in conscious sedation  
126 only.

127 **Conscious Sedation in Adults**

128 ROMAZICON was studied in four trials in 970 patients who received an  
129 average of 30 mg diazepam or 10 mg midazolam for sedation (with or without  
130 a narcotic) in conjunction with both inpatient and outpatient diagnostic or  
131 surgical procedures. ROMAZICON was effective in reversing the sedating  
132 and psychomotor effects of the benzodiazepine; however, amnesia was less  
133 completely and less consistently reversed. In these studies, ROMAZICON

134 was administered as an initial dose of 0.4 mg IV (two doses of 0.2 mg) with  
135 additional 0.2 mg doses as needed to achieve complete awakening, up to a  
136 maximum total dose of 1 mg.

137 Seventy-eight percent of patients receiving flumazenil responded by becoming  
138 completely alert. Of those patients, approximately half responded to doses of  
139 0.4 mg to 0.6 mg, while the other half responded to doses of 0.8 mg to 1 mg.  
140 Adverse effects were infrequent in patients who received 1 mg of  
141 ROMAZICON or less, although injection site pain, agitation, and anxiety did  
142 occur. Reversal of sedation was not associated with any increase in the  
143 frequency of inadequate analgesia or increase in narcotic demand in these  
144 studies. While most patients remained alert throughout the 3-hour  
145 postprocedure observation period, re sedation was observed to occur in 3% to  
146 9% of the patients, and was most common in patients who had received high  
147 doses of benzodiazepines (see **PRECAUTIONS**).

#### 148 **General Anesthesia in Adults**

149 ROMAZICON was studied in four trials in 644 patients who received  
150 midazolam as an induction and/or maintenance agent in both balanced and  
151 inhalational anesthesia. Midazolam was generally administered in doses  
152 ranging from 5 mg to 80 mg, alone and/or in conjunction with muscle  
153 relaxants, nitrous oxide, regional or local anesthetics, narcotics and/or  
154 inhalational anesthetics. Flumazenil was given as an initial dose of 0.2 mg IV,  
155 with additional 0.2 mg doses as needed to reach a complete response, up to a  
156 maximum total dose of 1 mg. These doses were effective in reversing sedation  
157 and restoring psychomotor function, but did not completely restore memory as  
158 tested by picture recall. ROMAZICON was not as effective in the reversal of  
159 sedation in patients who had received multiple anesthetic agents in addition to  
160 benzodiazepines.

161 Eighty-one percent of patients sedated with midazolam responded to  
162 flumazenil by becoming completely alert or just slightly drowsy. Of those  
163 patients, 36% responded to doses of 0.4 mg to 0.6 mg, while 64% responded  
164 to doses of 0.8 mg to 1 mg.

165 Resedation in patients who responded to ROMAZICON occurred in 10% to  
166 15% of patients studied and was more common with larger doses of  
167 midazolam (>20 mg), long procedures (>60 minutes) and use of  
168 neuromuscular blocking agents (see **PRECAUTIONS**).

#### 169 **Management of Suspected Benzodiazepine Overdose in Adults**

170 ROMAZICON was studied in two trials in 497 patients who were presumed to  
171 have taken an overdose of a benzodiazepine, either alone or in combination  
172 with a variety of other agents. In these trials, 299 patients were proven to have  
173 taken a benzodiazepine as part of the overdose, and 80% of the 148 who  
174 received ROMAZICON responded by an improvement in level of

175 consciousness. Of the patients who responded to flumazenil, 75% responded  
176 to a total dose of 1 mg to 3 mg.

177 Reversal of sedation was associated with an increased frequency of symptoms  
178 of CNS excitation. Of the patients treated with flumazenil, 1% to 3% were  
179 treated for agitation or anxiety. Serious side effects were uncommon, but six  
180 seizures were observed in 446 patients treated with flumazenil in these  
181 studies. Four of these 6 patients had ingested a large dose of cyclic  
182 antidepressants, which increased the risk of seizures (see **WARNINGS**).

## 183 **INDIVIDUALIZATION OF DOSAGE**

### 184 **General Principles**

185 The serious adverse effects of ROMAZICON are related to the reversal of  
186 benzodiazepine effects. Using more than the minimally effective dose of  
187 ROMAZICON is tolerated by most patients but may complicate the  
188 management of patients who are physically dependent on benzodiazepines or  
189 patients who are depending on benzodiazepines for therapeutic effect (such as  
190 suppression of seizures in cyclic antidepressant overdose).

191 In high-risk patients, it is important to administer the smallest amount of  
192 ROMAZICON that is effective. The 1-minute wait between individual doses  
193 in the dose-titration recommended for general clinical populations may be too  
194 short for high-risk patients. This is because it takes 6 to 10 minutes for any  
195 single dose of flumazenil to reach full effects. Practitioners should slow the  
196 rate of administration of ROMAZICON administered to high-risk patients as  
197 recommended below.

### 198 **Anesthesia and Conscious Sedation in Adult Patients**

199 ROMAZICON is well tolerated at the recommended doses in individuals who  
200 have no tolerance to (or dependence on) benzodiazepines. The recommended  
201 doses and titration rates in anesthesia and conscious sedation (0.2 mg to 1 mg  
202 given at 0.2 mg/min) are well tolerated in patients receiving the drug for  
203 reversal of a single benzodiazepine exposure in most clinical settings (see  
204 **ADVERSE REACTIONS**). The major risk will be resedation because the  
205 duration of effect of a long-acting (or large dose of a short-acting)  
206 benzodiazepine may exceed that of ROMAZICON. Resedation may be treated  
207 by giving a repeat dose at no less than 20-minute intervals. For repeat  
208 treatment, no more than 1 mg (at 0.2 mg/min doses) should be given at any  
209 one time and no more than 3 mg should be given in any one hour.

### 210 **Benzodiazepine Overdose in Adult Patients**

211 The risk of confusion, agitation, emotional lability, and perceptual distortion  
212 with the doses recommended in patients with benzodiazepine overdose (3 mg  
213 to 5 mg administered as 0.5 mg/min) may be greater than that expected with  
214 lower doses and slower administration. The recommended doses represent a  
215 compromise between a desirable slow awakening and the need for prompt

216 response and a persistent effect in the overdose situation. If circumstances  
217 permit, the physician may elect to use the 0.2 mg/minute titration rate to  
218 slowly awaken the patient over 5 to 10 minutes, which may help to reduce  
219 signs and symptoms on emergence.

220 ROMAZICON has no effect in cases where benzodiazepines are not  
221 responsible for sedation. Once doses of 3 mg to 5 mg have been reached  
222 without clinical response, additional ROMAZICON is likely to have no effect.

### 223 **Patients Tolerant to Benzodiazepines**

224 ROMAZICON may cause benzodiazepine withdrawal symptoms in  
225 individuals who have been taking benzodiazepines long enough to have some  
226 degree of tolerance. Patients who had been taking benzodiazepines prior to  
227 entry into the ROMAZICON trials, who were given flumazenil in doses over  
228 1 mg, experienced withdrawal-like events 2 to 5 times more frequently than  
229 patients who received less than 1 mg.

230 In patients who may have tolerance to benzodiazepines, as indicated by  
231 clinical history or by the need for larger than usual doses of benzodiazepines,  
232 slower titration rates of 0.1 mg/min and lower total doses may help reduce the  
233 frequency of emergent confusion and agitation. In such cases, special care  
234 must be taken to monitor the patients for re sedation because of the lower  
235 doses of ROMAZICON used.

### 236 **Patients Physically Dependent on Benzodiazepines**

237 ROMAZICON is known to precipitate withdrawal seizures in patients who are  
238 physically dependent on benzodiazepines, even if such dependence was  
239 established in a relatively few days of high-dose sedation in Intensive Care  
240 Unit (ICU) environments. The risk of either seizures or re sedation in such  
241 cases is high and patients have experienced seizures before regaining  
242 consciousness. ROMAZICON should be used in such settings with extreme  
243 caution, since the use of flumazenil in this situation has not been studied and  
244 no information as to dose and rate of titration is available. ROMAZICON  
245 should be used in such patients only if the potential benefits of using the drug  
246 outweigh the risks of precipitated seizures. Physicians are directed to the  
247 scientific literature for the most current information in this area.

## 248 **INDICATIONS AND USAGE**

### 249 **Adult Patients**

250 ROMAZICON is indicated for the complete or partial reversal of the sedative  
251 effects of benzodiazepines in cases where general anesthesia has been induced  
252 and/or maintained with benzodiazepines, where sedation has been produced  
253 with benzodiazepines for diagnostic and therapeutic procedures, and for the  
254 management of benzodiazepine overdose.

**255 Pediatric Patients (aged 1 to 17)**

256 ROMAZICON is indicated for the reversal of conscious sedation induced with  
257 benzodiazepines (see **PRECAUTIONS: Pediatric Use**).

**258 CONTRAINDICATIONS**

259 ROMAZICON is contraindicated:

- 260 • in patients with a known hypersensitivity to flumazenil or  
261 benzodiazepines.
- 262 • in patients who have been given a benzodiazepine for control of a  
263 potentially life-threatening condition (eg, control of intracranial pressure  
264 or status epilepticus).
- 265 • in patients who are showing signs of serious cyclic antidepressant  
266 overdose (see **WARNINGS**).

**267 WARNINGS**

268 **THE USE OF ROMAZICON HAS BEEN ASSOCIATED WITH THE**  
269 **OCCURRENCE OF SEIZURES.**

270 **THESE ARE MOST FREQUENT IN PATIENTS WHO HAVE BEEN**  
271 **ON BENZODIAZEPINES FOR LONG-TERM SEDATION OR IN**  
272 **OVERDOSE CASES WHERE PATIENTS ARE SHOWING SIGNS OF**  
273 **SERIOUS CYCLIC ANTIDEPRESSANT OVERDOSE.**

274 **PRACTITIONERS SHOULD INDIVIDUALIZE THE DOSAGE OF**  
275 **ROMAZICON AND BE PREPARED TO MANAGE SEIZURES.**

**276 Risk of Seizures**

277 **The reversal of benzodiazepine effects may be associated with the onset of**  
278 **seizures in certain high-risk populations. Possible risk factors for seizures**  
279 **include: concurrent major sedative-hypnotic drug withdrawal, recent**  
280 **therapy with repeated doses of parenteral benzodiazepines, myoclonic**  
281 **jerking or seizure activity prior to flumazenil administration in overdose**  
282 **cases, or concurrent cyclic antidepressant poisoning.**

283 **ROMAZICON is not recommended in cases of serious cyclic**  
284 **antidepressant poisoning, as manifested by motor abnormalities**  
285 **(twitching, rigidity, focal seizure), dysrhythmia (wide QRS, ventricular**  
286 **dysrhythmia, heart block), anticholinergic signs (mydriasis, dry mucosa,**  
287 **hypoperistalsis), and cardiovascular collapse at presentation. In such**  
288 **cases ROMAZICON should be withheld and the patient should be**  
289 **allowed to remain sedated (with ventilatory and circulatory support as**  
290 **needed) until the signs of antidepressant toxicity have subsided.**  
291 **Treatment with ROMAZICON has no known benefit to the seriously ill**

292 **mixed-overdose patient other than reversing sedation and should not be**  
293 **used in cases where seizures (from any cause) are likely.**

294 **Most convulsions associated with flumazenil administration require**  
295 **treatment and have been successfully managed with benzodiazepines,**  
296 **phenytoin or barbiturates. Because of the presence of flumazenil, higher**  
297 **than usual doses of benzodiazepines may be required.**

## 298 **Hypoventilation**

299 **Patients who have received ROMAZICON for the reversal of**  
300 **benzodiazepine effects (after conscious sedation or general anesthesia)**  
301 **should be monitored for re sedation, respiratory depression, or other**  
302 **residual benzodiazepine effects for an appropriate period (up to 120**  
303 **minutes) based on the dose and duration of effect of the benzodiazepine**  
304 **employed.**

305 **This is because ROMAZICON has not been established in patients as an**  
306 **effective treatment for hypoventilation due to benzodiazepine**  
307 **administration. In healthy male volunteers, ROMAZICON is capable of**  
308 **reversing benzodiazepine-induced depression of the ventilatory responses**  
309 **to hypercapnia and hypoxia after a benzodiazepine alone. However, such**  
310 **depression may recur because the ventilatory effects of typical doses of**  
311 **ROMAZICON (1 mg or less) may wear off before the effects of many**  
312 **benzodiazepines. The effects of ROMAZICON on ventilatory response**  
313 **following sedation with a benzodiazepine in combination with an opioid**  
314 **are inconsistent and have not been adequately studied. The availability of**  
315 **flumazenil does not diminish the need for prompt detection of**  
316 **hypoventilation and the ability to effectively intervene by establishing an**  
317 **airway and assisting ventilation.**

318 **Overdose cases should always be monitored for re sedation until the**  
319 **patients are stable and re sedation is unlikely.**

## 320 **PRECAUTIONS**

### 321 **Return of Sedation**

322 **ROMAZICON may be expected to improve the alertness of patients**  
323 **recovering from a procedure involving sedation or anesthesia with**  
324 **benzodiazepines, but should not be substituted for an adequate period of**  
325 **postprocedure monitoring. The availability of ROMAZICON does not reduce**  
326 **the risks associated with the use of large doses of benzodiazepines for**  
327 **sedation.**

328 **Patients should be monitored for re sedation, respiratory depression (see**  
329 **WARNINGS) or other persistent or recurrent agonist effects for an adequate**  
330 **period of time after administration of ROMAZICON.**

331 Resedation is least likely in cases where ROMAZICON is administered to  
332 reverse a low dose of a short-acting benzodiazepine (<10 mg midazolam). It is  
333 most likely in cases where a large single or cumulative dose of a  
334 benzodiazepine has been given in the course of a long procedure along with  
335 neuromuscular blocking agents and multiple anesthetic agents.

336 Profound resedation was observed in 1% to 3% of adult patients in the clinical  
337 studies. In clinical situations where resedation must be prevented in adult  
338 patients, physicians may wish to repeat the initial dose (up to 1 mg of  
339 ROMAZICON given at 0.2 mg/min) at 30 minutes and possibly again at 60  
340 minutes. This dosage schedule, although not studied in clinical trials, was  
341 effective in preventing resedation in a pharmacologic study in normal  
342 volunteers.

343 The use of ROMAZICON to reverse the effects of benzodiazepines used for  
344 conscious sedation has been evaluated in one open-label clinical trial  
345 involving 107 pediatric patients between the ages of 1 and 17 years. This  
346 study suggested that pediatric patients who have become fully awake  
347 following treatment with flumazenil may experience a recurrence of sedation,  
348 especially younger patients (ages 1 to 5). Resedation was experienced in 7 of  
349 60 patients who were fully alert 10 minutes after the start of ROMAZICON  
350 administration. No patient experienced a return to the baseline level of  
351 sedation. Mean time to resedation was 25 minutes (range: 19 to 50 minutes)  
352 (see **PRECAUTIONS: Pediatric Use**). The safety and effectiveness of  
353 repeated flumazenil administration in pediatric patients experiencing  
354 resedation have not been established.

### 355 **Use in the ICU**

356 ROMAZICON should be used with caution in the ICU because of the  
357 increased risk of unrecognized benzodiazepine dependence in such settings.  
358 ROMAZICON may produce convulsions in patients physically dependent on  
359 benzodiazepines (see **INDIVIDUALIZATION OF DOSAGE** and  
360 **WARNINGS**).

361 Administration of ROMAZICON to diagnose benzodiazepine-induced  
362 sedation in the ICU is not recommended due to the risk of adverse events as  
363 described above. In addition, the prognostic significance of a patient's failure  
364 to respond to flumazenil in cases confounded by metabolic disorder, traumatic  
365 injury, drugs other than benzodiazepines, or any other reasons not associated  
366 with benzodiazepine receptor occupancy is unknown.

### 367 **Use in Benzodiazepine Overdosage**

368 ROMAZICON is intended as an adjunct to, not as a substitute for, proper  
369 management of airway, assisted breathing, circulatory access and support,  
370 internal decontamination by lavage and charcoal, and adequate clinical  
371 evaluation.

372 Necessary measures should be instituted to secure airway, ventilation and  
373 intravenous access prior to administering flumazenil. Upon arousal, patients  
374 may attempt to withdraw endotracheal tubes and/or intravenous lines as the  
375 result of confusion and agitation following awakening.

### 376 **Head Injury**

377 ROMAZICON should be used with caution in patients with head injury as it  
378 may be capable of precipitating convulsions or altering cerebral blood flow in  
379 patients receiving benzodiazepines. It should be used only by practitioners  
380 prepared to manage such complications should they occur.

### 381 **Use With Neuromuscular Blocking Agents**

382 ROMAZICON should not be used until the effects of neuromuscular blockade  
383 have been fully reversed.

### 384 **Use in Psychiatric Patients**

385 ROMAZICON has been reported to provoke panic attacks in patients with a  
386 history of panic disorder.

### 387 **Pain on Injection**

388 To minimize the likelihood of pain or inflammation at the injection site,  
389 ROMAZICON should be administered through a freely flowing intravenous  
390 infusion into a large vein. Local irritation may occur following extravasation  
391 into perivascular tissues.

### 392 **Use in Respiratory Disease**

393 The primary treatment of patients with serious lung disease who experience  
394 serious respiratory depression due to benzodiazepines should be appropriate  
395 ventilatory support (see **PRECAUTIONS**) rather than the administration of  
396 ROMAZICON. Flumazenil is capable of partially reversing benzodiazepine-  
397 induced alterations in ventilatory drive in healthy volunteers, but has not been  
398 shown to be clinically effective.

### 399 **Use in Cardiovascular Disease**

400 ROMAZICON did not increase the work of the heart when used to reverse  
401 benzodiazepines in cardiac patients when given at a rate of 0.1 mg/min in total  
402 doses of less than 0.5 mg in studies reported in the clinical literature.  
403 Flumazenil alone had no significant effects on cardiovascular parameters  
404 when administered to patients with stable ischemic heart disease.

### 405 **Use in Liver Disease**

406 The clearance of ROMAZICON is reduced to 40% to 60% of normal in  
407 patients with mild to moderate hepatic disease and to 25% of normal in  
408 patients with severe hepatic dysfunction (see **CLINICAL**  
409 **PHARMACOLOGY: Pharmacokinetics**). While the dose of flumazenil

410 used for initial reversal of benzodiazepine effects is not affected, repeat doses  
411 of the drug in liver disease should be reduced in size or frequency.

### 412 **Use in Drug- and Alcohol-Dependent Patients**

413 ROMAZICON should be used with caution in patients with alcoholism and  
414 other drug dependencies due to the increased frequency of benzodiazepine  
415 tolerance and dependence observed in these patient populations.

416 ROMAZICON is not recommended either as a treatment for benzodiazepine  
417 dependence or for the management of protracted benzodiazepine abstinence  
418 syndromes, as such use has not been studied.

419 The administration of flumazenil can precipitate benzodiazepine withdrawal  
420 in animals and man. This has been seen in healthy volunteers treated with  
421 therapeutic doses of oral lorazepam for up to 2 weeks who exhibited effects  
422 such as hot flushes, agitation and tremor when treated with cumulative doses  
423 of up to 3 mg doses of flumazenil.

424 Similar adverse experiences suggestive of flumazenil precipitation of  
425 benzodiazepine withdrawal have occurred in some adult patients in clinical  
426 trials. Such patients had a short-lived syndrome characterized by dizziness,  
427 mild confusion, emotional lability, agitation (with signs and symptoms of  
428 anxiety), and mild sensory distortions. This response was dose-related, most  
429 common at doses above 1 mg, rarely required treatment other than reassurance  
430 and was usually short lived. When required, these patients (5 to 10 cases)  
431 were successfully treated with usual doses of a barbiturate, a benzodiazepine,  
432 or other sedative drug.

433 Practitioners should assume that flumazenil administration may trigger dose-  
434 dependent withdrawal syndromes in patients with established physical  
435 dependence on benzodiazepines and may complicate the management of  
436 withdrawal syndromes for alcohol, barbiturates and cross-tolerant sedatives.

### 437 **Drug Interactions**

438 Interaction with central nervous system depressants other than  
439 benzodiazepines has not been specifically studied; however, no deleterious  
440 interactions were seen when ROMAZICON was administered after narcotics,  
441 inhalational anesthetics, muscle relaxants and muscle relaxant antagonists  
442 administered in conjunction with sedation or anesthesia.

443 Particular caution is necessary when using ROMAZICON in cases of mixed  
444 drug overdose since the toxic effects (such as convulsions and cardiac  
445 dysrhythmias) of other drugs taken in overdose (especially cyclic  
446 antidepressants) may emerge with the reversal of the benzodiazepine effect by  
447 flumazenil (see **WARNINGS**).

448 The use of ROMAZICON is not recommended in epileptic patients who have  
449 been receiving benzodiazepine treatment for a prolonged period. Although

450 ROMAZICON exerts a slight intrinsic anticonvulsant effect, its abrupt  
451 suppression of the protective effect of a benzodiazepine agonist can give rise  
452 to convulsions in epileptic patients.

453 ROMAZICON blocks the central effects of benzodiazepines by competitive  
454 interaction at the receptor level. The effects of nonbenzodiazepine agonists at  
455 benzodiazepine receptors, such as zopiclone, triazolopyridazines and others,  
456 are also blocked by ROMAZICON.

457 The pharmacokinetics of benzodiazepines are unaltered in the presence of  
458 flumazenil and vice versa.

459 There is no pharmacokinetic interaction between ethanol and flumazenil.

#### 460 **Use in Ambulatory Patients**

461 The effects of ROMAZICON may wear off before a long-acting  
462 benzodiazepine is completely cleared from the body. In general, if a patient  
463 shows no signs of sedation within 2 hours after a 1-mg dose of flumazenil,  
464 serious re sedation at a later time is unlikely. An adequate period of  
465 observation must be provided for any patient in whom either long-acting  
466 benzodiazepines (such as diazepam) or large doses of short-acting  
467 benzodiazepines (such as >10 mg of midazolam) have been used (see  
468 **INDIVIDUALIZATION OF DOSAGE**).

469 Because of the increased risk of adverse reactions in patients who have been  
470 taking benzodiazepines on a regular basis, it is particularly important that  
471 physicians query patients or their guardians carefully about benzodiazepine,  
472 alcohol and sedative use as part of the history prior to any procedure in which  
473 the use of ROMAZICON is planned (see **PRECAUTIONS: Use in Drug-  
474 and Alcohol-Dependent Patients**).

#### 475 **Information for Patients**

476 ROMAZICON does not consistently reverse amnesia. Patients cannot be  
477 expected to remember information told to them in the postprocedure period  
478 and instructions given to patients should be reinforced in writing or given to a  
479 responsible family member. Physicians are advised to discuss with patients or  
480 their guardians, both before surgery and at discharge, that although the patient  
481 may feel alert at the time of discharge, the effects of the benzodiazepine (eg,  
482 sedation) may recur. As a result, the patient should be instructed, preferably in  
483 writing, that their memory and judgment may be impaired and specifically  
484 advised:

- 485 1. Not to engage in any activities requiring complete alertness, and not to  
486 operate hazardous machinery or a motor vehicle during the first 24 hours  
487 after discharge, and it is certain no residual sedative effects of the  
488 benzodiazepine remain.

489 2. Not to take any alcohol or non-prescription drugs during the first 24 hours  
490 after flumazenil administration or if the effects of the benzodiazepine  
491 persist.

## 492 **Laboratory Tests**

493 No specific laboratory tests are recommended to follow the patient's response  
494 or to identify possible adverse reactions.

## 495 **Drug/Laboratory Test Interactions**

496 The possible interaction of flumazenil with commonly used laboratory tests  
497 has not been evaluated.

## 498 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

### 499 **Carcinogenesis**

500 No studies in animals to evaluate the carcinogenic potential of flumazenil  
501 have been conducted.

### 502 **Mutagenesis**

503 No evidence for mutagenicity was noted in the Ames test using five different  
504 tester strains. Assays for mutagenic potential in *S. cerevisiae* D7 and in  
505 Chinese hamster cells were considered to be negative as were blastogenesis  
506 assays in vitro in peripheral human lymphocytes and in vivo in a mouse  
507 micronucleus assay. Flumazenil caused a slight increase in unscheduled DNA  
508 synthesis in rat hepatocyte culture at concentrations which were also  
509 cytotoxic; no increase in DNA repair was observed in male mouse germ cells  
510 in an in vivo DNA repair assay.

### 511 **Impairment of Fertility**

512 A reproduction study in male and female rats did not show any impairment of  
513 fertility at oral dosages of 125 mg/kg/day. From the available data on the area  
514 under the curve (AUC) in animals and man the dose represented 120x the  
515 human exposure from a maximum recommended intravenous dose of 5 mg.

## 516 **Pregnancy**

### 517 **Pregnancy Category C**

518 There are no adequate and well-controlled studies of the use of flumazenil in  
519 pregnant women. Flumazenil should be used during pregnancy only if the  
520 potential benefit justifies the potential risk to the fetus.

## 521 **Teratogenic Effects**

522 Flumazenil has been studied for teratogenicity in rats and rabbits following  
523 oral treatments of up to 150 mg/kg/day. The treatments during the major  
524 organogenesis were on days 6 to 15 of gestation in the rat and days 6 to 18 of

525 gestation in the rabbit. No teratogenic effects were observed in rats or rabbits  
526 at 150 mg/kg; the dose, based on the available data on the area under the  
527 plasma concentration-time curve (AUC) represented 120x to 600x the human  
528 exposure from a maximum recommended intravenous dose of 5 mg in  
529 humans. In rabbits, embryocidal effects (as evidenced by increased  
530 preimplantation and postimplantation losses) were observed at 50 mg/kg or  
531 200x the human exposure from a maximum recommended intravenous dose of  
532 5 mg. The no-effect dose of 15 mg/kg in rabbits represents 60x the human  
533 exposure.

#### 534 **Nonteratogenic Effects**

535 An animal reproduction study was conducted in rats at oral dosages of 5, 25,  
536 and 125 mg/kg/day of flumazenil. Pup survival was decreased during the  
537 lactating period, pup liver weight at weaning was increased for the high-dose  
538 group (125 mg/kg/day) and incisor eruption and ear opening in the offspring  
539 were delayed; the delay in ear opening was associated with a delay in the  
540 appearance of the auditory startle response. No treatment-related adverse  
541 effects were noted for the other dose groups. Based on the available data from  
542 AUC, the effect level (125 mg/kg) represents 120x the human exposure from  
543 5 mg, the maximum recommended intravenous dose in humans. The no-effect  
544 level represents 24x the human exposure from an intravenous dose of 5 mg.

#### 545 **Labor and Delivery**

546 The use of ROMAZICON to reverse the effects of benzodiazepines used  
547 during labor and delivery is not recommended because the effects of the drug  
548 in the newborn are unknown.

#### 549 **Nursing Mothers**

550 Caution should be exercised when deciding to administer ROMAZICON to a  
551 nursing woman because it is not known whether flumazenil is excreted in  
552 human milk.

#### 553 **Pediatric Use**

554 The safety and effectiveness of ROMAZICON have been established in  
555 pediatric patients 1 year of age and older. Use of ROMAZICON in this age  
556 group is supported by evidence from adequate and well-controlled studies of  
557 ROMAZICON in adults with additional data from uncontrolled pediatric  
558 studies including one open-label trial.

559 The use of ROMAZICON to reverse the effects of benzodiazepines used for  
560 conscious sedation was evaluated in one uncontrolled clinical trial involving  
561 107 pediatric patients between the ages of 1 and 17 years. At the doses used,  
562 ROMAZICON's safety was established in this population. Patients received  
563 up to 5 injections of 0.01 mg/kg flumazenil up to a maximum total dose of 1.0  
564 mg at a rate not exceeding 0.2 mg/min.

565 Of 60 patients who were fully alert at 10 minutes, 7 experienced re sedation.  
566 Re sedation occurred between 19 and 50 minutes after the start of  
567 ROMAZICON administration. None of the patients experienced a return to  
568 the baseline level of sedation. All 7 patients were between the ages of 1 and 5  
569 years. The types and frequency of adverse events noted in these pediatric  
570 patients were similar to those previously documented in clinical trials with  
571 ROMAZICON to reverse conscious sedation in adults. No patient experienced  
572 a serious adverse event attributable to flumazenil.

573 The safety and efficacy of ROMAZICON in the reversal of conscious  
574 sedation in pediatric patients below the age of 1 year have not been  
575 established (see **CLINICAL PHARMACOLOGY: Pharmacokinetics in**  
576 **Pediatric Patients**).

577 The safety and efficacy of ROMAZICON have not been established in  
578 pediatric patients for reversal of the sedative effects of benzodiazepines used  
579 for induction of general anesthesia, for the management of overdose, or for the  
580 resuscitation of the newborn, as no well-controlled clinical studies have been  
581 performed to determine the risks, benefits and dosages to be used. However,  
582 published anecdotal reports discussing the use of ROMAZICON in pediatric  
583 patients for these indications have reported similar safety profiles and dosing  
584 guidelines to those described for the reversal of conscious sedation.

585 The risks identified in the adult population with ROMAZICON use also apply  
586 to pediatric patients. Therefore, consult the **CONTRAINDICATIONS,**  
587 **WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS** sections  
588 when using ROMAZICON in pediatric patients.

### 589 **Geriatric Use**

590 Of the total number of subjects in clinical studies of flumazenil, 248 were 65  
591 and over. No overall differences in safety or effectiveness were observed  
592 between these subjects and younger subjects. Other reported clinical  
593 experience has not identified differences in responses between the elderly and  
594 younger patients, but greater sensitivity of some older individuals cannot be  
595 ruled out.

596 The pharmacokinetics of flumazenil have been studied in the elderly and are  
597 not significantly different from younger patients. Several studies of  
598 ROMAZICON in subjects over the age of 65 and one study in subjects over  
599 the age of 80 suggest that while the doses of benzodiazepine used to induce  
600 sedation should be reduced, ordinary doses of ROMAZICON may be used for  
601 reversal.

## 602 **ADVERSE REACTIONS**

### 603 **Serious Adverse Reactions**

604 Deaths have occurred in patients who received ROMAZICON in a variety of  
605 clinical settings. The majority of deaths occurred in patients with serious

606 underlying disease or in patients who had ingested large amounts of non-  
607 benzodiazepine drugs (usually cyclic antidepressants), as part of an overdose.

608 Serious adverse events have occurred in all clinical settings, and convulsions  
609 are the most common serious adverse events reported. ROMAZICON  
610 administration has been associated with the onset of convulsions in patients  
611 with severe hepatic impairment and in patients who are relying on  
612 benzodiazepine effects to control seizures, are physically dependent on  
613 benzodiazepines, or who have ingested large doses of other drugs (mixed-drug  
614 overdose) (see **WARNINGS**).

615 Two of the 446 patients who received ROMAZICON in controlled clinical  
616 trials for the management of a benzodiazepine overdose had cardiac  
617 dysrhythmias (1 ventricular tachycardia, 1 junctional tachycardia).

### 618 **Adverse Events in Clinical Studies**

619 The following adverse reactions were considered to be related to  
620 ROMAZICON administration (both alone and for the reversal of  
621 benzodiazepine effects) and were reported in studies involving 1875  
622 individuals who received flumazenil in controlled trials. Adverse events most  
623 frequently associated with flumazenil alone were limited to dizziness,  
624 injection site pain, increased sweating, headache, and abnormal or blurred  
625 vision (3% to 9%).

626 *Body as a Whole:* fatigue (asthenia, malaise), headache, injection site pain\*,  
627 injection site reaction (thrombophlebitis, skin abnormality, rash)

628 *Cardiovascular System:* cutaneous vasodilation (sweating, flushing, hot  
629 flushes)

630 *Digestive System:* nausea, vomiting (11%)

631 *Nervous System:* agitation (anxiety, nervousness, dry mouth, tremor,  
632 palpitations, insomnia, dyspnea, hyperventilation)\*, dizziness (vertigo, ataxia)  
633 (10%), emotional lability (crying abnormal, depersonalization, euphoria,  
634 increased tears, depression, dysphoria, paranoia)

635 *Special Senses:* abnormal vision (visual field defect, diplopia), paresthesia  
636 (sensation abnormal, hypoesthesia)

637 All adverse reactions occurred in 1% to 3% of cases unless otherwise marked.

638 \*indicates reaction in 3% to 9% of cases.

639 Observed percentage reported if greater than 9%.

640 The following adverse events were observed infrequently (less than 1%) in the  
641 clinical studies, but were judged as probably related to ROMAZICON  
642 administration and/or reversal of benzodiazepine effects:

643 *Nervous System:* confusion (difficulty concentrating, delirium), convulsions  
644 (see **WARNINGS**), somnolence (stupor)

645 *Special Senses:* abnormal hearing (transient hearing impairment, hyperacusis,  
646 tinnitus)

647 The following adverse events occurred with frequencies less than 1% in the  
648 clinical trials. Their relationship to ROMAZICON administration is unknown,  
649 but they are included as alerting information for the physician.

650 *Body as a Whole:* rigors, shivering

651 *Cardiovascular System:* arrhythmia (atrial, nodal, ventricular extrasystoles),  
652 bradycardia, tachycardia, hypertension, chest pain

653 *Digestive System:* hiccup

654 *Nervous System:* speech disorder (dysphonia, thick tongue)

655 Not included in this list is operative site pain that occurred with the same  
656 frequency in patients receiving placebo as in patients receiving flumazenil for  
657 reversal of sedation following a surgical procedure.

### 658 **Additional Adverse Reactions Reported During Postmarketing** 659 **Experience**

660 The following events have been reported during postapproval use of  
661 ROMAZICON.

662 *Nervous System:* Fear, panic attacks in patients with a history of panic  
663 disorders.

664 Withdrawal symptoms may occur following rapid injection of ROMAZICON  
665 in patients with long-term exposure to benzodiazepines.

### 666 **DRUG ABUSE AND DEPENDENCE**

667 ROMAZICON acts as a benzodiazepine antagonist, blocks the effects of  
668 benzodiazepines in animals and man, antagonizes benzodiazepine  
669 reinforcement in animal models, produces dysphoria in normal subjects, and  
670 has had no reported abuse in foreign marketing.

671 Although ROMAZICON has a benzodiazepine-like structure it does not act as  
672 a benzodiazepine agonist in man and is not a controlled substance.

### 673 **OVERDOSAGE**

674 There is limited experience of acute overdose with ROMAZICON.

675 There is no specific antidote for overdose with ROMAZICON. Treatment of  
676 an overdose with ROMAZICON should consist of general supportive  
677 measures including monitoring of vital signs and observation of the clinical  
678 status of the patient.

679 Intravenous bolus administration of doses ranging from 2.5 to 100 mg  
680 (exceeding those recommended) of ROMAZICON, when administered to  
681 healthy normal volunteers in the absence of a benzodiazepine agonist,  
682 produced no serious adverse reactions, severe signs or symptoms, or clinically  
683 significant laboratory test abnormalities. In clinical studies, most adverse  
684 reactions to flumazenil were an extension of the pharmacologic effects of the  
685 drug in reversing benzodiazepine effects.

686 Reversal with an excessively high dose of ROMAZICON may produce  
687 anxiety, agitation, increased muscle tone, hyperesthesia and possibly  
688 convulsions. Convulsions have been treated with barbiturates,  
689 benzodiazepines and phenytoin, generally with prompt resolution of the  
690 seizures (see **WARNINGS**).

### 691 **DOSAGE AND ADMINISTRATION**

692 ROMAZICON is recommended for intravenous use only. It is compatible  
693 with 5% dextrose in water, lactated Ringer's and normal saline solutions. If  
694 ROMAZICON is drawn into a syringe or mixed with any of these solutions, it  
695 should be discarded after 24 hours. For optimum sterility, ROMAZICON  
696 should remain in the vial until just before use. As with all parenteral drug  
697 products, ROMAZICON should be inspected visually for particulate matter  
698 and discoloration prior to administration, whenever solution and container  
699 permit.

700 To minimize the likelihood of pain at the injection site, ROMAZICON should  
701 be administered through a freely running intravenous infusion into a large  
702 vein.

### 703 **Reversal of Conscious Sedation**

#### 704 **Adult Patients**

705 For the reversal of the sedative effects of benzodiazepines administered for  
706 conscious sedation, the recommended initial dose of ROMAZICON is 0.2 mg  
707 (2 mL) administered intravenously over 15 seconds. If the desired level of  
708 consciousness is not obtained after waiting an additional 45 seconds, a second  
709 dose of 0.2 mg (2 mL) can be injected and repeated at 60-second intervals  
710 where necessary (up to a maximum of 4 additional times) to a maximum total  
711 dose of 1 mg (10 mL). The dosage should be individualized based on the  
712 patient's response, with most patients responding to doses of 0.6 mg to 1 mg  
713 (see **INDIVIDUALIZATION OF DOSAGE**).

714 In the event of re-sedation, repeated doses may be administered at 20-minute  
715 intervals as needed. For repeat treatment, no more than 1 mg (given as 0.2  
716 mg/min) should be administered at any one time, and no more than 3 mg  
717 should be given in any one hour.

718 It is recommended that ROMAZICON be administered as the series of small  
719 injections described (not as a single bolus injection) to allow the practitioner

720 to control the reversal of sedation to the approximate endpoint desired and to  
721 minimize the possibility of adverse effects (see **INDIVIDUALIZATION OF**  
722 **DOSAGE**).

### 723 Pediatric Patients

724 For the reversal of the sedative effects of benzodiazepines administered for  
725 conscious sedation in pediatric patients greater than 1 year of age, the  
726 recommended initial dose is 0.01 mg/kg (up to 0.2 mg) administered  
727 intravenously over 15 seconds. If the desired level of consciousness is not  
728 obtained after waiting an additional 45 seconds, further injections of 0.01  
729 mg/kg (up to 0.2 mg) can be administered and repeated at 60-second intervals  
730 where necessary (up to a maximum of 4 additional times) to a maximum total  
731 dose of 0.05 mg/kg or 1 mg, whichever is lower. The dose should be  
732 individualized based on the patient's response. The mean total dose  
733 administered in the pediatric clinical trial of flumazenil was 0.65 mg (range:  
734 0.08 mg to 1.00 mg). Approximately one-half of patients required the  
735 maximum of five injections.

736 Resedation occurred in 7 of 60 pediatric patients who were fully alert 10  
737 minutes after the start of ROMAZICON administration (see  
738 **PRECAUTIONS: Pediatric Use**). The safety and efficacy of repeated  
739 flumazenil administration in pediatric patients experiencing resedation have  
740 not been established.

741 It is recommended that ROMAZICON be administered as the series of small  
742 injections described (not as a single bolus injection) to allow the practitioner  
743 to control the reversal of sedation to the approximate endpoint desired and to  
744 minimize the possibility of adverse effects (see **INDIVIDUALIZATION OF**  
745 **DOSAGE**).

746 The safety and efficacy of ROMAZICON in the reversal of conscious  
747 sedation in pediatric patients below the age of 1 year have not been  
748 established.

### 749 Reversal of General Anesthesia in Adult Patients

750 For the reversal of the sedative effects of benzodiazepines administered for  
751 general anesthesia, the recommended initial dose of ROMAZICON is 0.2 mg  
752 (2 mL) administered intravenously over 15 seconds. If the desired level of  
753 consciousness is not obtained after waiting an additional 45 seconds, a further  
754 dose of 0.2 mg (2 mL) can be injected and repeated at 60-second intervals  
755 where necessary (up to a maximum of 4 additional times) to a maximum total  
756 dose of 1 mg (10 mL). The dosage should be individualized based on the  
757 patient's response, with most patients responding to doses of 0.6 mg to 1 mg  
758 (see **INDIVIDUALIZATION OF DOSAGE**).

759 In the event of resedation, repeated doses may be administered at 20-minute  
760 intervals as needed. For repeat treatment, no more than 1 mg (given as 0.2

761 mg/min) should be administered at any one time, and no more than 3 mg  
762 should be given in any one hour.

763 It is recommended that ROMAZICON be administered as the series of small  
764 injections described (not as a single bolus injection) to allow the practitioner  
765 to control the reversal of sedation to the approximate endpoint desired and to  
766 minimize the possibility of adverse effects (see **INDIVIDUALIZATION OF**  
767 **DOSAGE**).

### 768 **Management of Suspected Benzodiazepine Overdose in Adult** 769 **Patients**

770 For initial management of a known or suspected benzodiazepine overdose, the  
771 recommended initial dose of ROMAZICON is 0.2 mg (2 mL) administered  
772 intravenously over 30 seconds. If the desired level of consciousness is not  
773 obtained after waiting 30 seconds, a further dose of 0.3 mg (3 mL) can be  
774 administered over another 30 seconds. Further doses of 0.5 mg (5 mL) can be  
775 administered over 30 seconds at 1-minute intervals up to a cumulative dose of  
776 3 mg.

777 Do not rush the administration of ROMAZICON. Patients should have a  
778 secure airway and intravenous access before administration of the drug and be  
779 awakened gradually (see **PRECAUTIONS**).

780 Most patients with a benzodiazepine overdose will respond to a cumulative  
781 dose of 1 mg to 3 mg of ROMAZICON, and doses beyond 3 mg do not  
782 reliably produce additional effects. On rare occasions, patients with a partial  
783 response at 3 mg may require additional titration up to a total dose of 5 mg  
784 (administered slowly in the same manner).

785 If a patient has not responded 5 minutes after receiving a cumulative dose of 5  
786 mg of ROMAZICON, the major cause of sedation is likely not to be due to  
787 benzodiazepines, and additional ROMAZICON is likely to have no effect.

788 In the event of re sedation, repeated doses may be given at 20-minute intervals  
789 if needed. For repeat treatment, no more than 1 mg (given as 0.5 mg/min)  
790 should be given at any one time and no more than 3 mg should be given in  
791 any one hour.

### 792 **Safety and Handling**

793 ROMAZICON is supplied in sealed dosage forms and poses no known risk to  
794 the healthcare provider. Routine care should be taken to avoid aerosol  
795 generation when preparing syringes for injection, and spilled medication  
796 should be rinsed from the skin with cool water.

797 **HOW SUPPLIED**

798 5 mL multiple-use vials containing 0.1 mg/mL flumazenil — boxes of 10  
799 (NDC 0004-6911-06); 10 mL multiple-use vials containing 0.1 mg/mL  
800 flumazenil — boxes of 10 (NDC 0004-6912-06).

801 **Storage**

802 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See  
803 USP Controlled Room Temperature].

804

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