

1 CARBATROL®
2 (carbamazepine) Extended-Release Capsules
3 100 mg, 200 mg and 300 mg
4 **Rx only**

5
6 **Prescribing information**
7

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE-CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

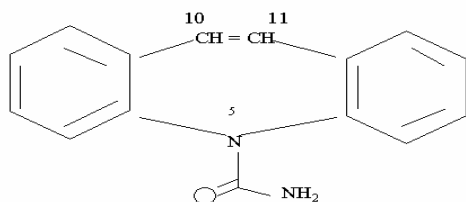
BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON CARBAMAZEPINE ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

8
9 **Before prescribing Carbatrol, the physician should be thoroughly familiar with the details of this prescribing information, particularly**
10 **regarding use with other drugs, especially those which accentuate toxicity potential.**

11
12 **DESCRIPTION**

13 CARBATROL* is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as 100 mg, 200 mg and 300
14 mg extended-release capsules of Carbamazepine, USP. Carbamazepine is a white to off-white powder, practically insoluble in water and soluble
15 in alcohol and in acetone. Its molecular weight is 236.27. Its chemical name is 5H-dibenz[b,f]azepine-5-carboxamide, and its structural formula is:

16
17
18
19 * Registered in the US Patent and Trade Office.



CARBAMAZEPINE

Carbatrol is a multi-component capsule formulation consisting of three different types of beads: immediate-release beads, extended-release beads, and enteric-release beads. The three bead types are combined in a specific ratio to provide twice daily dosing of Carbatrol.

Inactive ingredients: citric acid, colloidal silicon dioxide, lactose monohydrate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, talc, triethyl citrate and other ingredients.

The 100 mg capsule shells contain gelatin-NF, FD&C Blue #2, Yellow Iron Oxide, and titanium dioxide and are imprinted with white ink; the 200 mg capsule shells contain gelatin-NF, FD&C Red #3, FD&C Yellow #6, Yellow Iron Oxide, FD&C Blue #2, and titanium dioxide, and are imprinted with white ink; and the 300 mg capsule shells contain gelatin-NF, FD&C Blue #2, FD&C Yellow #6, Red Iron Oxide, Yellow Iron Oxide, and titanium dioxide, and are imprinted with white ink.

CLINICAL PHARMACOLOGY

In controlled clinical trials, carbamazepine has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

Mechanism of Action

Carbamazepine has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Carbamazepine greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Carbamazepine is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

46 The principal metabolite of carbamazepine, carbamazepine-10,11-epoxide, has anticonvulsant activity as demonstrated in several *in vivo* animal
47 models of seizures. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and
48 efficacy of carbamazepine has not been established.

49 50 **Pharmacokinetics**

51 **Carbamazepine (CBZ):** Taken every 12 hours, carbamazepine extended-release capsules provide steady state plasma levels comparable to
52 immediate-release carbamazepine tablets given every 6 hours, when administered at the same total mg daily dose.

53
54 Following a single 200 mg oral extended-release dose of carbamazepine, peak plasma concentration was 1.9 ± 0.3 $\mu\text{g/mL}$ and the time to reach
55 the peak was 19 ± 7 hours. Following chronic administration (800 mg every 12 hours), the peak levels were 11.0 ± 2.5 $\mu\text{g/mL}$ and the time to
56 reach the peak was 5.9 ± 1.8 hours. The pharmacokinetics of extended-release carbamazepine is linear over the single dose range of 200-800
57 mg.

58
59 Carbamazepine is 76% bound to plasma proteins. Carbamazepine is primarily metabolized in the liver. Cytochrome P450 3A4 was identified as
60 the major isoform responsible for the formation of carbamazepine-10,11-epoxide. Since carbamazepine induces its own metabolism, the half-life is
61 also variable. Following a single extended-release dose of carbamazepine, the average half-life range from 35-40 hours and 12-17 hours on
62 repeated dosing. The apparent oral clearance following a single dose was 25 ± 5 mL/min and following multiple dosing was 80 ± 30 mL/min.

63
64 After oral administration of ^{14}C -carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary
65 radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine.

66
67 **Carbamazepine-10,11-epoxide (CBZ-E):** Carbamazepine-10,11-epoxide is considered to be an active metabolite of carbamazepine. Following a
68 single 200 mg oral extended-release dose of carbamazepine, the peak plasma concentration of carbamazepine-10,11-epoxide was 0.11 ± 0.012
69 $\mu\text{g/mL}$ and the time to reach the peak was 36 ± 6 hours. Following chronic administration of a extended-release dose of carbamazepine (800 mg
70 every 12 hours), the peak levels of carbamazepine-10,11-epoxide were 2.2 ± 0.9 $\mu\text{g/mL}$ and the time to reach the peak was 14 ± 8 hours. The
71 plasma half-life of carbamazepine-10,11-epoxide following administration of carbamazepine is 34 ± 9 hours. Following a single oral dose of
72 extended-release carbamazepine (200-800 mg) the AUC and C_{max} of carbamazepine-10,11-epoxide were less than 10% of carbamazepine.
73 Following multiple dosing of extended-release carbamazepine (800-1600 mg daily for 14 days), the AUC and C_{max} of carbamazepine-10,11-
74 epoxide were dose related, ranging from 15.7 $\mu\text{g}\cdot\text{hr/mL}$ and 1.5 $\mu\text{g/mL}$ at 800 mg/day to 32.6 $\mu\text{g}\cdot\text{hr/mL}$ and 3.2 $\mu\text{g/mL}$ at 1600 mg/day,
75 respectively, and were less than 30% of carbamazepine. Carbamazepine-10,11-epoxide is 50% bound to plasma proteins.

76
77 **Food Effect:** A high fat meal diet increased the rate of absorption of a single 400 mg dose (mean T_{max} was reduced from 24 hours, in the fasting
78 state, to 14 hours and C_{max} increased from 3.2 to 4.3 $\mu\text{g/mL}$) but not the extent (AUC) of absorption. The elimination half-life remains unchanged
79 between fed and fasting state. The multiple dose study conducted in the fed state showed that the steady-state C_{max} values were within the
80 therapeutic concentration range. The pharmacokinetic profile of extended-release carbamazepine was similar when given by sprinkling the beads
81 over applesauce compared to the intact capsule administered in the fasted state.

82

83

84 Special Populations

85 **Hepatic Dysfunction:** The effect of hepatic impairment on the pharmacokinetics of carbamazepine is not known. However, given that
86 carbamazepine is primarily metabolized in the liver, it is prudent to proceed with caution in patients with hepatic dysfunction.

87

88 **Renal Dysfunction:** The effect of renal impairment on the pharmacokinetics of carbamazepine is not known.

89

90 **Gender:** No difference in the mean AUC and C_{max} of carbamazepine and carbamazepine-10,11-epoxide was found between males and females.

91

92 **Age:** Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide in young children than adults. In children below the age of 15,
93 there is an inverse relationship between CBZ-E/CBZ ratio and increasing age.

94

95 **Race:** No information is available on the effect of race on the pharmacokinetics of carbamazepine.

96

97 INDICATIONS AND USAGE**98 Epilepsy**

99 Carbatrol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of carbamazepine as an anticonvulsant was derived from
100 active drug-controlled studies that enrolled patients with the following seizure types:

- 101 1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater
102 improvements than those with other types.
- 103 2. Generalized tonic-clonic seizures (grand mal).
- 104 3. Mixed seizure patterns which include the above, or other partial or generalized seizures. Absence seizures (petit mal) do not appear to
105 be controlled by carbamazepine (see PRECAUTIONS, General).

106

107 Trigeminal Neuralgia

108 Carbatrol is indicated in the treatment of the pain associated with true trigeminal neuralgia. Beneficial results have also been reported in
109 glossopharyngeal neuralgia. This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

110

111 CONTRAINDICATIONS

112 Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known
113 sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline and nortriptyline. Likewise, on theoretical
114 grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be
115 discontinued for a minimum of 14 days, or longer if the clinical situation permits.

116

117 WARNINGS

118 Patients should be made aware that Carbatrol contains carbamazepine and should not be used in combination with any other medications
119 containing carbamazepine.

120

Usage in Pregnancy

121 Carbamazepine can cause fetal harm when administered to a pregnant woman.

123

124 Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital
125 malformations, including spina bifida. The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling
126 women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should
127 be apprised of the potential hazard to the fetus.

128

129 Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with
130 the use of anticonvulsants in combination therapy.

131

132 In humans, transplacental passage of carbamazepine is rapid (30-60 minutes), and the drug is accumulated in the fetal tissues, with higher levels
133 found in liver and kidney than in brain and lung.

134

135 Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum
136 human daily dosage (MHDD) of 1200 mg on a mg/kg basis or 1.5-4 times the MHDD on a mg/m² basis. In rat teratology studies, 2 of 135 offspring
137 showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In
138 reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200
139 mg/kg.

140

141 Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the
142 strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of
143 the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be
144 considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the
145 developing embryo or fetus.

146

147 Tests to detect defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving
148 carbamazepine.

149

General

150 Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

152

153 Severe dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome have been reported with
154 carbamazepine. These reactions have been extremely rare. However, a few fatalities have been reported.

155

156 In patients with seizure disorder, carbamazepine should not be discontinued abruptly because of the strong possibility of precipitating status
157 epilepticus with attendant hypoxia and threat to life.

158
159 Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during
160 therapy.

161
162 Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of
163 confusion or agitation should be considered.

164
165 Co-administration of carbamazepine and delavirdine may lead to loss of virologic response and possible resistance to PRESCRIPTOR or to the
166 class of non-nucleoside reverse transcriptase inhibitors.

167 168 **PRECAUTIONS**

169 **General**

170 Before initiating therapy, a detailed history and physical examination should be made.

171
172 Carbamazepine should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these
173 patients carbamazepine has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

174
175 Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic, or renal damage; adverse
176 hematologic reaction to other drugs; or interrupted courses of therapy with carbamazepine.

177 178 **Information for Patients**

179 Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers
180 in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or
181 symptoms appear.

182
183 Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in
184 other potentially dangerous tasks.

185
186 If necessary, the Carbatrol capsules can be opened and the contents sprinkled over food, such as a teaspoon of applesauce or other similar food
187 products. Carbatrol capsules or their contents should not be crushed or chewed.

188
189 Carbatrol may interact with some drugs. Therefore, patients should be advised to report to their doctors the use of any other prescription or non-
190 prescription medication or herbal products.

191 192 **Laboratory Tests**

193 Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in
194 the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of
195 the drug should be considered if any evidence of significant bone marrow depression develops.

196
197 Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with
198 this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver
199 disease.

200
201 Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and
202 related drugs have been shown to cause eye changes.

203
204 Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed
205 renal dysfunction.

206
207 Increases in total cholesterol, LDL and HDL have been observed in some patients taking anticonvulsants. Therefore, periodic evaluation of these
208 parameters is also recommended.

209
210 Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be
211 particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum
212 levels may aid in determining the cause of toxicity when more than one medication is being used.

213
214 Thyroid function tests have been reported to show decreased values with carbamazepine administered alone.

215
216 Hyponatremia has been reported in association with carbamazepine use, either alone or in combination with other drugs.

217
218 Interference with some pregnancy tests has been reported.

219 220 **Drug Interactions**

221 Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to the following:

222 223 **Agents Highly Bound to Plasma Protein:**

224 Carbamazepine is not highly bound to plasma proteins; therefore, administration of Carbatrol® to a patient taking another drug that is highly
225 protein bound should not cause increased free concentrations of the other drug.

226 227 **Agents that Inhibits Cytochrome P450 Isoenzymes and/or Epoxide Hydrolase:**

228 Carbamazepine is metabolized mainly by cytochrome P450 (CYP) 3A4 to the active carbamazepine 10,11-epoxide, which is further metabolized
229 to the trans-diol by epoxide hydrolase. Therefore, the potential exists for interaction between carbamazepine and any agent that inhibits CYP3A4

230 and/or epoxide hydrolase. Agents that are CYP3A4 inhibitors that have been found, or are expected, to increase plasma levels of Carbatrol® are
231 the following:

232
233 *Acetazolamide, azole antifungals, cimetidine, clarithromycin⁽¹⁾, dalfopristin, danazol, delavirdine, diltiazem, erythromycin⁽¹⁾, fluoxetine,*
234 *fluvoxamine, grapefruit juice, isoniazid, itraconazole, ketoconazole, loratadine, nefazadone, niacinamide, nicotinamide, protease*
235 *inhibitors, propoxyphene, quinine, quinupristin, troleandomycin, valproate⁽¹⁾, verapamil, zileuton.*

236
237 ⁽¹⁾also inhibits epoxide hydrolase resulting in increased levels of the active metabolite carbamazepine 10, 11- epoxide

238
239 Thus, if a patient has been titrated to a stable dosage of Carbatrol®, and then begins a course of treatment with one of these CYP3A4 or epoxide
240 hydrolase inhibitors, it is reasonable to expect that a dose reduction for Carbatrol® may be necessary.

241 **Agents that Induce Cytochrome P450 Isoenzymes:**

242 Carbamazepine is metabolized by CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent that induces
243 CYP3A4. Agents that are CYP inducers that have been found, or are expected, to decrease plasma levels of Carbatrol® are the following:

244
245 *Cisplatin, doxorubicin HCL, felbamate, rifampin, phenobarbital, phenytoin⁽²⁾, primidone, methsuximide, and theophylline*

246
247
248 ⁽²⁾Phenytoin plasma levels have also been reported to increase and decrease in the presence of carbamazepine, see below.

249
250 Thus, if a patient has been titrated to a stable dosage on Carbatrol®, and then begins a course of treatment with one of these CYP3A4 inducers, it
251 is reasonable to expect that a dose increase for Carbatrol® may be necessary.

252 **Agents with Decreased Levels in the Presence of Carbamazepine due to Induction of Cytochrome P450 Enzymes:**

253 Carbamazepine is known to induce CYP1A2 and CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent
254 metabolized by one (or more) of these enzymes. Agents that have been found, or are expected to have decreased plasma levels in the presence
255 of Carbatrol® due to induction of CYP enzymes are the following:

256
257
258 *Acetaminophen, alprazolam, amitriptyline, bupropion, buspirone, citalopram, clobazam, clonazepam, clozapine, cyclosporin, delavirdine,*
259 *desipramine, diazepam, dicumarol, doxycycline, ethosuximide, felbamate, felodipine, glucocorticoids, haloperidol, itraconazole,*
260 *lamotrigine, levothyroxine, lorazepam, methadone, midazolam, mirtazapine, nortriptyline, olanzapine, oral contraceptives⁽³⁾,*
261 *oxcarbazepine, phenytoin⁽⁴⁾, praziquantel, protease inhibitors, quetiapine, risperidone, theophylline, topiramate, tiagabine, tramadol,*
262 *triazolam, trazodone⁽⁵⁾, valproate, warfarin⁽⁶⁾, ziprasidone, and zonisamide.*

263
264 ⁽³⁾Break through bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be
265 adversely affected.

266 ⁽⁴⁾Phenytoin has also been reported to increase in the presence of carbamazepine. Careful monitoring of phenytoin plasma levels
267 following co-medication with carbamazepine is advised.

268 ⁽⁵⁾Following co-administration of carbamazepine 400 mg/day with trazodone 100 mg to 300 mg daily, carbamazepine reduced trough
269 plasma concentrations of trazodone (as well as meta-chlorophenylpiperazine [mCPP]) by 76 and 60%, respectively, compared to
270 precarbamazepine values.

271 ⁽⁶⁾Warfarin's anticoagulant effect can be reduced in the presence of carbamazepine.

272
273 Thus, if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of treatment with
274 Carbatrol®, it is reasonable to expect that a dose increase for the concomitant agent may be necessary.

275 **Agents with Increased Levels in the Presence of Carbamazepine:**

276 Carbatrol® increases the plasma levels of the following agents:

277
278 *Clomipramine HCl, phenytoin⁽⁷⁾, and primidone*

280
281 ⁽⁷⁾Phenytoin has also been reported to decrease in the presence of carbamazepine. Careful monitoring of phenytoin plasma levels
282 following co-medication with carbamazepine is advised.

283
284 Thus, if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of the treatment
285 with Carbatrol®, it is reasonable to expect that a dose decrease for the concomitant agent may be necessary.

286 **Pharmacological/Pharmacodynamic Interactions with Carbamazepine**

287 Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

288
289 Given the anticonvulsant properties of carbamazepine, Carbatrol® may reduce the thyroid function as has been reported with other
290 anticonvulsants. Additionally, anti-malarial drugs, such as chloroquine and mefloquine, may antagonize the activity of carbamazepine.

291
292 Thus if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of treatment with Carbatrol®,
293 it is reasonable to expect that a dose adjustment may be necessary.

294
295 Because of its primary CNS effect, caution should be used when Carbatrol® is taken with other centrally acting drugs and alcohol.

296 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

297
298 Administration of carbamazepine to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day (low dose approximately
299 0.2 times the maximum human daily dose of 1200 mg on a mg/m² basis), resulted in a dose-related increase in the incidence of hepatocellular
300 tumors in females and of benign interstitial cell adenomas in the testes of males.

301
302

303 Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using
304 carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present,
305 unknown.

306

307 **Usage in Pregnancy**

308 Pregnancy Category D (See WARNINGS)

309

310 **Labor and Delivery**

311 The effect of carbamazepine on human labor and delivery is unknown.

312

313 **Nursing Mothers**

314 Carbamazepine and its epoxide metabolite are transferred to breast milk and during lactation. The concentrations of carbamazepine and its
315 epoxide metabolite are approximately 50% of the maternal plasma concentration. Because of the potential for serious adverse reactions in nursing
316 infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the
317 importance of the drug to the mother.

318

319 **Pediatric Use**

320 Substantial evidence of carbamazepine effectiveness for use in the management of children with epilepsy (see INDICATIONS for specific seizure
321 types) is derived from clinical investigations performed in adults and from studies in several *in vitro* systems which support the conclusion that (1)
322 the pathogenic mechanisms underlying seizure propagation are essentially identical in adults and children, and (2) the mechanism of action of
323 carbamazepine in treating seizures is essentially identical in adults and children.

324

325 Taken as a whole, this information supports a conclusion that the generally acceptable therapeutic range of total carbamazepine in plasma (i.e., 4-
326 12 µg/mL) is the same in children and adults.

327

328 The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in children has been
329 systematically studied up to 6 months. No longer term data from clinical trials is available.

330

331 **Geriatric Use**

332 No systematic studies in geriatric patients have been conducted.

333

334 **ADVERSE REACTIONS**

335 **General:** If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of
336 any anticonvulsant drug in a responsive patient with epilepsy may lead to seizures or even status epilepticus with its life-threatening hazards.

337

338 The most severe adverse reactions previously observed with carbamazepine were reported in the hemopoietic system (see BOX WARNING), the
339 skin, and the cardiovascular system.

340
341 The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness,
342 nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the lowest dosage recommended.
343

344 The following additional adverse reactions were previously reported with carbamazepine:
345

346 **Hemopoietic System:** Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis,
347 eosinophilia, acute intermittent porphyria.
348

349 **Skin:** Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome
350 (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura,
351 aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary.
352 Isolated cases of hirsutism have been reported, but a causal relationship is not clear.
353

354 **Cardiovascular System:** Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of
355 coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy. Some of these
356 cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.
357

358 **Liver:** Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.
359

360 **Respiratory System:** Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.
361

362 **Genitourinary System:** Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence.
363 Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported.
364

365 Testicular atrophy occurred in rats receiving carbamazepine orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats
366 receiving carbamazepine in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy
367 and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50
368 mg/kg/day and higher. Relevance of these findings to humans is unknown.
369

370 **Nervous System:** Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations,
371 transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and
372 paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.
373

374 There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions
375 to the drug has not been established.
376

377 Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of psychotropic drugs.

378

379 **Digestive System:** Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and
380 pharynx, including glossitis and stomatitis.

381

382 **Eyes:** Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been
383 established, many phenothiazines and related drugs have been shown to cause eye changes.

384

385 **Musculoskeletal System:** Aching joints and muscles, and leg cramps.

386

387 **Metabolism:** Fever and chills, inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication,
388 with decreased serum sodium (hyponatremia) and confusion have been reported in association with carbamazepine use (see PRECAUTIONS,
389 Laboratory Tests). Decreased levels of plasma calcium have been reported.

390

391 **Other:** Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of
392 cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.

393

394 A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in
395 combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with
396 carbamazepine.

397

398 **DRUG ABUSE AND DEPENDENCE**

399 No evidence of abuse potential has been associated with carbamazepine, nor is there evidence of psychological or physical dependence in
400 humans.

401

402 **OVERDOSAGE**

403 **Acute Toxicity**

404 Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-
405 year-old boy); small children, 5 g (3-year-old girl).

406

407 Oral LD₅₀ in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

408

409 **Signs and Symptoms**

410 The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally
411 milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

412

413 **Respiration:** Irregular breathing, respiratory depression.

414
415 **Cardiovascular System:** Tachycardia, hypotension or hypertension, shock, conduction disorders.
416

417 **Nervous System and Muscles:** Impairment of consciousness ranging in severity to deep coma.
418 Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness,
419 dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.
420

421 **Gastrointestinal Tract:** Nausea, vomiting.
422

423 **Kidneys and Bladder:** Anuria or oliguria, urinary retention
424

425 **Laboratory Findings:** Isolated instances of overdose have included leukocytosis, reduced leukocyte count, glycosuria, and acetonuria. EEG
426 may show dysrhythmias.
427

428 **Combined Poisoning:** When alcohol, tricyclic antidepressants, barbiturates, or hydantoins are taken at the same time, the signs and symptoms
429 of acute poisoning with carbamazepine may be aggravated or modified.
430

431 **Treatment**

432 For the most up to date information on management of carbamazepine overdose, please contact the poison center for your area by calling
433 1-800-222-1222. The prognosis in cases of carbamazepine poisoning is generally favorable. Of 5,645 cases of carbamazepine exposures
434 reported to US poison centers in 2002, a total of 8 deaths (0.14% mortality rate) occurred. Over 39% of the cases reported to these poison
435 centers were managed safely at home with conservative care. Successful management of large or intentional carbamazepine exposures requires
436 implementation of supportive care, frequent monitoring of serum drug concentrations, as well as aggressive but appropriate gastric
437 decontamination.
438

439 **Elimination of the Drug:** The primary method for gastric decontamination of carbamazepine overdose is use of activated charcoal. For
440 substantial recent ingestions, gastric lavage may also be considered. Administration of activated charcoal prior to hospital assessment has the
441 potential to significantly reduce drug absorption. There is no specific antidote. In overdose, absorption of carbamazepine may be prolonged and
442 delayed. More than one dose of activated charcoal may be beneficial in patients that have evidence of continued absorption (e.g., rising serum
443 carbamazepine levels).
444

445 **Measures to Accelerate Elimination:**

446 The data on use of dialysis to enhance elimination in carbamazepine is scarce. Dialysis, particularly high flux or high efficiency hemodialysis, may
447 be considered in patients with severe carbamazepine poisoning associated with renal failure or in cases of status epilepticus, or where there are
448 rising serum drug levels and worsening clinical status despite appropriate supportive care and gastric decontamination. For severe cases of
449 carbamazepine overdose unresponsive to other measures, charcoal hemoperfusion may be used to enhance drug clearance.
450

451 **Respiratory Depression:** Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of
452 oxygen.

453
454 **Hypotension, Shock:** Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to
455 increase plasma volume, use of vasoactive substances should be considered.

456
457 **Convulsions:** Diazepam or barbiturates.

458
459 **Warning:** Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates
460 should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within 1
461 week).

462
463 **Surveillance:** Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder
464 function should be monitored for several days.

465
466 **Treatment of Blood Count Abnormalities:** If evidence of significant bone marrow depression develops, the following recommendations are
467 suggested: (1) stop the drug, (2) perform daily CBC, platelet, and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy
468 immediately and repeat with sufficient frequency to monitor recovery.

469
470 Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ⁵⁹Fe-ferrokinetic studies, (3) peripheral blood cell
471 typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin
472 electrophoresis for A₂ and F hemoglobin, and (7) serum folic acid and B₁₂ levels.

473
474 A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

475 476 **DOSAGE AND ADMINISTRATION**

477 Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be
478 adjusted to the needs of the individual patients. A low initial daily dosage with gradual increase is advised. As soon as adequate control is
479 achieved, the dosage may be reduced very gradually to the minimum effective level. The Carbatrol capsules may be opened and the beads
480 sprinkled over food, such as a teaspoon of applesauce or other similar food products if this method of administration is preferred. Carbatrol
481 capsules or their contents should not be crushed or chewed. Carbatrol can be taken with or without meals.

482
483 Carbatrol is an extended-release formulation for twice a day administration. When converting patients from immediate release carbamazepine to
484 Carbatrol extended-release capsules, the same total daily mg dose of carbamazepine should be administered.

485
486 **Epilepsy** (see INDICATIONS AND USAGE)

487 **Adults and children over 12 years of age. Initial:** 200 mg twice daily. Increase at weekly intervals by adding up to 200 mg/day until the optimal
 488 response is obtained. Dosage generally should not exceed 1000 mg per day in children 12-15 years of age, and 1200 mg daily in patients above
 489 15 years of age. Doses up to 1600 mg daily have been used in adults. **Maintenance:** Adjust dosage to the minimum effective level, usually 800-
 490 1200 mg daily.

491
 492 **Children under 12 years of age:** Children taking total daily dosages of immediate-release carbamazepine of 400 mg or greater may be converted
 493 to the same total daily dosage of Carbatrol extended-release capsules, using a twice daily regimen. Ordinarily, optimal clinical response is
 494 achieved at daily doses below 35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine
 495 whether or not they are in the therapeutic range. No recommendation regarding the safety of Carbatrol for use at doses above 35 mg/kg/24 hours
 496 can be made.

497
 498 **Combination Therapy:** Carbatrol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug
 499 should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be
 500 increased (see PRECAUTIONS, Drug Interactions, and Pregnancy Category D).

501
 502 **Trigeminal Neuralgia** (see INDICATIONS AND USAGE)

503 **Initial:** On the first day, start with one 200 mg capsule. This daily dose may be increased by up to 200 mg/day every 12 hours only as needed to
 504 achieve freedom from pain. Do not exceed 1200 mg daily.

505
 506 **Maintenance:** Control of pain can be maintained in most patients with 400-800 mg daily. However, some patients may be maintained on as little
 507 as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts
 508 should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

509
 510 **HOW SUPPLIED**

511 **Carbatrol (carbamazepine) extended-release capsules is supplied in three dosage strengths.**

512
 513 **100 mg-Two-piece hard gelatin capsule (bluish green opaque body and cap) printed with the Shire logo in white ink.**

514
 515 Supplied in bottles of 120..... NDC 54092-171-12

516
 517 **200 mg-Two-piece hard gelatin capsule (light gray opaque body with bluish green opaque cap) printed with the Shire logo in white ink.**

518
 519 Supplied in bottles of 120NDC 58521-172-12

520
 521 **300 mg-Two-piece hard gelatin capsule (black opaque body with bluish green opaque cap) printed with the Shire logo in white ink.**

522

523 Supplied in bottles of 120NDC 58521-173-12

524

525 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature].

526 PROTECT FROM LIGHT AND MOISTURE.

527

528 Manufactured for:

529 **Shire US Inc.**

530 725 Chesterbrook Blvd, Wayne PA 19087

531 1-800-828-2088, Made in U.S.A. © 2005 Shire US Inc.

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534