

Note: Pharma code/ Bar code and adjacent text must be visible on folded leaflet.

Carbamazepine Tablets, USP, 200 mg, and Carbamazepine Tablets, USP (Chewable),100 mg Rx Only

Prescribing Information

WARNINGS

4525

Carbamazepine

Tablets, USP, 200 mg

and Carbamazepine

Tablets, USP (Chewable)

100 ma

08099964

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH CARBAMAZEPINE. THESE REACTIONS ARE ESTIMATED TO OCCUB IN 1 TO 6 PER 10.000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS O ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD B SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH CARBAMAZEPINE. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH CARBAMAZEPINE UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE WARNINGS AND PRECAUTIONS, LABORATORY TESTS).

APLASTIC ANEMIA AND AGRANULOCYTOSIS 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 TO 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 OB OUTCOME HOWEVER THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OF AGRANULOCYTOSIS.

BECALLSE OF THE VERY LOW INCIDENCE OF AGRANILL OCYTOSIS 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.

Before prescribing carbamazepine, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential. DESCRIPTION

Carbamazepine USP, is an anticonvulsant and specific analogsic for trigeminal neuralgia, available for oral administration as chewable tablets of 100 mg and tablets of 200 mg. Its chemical name is 5H-dibenz[b,f]azepine-5-carboxamide, and its structural formula is



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Carbamazepine tablets, USP, 200 mg contain the inactive ingredients: colloidal silicon dioxide, FD&C Red #40 aluminum lake, hypromellose, magnesium stearate, pregelatinized maize starch, corn starch, and sodium starch glycolate.

Carbamazepine tablets. USP. (chewable) contain the inactive ingredients: artificial flavors, colloidal silicon dioxide, compressible sugar, corn starch, FD&C Red #40 aluminum lake, hydroxypropyl methyl cellulose, magnesium stearate, and sodium starch glycolate.

Carbamazepine tablets, USP, 200 mg meet USP Dissolution Test 2 and Carbamazepine Tablets USP (Chewable), 100 mg meet USP Diss olution Test 1

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.

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

Pharmacokinetics

In clinical studies, Tegretol suspension, conventional tablets, and extended-release tablets delivered somewhat faster, and the extended-release tablet slightly slower, than the conventional tablet. The bioavailability of the extended-release tablet was 89% compared to suspension. Following a twice a day dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On the other hand, following a three times a day dosage regimen, Tegretol suspension affords steady-state plasma levels comparable to carbamazepine tablets given twice a day when administered at the same total mg daily dose. Following a twice a day dosage regimen, Tegretol-XR tablets afford steady-state plasma levels comparable to conventional carbamazepine tablets given four times a day, when administered at the same total mg daily dose. Carbamazepine in blood is 76% bound to plasma proteins. Plasma levels of carbamagepine are variable and may range from 0.5 to 25 mg/mL, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 mg/mL. In polytherapy, the concentration of carbamazepine and concomitant drugs may be increased o ring therapy, and drug effects may be altered (see PRECAUTIONS, Drug Interact Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4 to 5 hours after administration of conventional carbamazepine tablets, and 3 to 12 hours after administration of Tegretol-XR tablets. The CSF/serum ratio is 0.22, similar to the 24% unbound carbamazepine in serum. Because carbamazepine induces its own metabolism, the half-life s also variable. Autoinduction is completed after 3 to 5 weeks of a fixed dosing regimen. Initial half-life values range from 25 to 65 hours, decreasing to 12 to 17 hours on repeated doses. Carbamazepine is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from carbamazepine. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide. After oral adm ¹⁴C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites with only 3% of unchanged carbamazepine.

The pharmacokinetic parameters of carbamazepine disposition are similar in children and in adults. However there is a poor correlation between plasma concentrations of carbamazenine and carbamazepine dose in children. Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide (a metabolite shown to be equipotent to carbamazepine as an cardinazepine to, in reported a metabolic shown to be equipotent to cardinazepine as an anticonvilsanti in animal screens) in the younger age groups than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age (in one report from 0.44 in children below the age of 1 year to 0.18 in children between 10 to 15 years of age). The effects of race and gender on carbamazepine pharmacokinetics have not been systematically

INDICATIONS AND USAGE

Epilepsy

Carbamazepine is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled

natients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these eizures appear to show greater improvement than those with other types Generalized tonic-clonic seizures (grand mal).

3. Mixed seizure patterns which include the above, or other partial or generalized seizures. Absence seizures (petit mal) do not appear to be controlled by carbamazepine (see PRECAUTIONS, General)

Trigeminal Neuralgia

Carbamazepine is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia. This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains

CONTRAINDICATIONS

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

Coadministration of carbamazepine and nefazodone may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve a therapeutic effect. Coadministration of carbamazepine with nefazodone is contraindicated.

WARNINGS Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with carbamazepine treatment. The risk of these events is estimated to be about 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. However, the risk in some Asian countries is estimated to be about 10 times higher. Carbamazepine should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

SJS/TEN and HLA-B*1502 Allele

etrospective case-control studies have found that in patients of Chinese ancestry there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of an inherited variant of the HLA-B gene, HLA-B*1502. The occurrence of higher rates of these reactions in countries with higher frequencies of this allele suggests that the risk may be increased in allele-positive individuals of any ethnicity.

Across Asian populations, notable variation exists in the prevalence of HLA-B*1502. Greater than 15% of the population is reported positive in Horn Kong, Thaland, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B*1502, averaging 2% to 4%, but higher in some groups. HLA-B*1502 is present in less than 1% of the population in Japan and Korea. HLA-B*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, lispanics and Native Americans)

Prior to initiating carbamazepine therapy, testing for HLA-B*1502 should be performed in patients with ancestry in populations in which HLAB*1502 may be present. In deciding which patients to screen, the rates provided above for the prevalence of HLA-B*1502 may offer a rough

uide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood and of mixed ancestry. Carbamazepine should not be used in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks. Tested patients who are found to be negative for the allele are thought to have a low risk of SJS/TEN (see BOXED WARNING and PRECAUTIONS, Laboratory Tests).

Over 90% of carbamazepine treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration in determining the need for screening of genetically at-risk patients currently on carbamazepine. The HI A-B*1502 allele has not been found to predict risk of less severe adverse cutaneous reactions

from carbamazepine, such as maculopapular eruption (MPE) or to predict Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in

patients of Chinese ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable.

Hypersensitivity Reactions and HLA-A*3101 Allele

Retrospective case-control studies in patients of European, Korean, and Japanese ancestry have found a moderate association between the risk of developing hypersensitivity reactions and the presence of HLA-A*3101, an inherited allelic variant of the HLA-A gene, in patients using carbamazepine. These ppersensitivity reactions include SJS/TEN, maculopapular eruptions, and Drug Reaction with osinophilia and Systemic Symptoms (see DRESS/Multiorgan hypersensitivity below). HLA-A*3101 is expected to be carried by more than 15% of patients of Japanese, Native American, Southern Indian (for example, Tamil Nadu), and some Arabic ancestry; up to about 10% in patients of Han Chinese, Korean, European, Latin American, and other Indian ancestry; and up to about 5% in African-Americans and patients of Thai, Taiwanese, and Chinese (Hong Kong) ancestry.

The risks and benefits of carbamazepine therapy should be weighed before considering carbamazepine in patients known to be positive for HLA-A*3101.

Application of HLA genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B *1502-positive and HLA-A *3101-positive patients treated with carbamazepine will not develop SJS/TEN or other ensitivity reactions, and these reactions can still occur infrequently in HLA-B*1502-negative welopment of, and morbidity from, SJS/TEN and other hypersensitivity reactions, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of natologic monitoring, have not been studied.

Aplastic Anemia and Agranulocytosis

Aplastic anemia and agranulocytosis have been reported in association with the use of carbamazepine (see BOXED WARNING). Patients with a history of adverse hematologic reaction to any drug may be particularly at risk of bone marrow depression.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has occurred with carbamazepine. Some of these events have been fatal or Infer-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Carbamazepir should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Hypersensitivity reactions to carbamazepine have been reported in patients who previously

experienced this reaction to anticonvulsants including phenytoin, primidone, and phenobarbital. If such history is present, benefits and risks should be carefully considered and, if carbamazepine is initiated, the signs and symptoms of hypersensitivity should be carefully monitored. Patients should be informed that about a third of patients who have had hypersensitivity reactions to

carbamazepine also experience hypersensitivity reactions with oxcarbazepine (Trileptal®). Anaphylaxis and Angioedema

Rare cases of anaphylaxis and angioedema involving the larynx, glottis, lips, and eyelids have been reported in patients after taking the first or subsequent doses of carbamazepine. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after nazepine, the drug should be discontinued and an alternative treatment started atment with carba hese patients should not be rechallenged with the drug.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including carbamazepine, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts o behavior, and/or any unusual changes in mood or behavior

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% Cl:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the nated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients wa 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as e after starting drug treatment with AEDs and persisted for the duration of treatme Because most trials included in the analysis did not extend beyond 24 weeks, the thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in The finding of increased risk with AEDs of varying mechanisms of action and a indications suggests that the risk applies to all AEDs used for any indication. The substantially by age (5 to 100 years) in the clinical trials analyzed. Table 1 shows abs risk by indication for all evaluated AEDs.

Indication	Placebo Patients with Events Per 1,000 Patients	Drug Patients with Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Dif Additior Patients Events F Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

nical trials for psychiatric or other conditions, but the absolute risk differences we epilepsy and psychiatric indications.

Anyone considering prescribing carbamazepine or any other AED must balance th thoughts or behavior with the risk of untreated illness. Epilepsy and many other illr AEDs are prescribed are themselves associated with morbidity and mortality and an suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge duri needs to consider whether the emergence of these symptoms in any give related to the illness being treated.

General

Carbamazepine has shown mild anticholinergic activity that may be associated intraocular pressure; therefore, patients with increased intraocular pressure sh observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility tent psychosis and, in elderly patients, of confusion or agitation should be borne The use of carbamazepine should be avoided in patients with a history of hepatic acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda). Acute att reported in such patients receiving carbamazepine therapy. Carbamazepine administ been demonstrated to increase porphyrin precursors in rodents, a presumed mec induction of acute attacks of porphyria

As with all antiepileptic drugs, carbamazepine should be withdrawn gradually potential of increased seizure frequency.

Hyponatremia can occur as a result of treatment with carbamazepine. In m hyponatremia appears to be caused by the syndrome of inappropriate antidiuretic ho SIADH). The risk of developing SIADH with carbamazepine treatment appears to Elderly patients and patients treated with diuretics are at greater risk of developing Signs and symptoms of hyponatermia include headache, new or increased se difficulty concentrating, memory impairment, confusion, weakness, and unsteadi lead to falls. Consider discontinuing carbamazepine in patients with symptomatic h Usage in Pregnancy

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

Epidemiological data suggest that there may be an association between the use of during pregnancy and congenital malformations, including spina bifida. There have a that associate carbamazepine with developmental disorders and congenital craniofacial defects, cardiovascular malformations, and anomalies involving various Developmental delays based on neurobehavioral assessments have been reported. counseling women of childbearing potential, the prescribing physician will wish to w of therapy against the risks. If this drug is used during pregnancy, or if the patient be while taking this drug, the patient should be apprised of the potential hazard to the fet Retrospective case reviews suggest that, compared with monotherapy, there m prevalence of teratogenic effects associated with the use of anticonvulsants in comb Therefore, if therapy is to be continued, monotherapy may be preferable for pregnan In humans, transplacental passage of carbamazepine is rapid (30 to 60 minutes), accumulated in the fetal tissues, with higher levels found in liver and kidney than in Carbamazepine has been shown to have adverse effects in reproduction studies in orally in dosages 10 to 25 times the maximum human daily dosage (MHDD) of 1200 basis or 1.5 to 4 times the MHDD on a mg/m² basis. In rat teratology studies, 2 howed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, n rated a lack of weight gain and an unkempt appearance at a maternal dos mg/kg.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug to prevent major seizures because of the strong possibility of precipitating status attendant hypoxia and threat to life. In individual cases where the severity and seizure disorder are such that removal of medication does not pose a serious thre ntinuation of the drug may be considered prior to and during pregnancy, altho said with any confidence that even minor seizures do not pose some hazard to embryo or fetus

Tests to detect defects using currently accepted procedures should be considered prenatal care in childbearing women receiving carbamazepine.

There have been a few cases of neonatal seizures and/or respiratory depression maternal carbamazepine and other concomitant anticonvulsant drug use. A few c vomiting, diarrhea, and/or decreased feeding have also beer reported in associatio carbamazepine use. These symptoms may represent a neonatal withdrawal syndrom

To provide information regarding the effects of in utero exposure to carbamazepin advised to recommend that pregnant patients taking carbamazepine enroll in the N Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the to 1-888-233-2334, and must be done by patients themselves. Information on the regis found at the website http://www.aedpregnancyregistry.org/. PRECAUTIONS

Before initiating therapy, a detailed history and physical examination should be made Carbamazepine should be used with caution in patients with a mixed seizure disor typical absence seizures, since in these patients carbamazepine has been associate requency of generalized convulsions (see INDICATIONS AND USAGE).

nerapy should be prescribed only after critical benefit-to-risk appraisal i cardiac conduction disturbance, including second- and third-degree AV heart block r renal damage; adverse hematologic or hypersensitivity reaction to other drugs, in to other anticonvulsants; or interrupted courses of therapy with carbamazepine. AV heart block, including second- and third-degree block, have been re

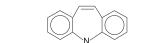
carbamazepine treatment. This occurred generally, but not solely, in patients with nalities or risk factors for conduction disturbances.

Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hep been reported (see ADVERSE REACTIONS and PRECAUTIONS, Laboratory Tests). hepatic effects may progress despite discontinuation of the drug. In addition r varishing bited duct syndrome have been reported. This syndrome consists of a chol with a variable clinical course ranging from fulminant to indolent, involving the c disappearance of the intrahepatic bile ducts. Some, but not all, cases are associate that overlap with other immunoallergenic syndromes, such as multiorgan hyperse ome) and serious dermatologic reactions. As an example there has been a re bile duct syndrome associated with Stevens-Johnson syndrome and in another case an association with fever and eosinophilia.

Information for Patients

Patients should be informed of the availability of a Medication Guide and they should be instructed to read the Medication Guide before taking carbamazepine.

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, as well as dermatologic, hypersensitivity or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising lymphadenopathy and petechial or purpuric hemorrhade, and in the case of liver reactions, anorexia nausea/vomiting, or iaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, the patient should be advised that these signs and symptoms should be orted even if mild or when occurring after extended use



NTRY : US	LOCATION : Indrad/Dahej			Supersedes A/W No.:		
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arly as one week ment assessed. e risk of suicidal	Patients should be advised that serious skin reactions have been reported in association with carbamazepine. In the event a skin reaction should occur while taking carbamazepine, patients should consult with their physician immediately (see WARNINGS).	because the plasma concentrations of the hormones may be decreased. Breakthrough bleeding and unintended pregnancies have been reported. Alternative or back-up methods of contraception should be considered.
he data analyzed.	Patients should be advised that anaphylactic reactions and angioedema may occur during treatment with carbamazepine (see WARNINGS). Advise patients to immediately report signs and symptoms	 Resistance to the neuromuscular blocking action of the nondepolarizing neuromuscular blocking agents pancuronium, vecuronium, rocuronium and cisatracurium has occurred in
cross a range of risk did not vary plute and relative	suggesting angioedema (swelling of the face, eyes, lips, or tongue, or difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their healthcare provider. Patients, their caregivers, and families should be counseled that AEDs, including carbamazepine,	patients chronically administered carbamazepine. Whether or not carbamazepine has the same effect on other non-depolarizing agents is unknown. Patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected, and infusion rate
voio.	may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert	requirements may be higher.
/sis < Difference:	for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of	 Concomitant use of carbamazepine with rivaroxaban, apixaban, dabigatran, and edoxaban (direct acting oral anticoagulants) is expected to result in decreased plasma concentrations of
litional Drug	concern should be reported immediately to healthcare providers.	these anticoagulants that may be insufficient to achieve the intended therapeutic effect. In
ents with	Carbamazepine may interact with some drugs. Therefore, patients should be advised to report to	general, coadministration of carbamazepine with rivaroxaban, apixaban, dabigatran, and edoxaban should be avoided.
nts Per 1,000 ents	their doctors the use of any other prescription or nonprescription medications or herbal products. Caution should be exercised if alcohol is taken in combination with carbamazepine therapy, due to a	Carcinogenesis, Mutagenesis, Impairment of Fertility
	possible additive sedative effect. Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of	Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors
	operating machinery or automobiles or engaging in other potentially dangerous tasks.	in females and of benign interstitial cell adenomas in the testes of males. Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial
	Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To	and mammalian mutagenicity studies using carbamazepine produced negative results. The
epilepsy than in	enroll, patients can call the toll free number 1-888-233-2334 (see WARNINGS, Usage in Pregnancy	significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.
re similar for the	subsection).	Usage in Pregnancy (see WARNINGS).
	Laboratory Tests For genetically at-risk patients (see WARNINGS), high-resolution 'HLA-B*1502 typing' is	Labor and Delivery
e risk of suicidal lesses for which	recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative	The effect of carbamazepine on human labor and delivery is unknown.
increased risk of	if no HLA-B*1502 alleles are detected. Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron,	Nursing Mothers
ng treatment, the n patient may be	should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased	Carbamazepine and its epoxide metabolite are transferred to breast milk. The ratio of the concentration in breast milk to that in maternal plasma is about 0.4 for carbamazepine and about 0.5
n pationt may be	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.	for the epoxide. The estimated doses given to the newborn during breastfeeding are in the range of 2 to 5 mg daily for carbamazepine and 1 to 2 mg daily for the epoxide.
with increased ould be closely	Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur (see	Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into
of activation of a	PRECAUTIONS, General and ADVERSE REACTIONS). Carbamazepine should be discontinued, based on clinical judgment, if indicated by newly occurring or worsening clinical or laboratory evidence of	account the importance of the drug to the mother. Pediatric Use
n mind.	liver dysfunction or hepatic damage, or in the case of active liver disease.	Substantial evidence of carbamazepine's effectiveness for use in the management of children with
porphyria (e.g.,	Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.	epilepsy (see INDICATIONS AND USAGE for specific seizure types) is derived from clinical investigations performed in adults and from studies in several <i>in vitro</i> systems which support the
tacks have been stration has also	Baseline and periodic complete urinalysis and BUN determinations are recommended for patients	conclusion that (1) the pathogenetic mechanisms underlying seizure propagation are essentially
chanism for the	treated with this agent because of observed renal dysfunction.	identical in adults and children, and (2) the mechanism of action of carbamazepine in treating
ta minimiza tha	Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of	seizures is essentially identical in adults and children. Taken as a whole, this information supports a conclusion that the generally accepted therapeutic
to minimize the	anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid	range of total carbamazepine in plasma (i.e., 4 to 12 mcg/mL) is the same in children and adults.
any cases, the	in determining the cause of toxicity when more than one medication is being used.	The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety
rmone secretion be dose-related.	Thyroid function tests have been reported to show decreased values with carbamazepine	of carbamazepine in children has been systematically studied up to 6 months. No longer-term data from clinical trials is available.
g hyponatremia.	administered alone. Interference with some pregnancy tests has been reported.	Geriatric Use
izure frequency, ness, which can	Drug Interactions	No systematic studies in geriatric patients have been conducted.
/ponatremia.	Clinically meaningful drug interactions have occurred with concomitant medications and include (but	ADVERSE REACTIONS If adverse reactions are of such severity that the drug must be discontinued, the physician must be
	are not limited to) the following:	aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may
f carbamazepine	Agents That May Affect Carbamazepine Plasma Levels When carbamazepine is given with drugs that can increase or decrease carbamazepine levels, close	lead to seizures or even status epilepticus with its life-threatening hazards.
lso been reports	monitoring of carbamazepine levels is indicated and dosage adjustment may be required.	The most severe adverse reactions have been observed in the hemopoietic system and skin (see BOXED WARNING), the liver, and the cardiovascular system.
anomalies (e.g., body systems).	Agents That Increase Carbamazepine Levels	The most frequently observed adverse reactions, particularly during the initial phases of therapy, are
When treating or	CYP3A4 inhibitors inhibit carbamazepine metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels	dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the lowest dosage recommended.
eigh the benefits comes pregnant	include aprepitant, cimetidine, ciprofloxacin, danazol, diltiazem, macrolides (e.g., erythromycin,	The following additional adverse reactions have been reported:
us.	clarithromycin), fluoxetine, fluvoxamine, trazodone, omeprazole, oxybutynin, isoniazid, niacinamide (nicotinamide), azoles (e.g., ketaconazole, itraconazole, fluconazole, voriconazole), acetazolamide,	Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression,
hay be a higher bination therapy.	verapamil, ticlopidine, grapefruit juice, and protease inhibitors.	thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria, variegate
nt women.	Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10.11-transdiol derivative from carbamazepine-10.11 epoxide. Coadministration of	porphyria, porphyria cutanea tarda. Skin: Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) (see BOXED
and the drug is	inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11	WARNING), Acute Generalized Exanthematous Pustulosis (AGEP), pruritic and erythematous rashes
brain and lung.	epoxide plasma concentrations. Accordingly, the dosage of carbamazepine should be adjusted and/or the plasma levels monitored when used concomitantly with loxapine, quetiapine, valproic	urticaria, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia,
rats when given) mg on a mg/kg	acid, or brivaracetam.	diaphoresis, onychomadesis and hirsutism. In certain cases, discontinuation of therapy may be
of 135 offspring	Agents That Decrease Carbamazepine Levels	necessary.
anomalies (cleft irsing offspring	CYP3A4 inducers can increase the rate of carbamazepine metabolism. Drugs that have been shown,	Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block,
age level of 200	or that would be expected, to decrease plasma carbamazepine levels include cisplatin, doxorubicin HCI, felbamate, fosphenytoin, rifampin, phenobarbital, phenytoin, primidone, methsuximide, theophylline, aminophylline.	thrombophlebitis, thromboembolism (e.g., pulmonary embolism), and adenopathy or lymphadenopathy.
is administered epilepticus with	Effect of Carbamazepine on Plasma Levels of Concomitant Agents	Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.
requency of the	Decreased Levels of Concomitant Medications	<i>Liver:</i> Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis, very
at to the patient, ugh it cannot be	Carbamazepine is a potent inducer of hepatic 3A4 and is also known to be an inducer of CYP1A2,	rare cases of hepatic failure.
the developing	2B6, 2C8/9/19 and may therefore reduce plasma concentrations of co-medications mainly metabolized by CYP 1A2, 2B6, 2C8/9/19 and 3A4, through induction of their metabolism. When used	Pancreatic: Pancreatitis.
	concomitantly with carbamazepine, monitoring of concentrations or dosage adjustment of these	Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.
a part of routine	 when carbamazepine is added to aripiprazole, the aripiprazole dose should be doubled. 	Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood
associated with	Additional dose increases should be based on clinical evaluation. If carbamazepine is later	pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and
ases of neonatal on with maternal	 withdrawn, the aripiprazole dose should be reduced. When carbamazepine is used with tacrolimus, monitoring of tacrolimus blood concentrations 	microscopic deposits in the urine have also been reported. There have been rare reports of impaired male fertility and/or abnormal spermatogenesis.
ne.	and appropriate dosage adjustments are recommended.	Testicular atrophy occurred in rats receiving carbamazepine orally from 4 to 52 weeks at dosage
e, physicians are	 The use of concomitant strong CYP3A4 inducers, such as carbamazepine should be avoided with tempiralized. If activate must be academinistered extremestation with tempiralized activates and the second strength of the second strengt of the s	levels of 50 to 400 mg/kg/day. Additionally, rats receiving carbamazepine in the diet for 2 years at
North American toll free number	with temsirolimus. If patients must be coadministered carbamazepine with temsirolimus, an adjustment of temsirolimus dosage should be considered.	dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the
istry can also be	The use of carbamazepine with lapatinib should generally be avoided. If carbamazepine is	urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is
	started in a patient already taking lapatinib, the dose of lapatinib should be gradually titrated up. If carbamazepine is discontinued, the lapatinib dose should be reduced.	unknown. Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue,
	Concomitant use of carbamazepine with nefazodone results in plasma concentrations of	blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus,
e.	nefazodone and its active metabolite insufficient to achieve a therapeutic effect. Coadministration of carbamazepine with nefazodone is contraindicated (see	speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, hyperacusis, neuroleptic malignant syndrome.
der that includes d with increased	CONTRAINDICATIONS).	There have been reports of associated paralysis and other symptoms of cerebral arterial
a anni 110108360	· Monitor concentrations of valproate when carbamazepine is introduced or withdrawn in	insufficiency, but the exact relationship of these reactions to the drug has not been established.
with a history of	patients using valproic acid. In addition, carbamazanine causes, or would be expected to cause, decreased levels of the following	Isolated cases of neuroleptic malignant syndrome have been reported both with and without
cardiac, hepatic, cluding reactions	In addition, carbamazepine causes, or would be expected to cause, decreased levels of the following drugs, for which monitoring of concentrations or dosage adjustment may be necessary:	concomitant use of psychotropic drugs. Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation,
-	acetaminophen, albendazole, alprazolam, aprepitant, buprenorphone, bupropion, citalopram,	anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.
orted following underlying EKG	clonazepam, clozapine, corticosteroids (e.g., prednisolone, dexamethasone), cyclosporine, dicumarol, dihydropyridine calcium channel blockers (e.g., felodipine), doxycycline, eslicarbazepine,	Eyes: Scattered punctate cortical lens opacities, increased intraocular pressure (see WARNINGS,
andonyny LNU	ethosuximide, everolimus, haloperidol, imatinib, itraconazole, lamotrigine, levothyroxine,	General) as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.
atic failure have	methadone, methsuximide, mianserin, midazolam, olanzapine, oral and other hormonal contraceptives, oxcarbazepine, paliperidone, phensuximide, phenytoin, praziguantel, protease	Musculoskeletal System: Aching joints and muscles, and leg cramps.
In some cases, are instances of	inhibitors, risperidone, sertraline, sirolimus, tadalafil, theophylline, tiagabine, topiramate, tramadol,	Metabolism: Fever and chills. Hyponatremia (see WARNINGS, General). Decreased levels of plasma
plestatic process	trazodone, tricyclic antidepressants (e.g., imipramine, amitriptyline, nortriptyline), valproate, warfarin, ziprasidone, zonisamide.	calcium have been reported. Osteoporosis has been reported.
destruction and ed with features	Other Drug Interactions	Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients
nsitivity (DRESS port of vanishing	Cyclophosphamide is an inactive prodrug and is converted to its active metabolite in part by	taking anticonvulsants.
e an association	CYP3A. The rate of metabolism and the leukopenic activity of cyclophosphamide are reportedly increased by chronic coadministration of CYP3A4 inducers. There is a potential for	A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazenine in combination with other medications. The patient was
		recovery to a papern raking cardadazeolog in complication with other medications. The nation was

airment of Fertility

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

DRUG ABUSE AND DEPENDENCE

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

Acute Toxicity

Lowest known lethal dose: adults, 3.2 g (a 24-year-old woman died of a cardiac arrest and a 24-year-old man died of pneumonia and hypoxic encephalopathy); children, 4 g (a 14-year-old girl died of a cardiac arrest), 1.6 g (a 3-year-old girl died of aspiration pneumonia). Oral LD₅₀ in animals (mg/kg): mice, 1100 to 3750; rats, 3850 to 4025; rabbits, 1500 to 2680; guinea

Concomitant use of carbamazepine with hormonal contraceptive products (e.g., oral, and levonorgestrel subdermal implant contraceptives) may render the contraceptives less effective pigs, 920

increased cyclophosphamide toxicity when coadministered with carbamazepine

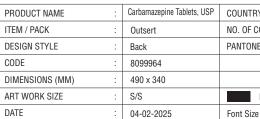
Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic

Concomitant use of carbamazepine with olanzapine, dantrolene, or ibuprofen may increase

Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity. Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

side effects.

plasma carbamazepine levels.



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a new medicine.

epilepticus).

tablets to take.

provider.

food.

chewable tablets?

worse.

tablets?

Signs and Symptoms

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

Respiration: Irregular breathing, respiratory depression,

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders, Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting Kidnevs and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced

leukocyte count, glycosuria, and acetonuria. EEG may show dysrhythmias. **Combined Poisoning:** When alcohol, tricyclic antidepressants, barbiturates, or hydantoins are taker

at the same time, the signs and symptoms of acute poisoning with carbamazepine may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the nach should be repeatedly irrigated, especially if the patient has also consumed alcohol Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion

is indicated in severe poisoning in small children. Respiratory Depression: Keep the airways free: resort, if necessary, to endotracheal intubation,

artificial respiration, and administration of oxygen. Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood essure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates 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 week) Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature. pupillary reflexes, and kidney and bladder function should be monitored for several days

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

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ⁵⁹Fe-ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A₂ and F hemoglobin, and (7) serum folic acid and B₁₀ levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sough

DOSAGE AND ADMINISTRATION (SEE TABLE BELOW)

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Conversion of patients from oral carbamazepine tablets to Tegretol suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., twice a day tablets to three times a day suspension).

Epilepsy (SEE INDICATIONS AND USAGE)

Adults and children over 12 years of age-Initial: 200 mg twice a day. Increase at weekly intervals by adding up to 200 mg/day using a three times a day or four times a day regimen until the optimal of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. used in adults in rare instances. *Maintenance:* Adjust dosage to the minimum effective level, usually 800 to 1200 mg daily

Children 6 to 12 years of age-Initial: 100 mg twice a day. Increase at weekly intervals by adding up to 100 mg/day using a three times a day or four times a day regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. Maintenance: Adjust dosage to the ninimum effective level, usually 400 to 800 mg daily.

Children under 6 years of age-Initial: 10 to 20 mg/kg/day twice a day or three times a day. Increase weekly to achieve optimal clinical response administered three times a day or four times a day. Maintenance: Ordinarily, optimal clinical response is achieved at daily doses below 35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to dete whether or not they are in the therapeutic range. No recommendation regarding the safety of carbamazepine for use at doses above 35 mg/kg/24 hours can be made.

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

Trigeminal Neuralgia (SEE INDICATIONS AND USAGE)

Initial: On the first day, 100 mg twice a day for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg/day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain. Do not exceed 1200 mg daily. *Maintenance*: Control of pain can be maintained in most patients with 400 to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months hroughout the treatment period, attempts should be made to reduce the dose to the min effective level or even to discontinue the drug.

Dosage Informatio

	Initial Dose	Subsequent Dose	Maximum Daily Dose
Indication	Tablet*	Tablet*	Tablet*
Epilepsy Under 6 yr	10 to 20 mg/kg/day twice a day or 3 times a day	Increase weekly to achieve optimal clinical response, 3 times a day or 4 times a day	35 mg/kg/24 hr (See Dosage and Administration section above)
6 to 12 yr	100 mg twice a day (200 mg/day)	Add up to 100 mg/day at weekly intervals, 3 times a day or 4 times a day	1000 mg/24 hr
Over 12 yr	200 mg twice a day (400 mg/day)	Add up to 200 mg/day at weekly intervals, 3 times a day or 4 times a day	1000 mg/24 hr (12 to 15 yr) 1200 mg/24 hr (>15 yr) 1600 mg/24 hr (adults, in rare instances)
Trigeminal Neuralgia	100 mg twice a day (200 mg/day)	Add up to 200 mg/day in increments of 100 mg every 12 hr	1200 mg/24 hr

* Tablet = Chewable or conventional tablets. HOW SUPPLIED

Carbamazenine Tablets USP (chewable) 100 mg are available in the following form: nink colored circular, strawberry/varilla flavored, flat beveled, uncoated tablets with "271" debossed on one side and scoreline on the other.

Bottle of 100	NDC 13668-271-0
Bottle of 500	NDC 13668-271-0
Bottle of 750	NDC 13668-271-4
Bottle of 1000	NDC 13668-271-1

Carbamazepine Tablets, USP, 200 mg are available in the following form: pink colored, capsule shaped, biconvex tablets with '268' debossed on one side and scored on the other side Bottle of 30 NDC 13668-268-30

Bottle of 100 NDC 13668-268-01 Bottle of 500 NDC 13668-268-05

Bottle of 1000 NDC 13668-268-1 Bottle of 2500 NDC 13668-268-31

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from light and moisture. Dispense in a tight, light-resistant container as defined in the USP Trademarks are the property of their respective owners.

MEDICATION GUIDE Carbamazepine (kar ba MAZ e peen) Tablets, USP, 200 mg and

Carbamazepine (kar ba MAZ e peen) Tablets, USP (Chewable), 100 mg Rx Only

Read this Medication Guide before you start taking carbamazepine tablets or chewable tablets and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment

What is the most important information I should know about carbamazepine tablets or chewable tablets?

Do not stop taking carbamazepine tablets or chewable tablets without first talking to your healthcare provider.

Stopping carbamazepine tablets or chewable tablets suddenly can cause serious problems.

Carbamazepine tablets or chewable tablets can cause serious side effects, including:

- 1. Carbamazepine tablets or chewable tablets may cause rare but serious skin rashes that may lead to death. These serious skin reactions are more likely to happen when you begin taking carbamazepine tablets or chewable tablets within the first four months of treatment but may occur at later times. These reactions can happen in anyone, but are more likely in people of Asian descent. If you are of Asian descent, you may need a genetic blood test before you take carbamazepine tablets or chewable tablets to see if you are at a higher risk for serious skin reactions with this medicine. Symptoms may include:
 - skin rash
 - hives
 - sores in your mouth
 - blistering or peeling of the skin

2. Carbamazepine tablets or chewable tablets may cause rare but serious blood problems. Symptoms may include:

- fever, sore throat, or other infections that come and go or do not go away
- easv bruising
- red or purple spots on your body
- bleeding gums or nose bleeds
- severe fatigue or weakness
- Carbamazepine tablets or chewable tablets may 3. cause allergic reactions or serious problems, which may affect organs and other parts of your body like the liver or blood cells. You may or may not have a rash with these types of reactions.

Call your healthcare provider right away if you have any of the following:

- swelling of your face, eyes, lips, or tongue
- a skin rash
- painful sores in the mouth or around your eyes
- unusual bruising or bleeding
- frequent infections or infections that do not go awav
- fever, swollen glands, or sore throat that do not go away or come and go
- trouble swallowing or breathing
- hives
- yellowing of your skin or eyes
- severe fatigue or weakness
- severe muscle pain
- 4. Like other antiepileptic drugs, carbamazepine tablets or chewable tablets may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)

- new or worse irritability
- acting aggressive, being angry, or violent acting on dangerous impulses
- an extreme increase in activity and talking

(mania) • other unusual changes in behavior or mood How can I watch for early symptoms of suicidal thoughts

- and actions? Pay attention to any changes, especially sudden • changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled

Call your healthcare provider between visits as needed. especially if you are worried about symptoms. Do not stop carbamazepine tablets or chewable tablets

without first talking to a healthcare provider.

Stopping carbamazepine tablets or chewable tablets suddenly can cause serious problems. You should talk to your healthcare provider before stopping.

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

What are carbamazepine tablets or chewable tablets? Carbamazepine tablets or chewable tablets are a prescription

- medicine used to treat:
- certain types of seizures (partial, tonic-clonic, mixed) • certain types of nerve pain (trigeminal and glossopharyngeal neuralgia)

Carbamazepine tablets or chewable tablets are not a regular pain medicine and should not be used for aches or pains.

Who should not take carbamazepine tablets or chewable tablets?

Do not take carbamazepine tablets or chewable tablets if have a history of bone marrow depression.

tablets.

not sure.

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take nefazodone.

medicines if you are not sure.

carbamazepine tablets or chewable tablets?

tablets, tell your healthcare provider if you:

depression, or mood problems

have or ever had heart problems

have or ever had blood problems

have or ever had kidney problems

have any other medical conditions

vou are pregnant.

1-888-233-2334.

drink grapefruit juice or eat grapefruit

carbamazepine tablets or chewable tablets.

have or ever had liver problems

are allergic to carbamazepine or any of the ingredients

in carbamazepine tablets or chewable tablets. See the

end of this Medication Guide for a complete list of

ingredients in carbamazepine tablets or chewable

antidepressants (TCAs). Ask your healthcare provider

or pharmacist for a list of these medicines if you are

have taken a medicine called a Monoamine Oxidase

Inhibitor (MAOI) in the last 14 days. Ask your

healthcare provider or pharmacist for a list of these

What should I tell my healthcare provider before taking

Before you take carbamazepine tablets or chewable

have or have had suicidal thoughts or actions,

have or ever had allergic reactions to medicines

have or ever had increased pressure in your eye

use birth control. Carbamazepine tablets or chewable

tablets may make your birth control less effective. Tell

your healthcare provider if your menstrual bleeding

changes while you take birth control and

are pregnant or plan to become pregnant.

Carbamazepine tablets or chewable tablets may harm

your unborn baby. Tell your healthcare provider right

away if you become pregnant while taking

carbamazepine tablets or chewable tablets. You and

your healthcare provider should decide if you should

take carbamazepine tablets or chewable tablets while

If you become pregnant while taking carbamazepine

tablets or chewable tablets, talk to your healthcare

provider about registering with the North American

Antiepileptic Drug (NAAED) Pregnancy Registry. The

purpose of this registry is to collect information about

the safety of antiepileptic medicine during pregnancy.

You can enroll in this registry by calling

Carbamazepine passes into breast milk. You and your

healthcare provider should discuss whether you

are breastfeeding or plan to breastfeed.

• are allergic to medicines called tricyclic

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ze 6 pt_Medi 10 pt	Approved By	Quality				

These details can be moved by printed to arrange pharma code/ Bar code and adjacent text visible on folded leaflet.

should take carbamazepine tablets or chewable tablets or breastfeed; you should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Taking carbamazepine tablets or chewable tablets with certain other medicines may cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get

How should I take carbamazepine tablets or chewable

 Do not stop taking carbamazepine tablets or chewable tablets without first talking to your healthcare provider. Stopping carbamazepine tablets or chewable tablets suddenly can cause serious problems. Stopping seizure medicine suddenly in a patient who has epilepsy may cause seizures that will not stop (status

Take carbamazepine tablets or chewable tablets exactly as prescribed. Your healthcare provider will tell you how many carbamazepine tablets or chewable

Your healthcare provider may change your dose. Do not change your dose of carbamazepine tablets or chewable tablets without talking to your healthcare

Take carbamazepine tablets or chewable tablets with

• If you take too many carbamazepine tablets or chewable tablets, call your healthcare provider or local Poison Control Center right away.

What should I avoid while taking carbamazepine tablets or

Do not drink alcohol or take other drugs that make you sleepy or dizzy while taking carbamazepine tablets or chewable tablets until you talk to your healthcare provider. Carbamazepine tablets or chewable tablets taken with alcohol or drugs that cause sleepiness or dizziness may make your sleepiness or dizziness

Do not drive, operate heavy machinery, or do other dangerous activities until you know how carbamazepine tablets or chewable tablets affect you. Carbamazepine tablets or chewable tablets may slow your thinking and motor skills.

What are the possible side effects of carbamazepine tablets or chewable tablets?

See "What is the most important information I should know about carbamazepine tablets or chewable tablets?" Carbamazepine tablets or chewable tablets may cause other

serious side effects. These include: Irregular heartbeat - symptoms include:

- o Fast, slow, or pounding heartbeat
- o Shortness of breath
- o Feeling lightheaded

o Fainting

dizziness

nausea

vomiting

drowsiness

(unsteadiness)

• Liver problems - symptoms include: o yellowing of your skin or the whites of your eyes o dark urine

o pain on the right side of your stomach area (abdominal pain)

o easy bruising

o loss of appetite o nausea or vomiting

Get medical help right away if you have any of the symptoms listed above or listed in "What is the mos important information I should know about carbamazepine tablets or chewable tablets?"

The most common side effects of carbamazepine tablets or chewable tablets include:

• problems with walking and coordination

These are not all the possible side effects of carbamazepine tablets or chewable tablets. For more information, ask your healthcare provider or pharmacist.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store carbamazepine tablets or chewable tablets?

 Store carbamazepine tablets or chewable tablets at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from light and moisture. Dispense in a tight, light-resistant container as defined in the USP.

Keep carbamazepine tablets or chewable tablets and all medicines out of the reach of children.

General Information about carbamazepine tablets or chewable tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use carbamazepine tablets or chewable tablets for a condition for which it was not prescribed. Do not give carbamazepine tablets or chewable tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about carbamazepine tablets or chewable tablets. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for the full prescribing information about carbamazepine tablets or chewable tablets that is written for health professionals.

For more information, go to <u>www.torrentpharma.com</u> or call 1-800-912-9561.

What are the ingredients in carbamazepine tablets or chewable tablets?

Active ingredient: carbamazepine, USP

Inactive ingredients:

Carbamazepine tablets: colloidal silicon dioxide, FD&C Red #40 aluminum lake, hypromellose, magnesium stearate. pregelatinized maize starch, corn starch, and sodium starch glycolate.

Carbamazepine tablets (Chewable): artificial flavors, colloidal silicon dioxide, compressible sugar, corn starch. FD&C Red #40 aluminum lake. hydroxypropyl methyl cellulose, magnesium stearate, and sodium starch glycolate. This Medication Guide has been approved by the U.S. Food and Drug Administration.

Dispense with Medication Guide available at: https://torrentpharma.com/pi/usa/products/

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