

No PML Seen With Natalizumab Since Summer '06

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Contributing Writer

CHICAGO — No new cases of progressive multifocal leukoencephalopathy were reported among 36,700 patients with multiple sclerosis treated with natalizumab since the summer of 2006.

Similarly, no drug-related deaths have been reported. And the incidence of adverse events (AEs) has been low, despite the fact that many patients have been us-

ing the drug for longer than 1 year to treat multiple sclerosis (MS), said Dr. Carmen M. Bozic, vice president for drug safety at Biogen Idec Inc., which markets natalizumab as Tysabri.

“The TOUCH [prescribing program], TYGRIS [safety study], and pregnancy registry will constitute the largest long-term follow-up undertaken by any sponsor for a single therapy for multiple sclerosis,” said Dr. Bozic at the annual meeting of the American Academy of Neurology.

Hepatic events occurred in less than 1/1,000 patients and were mostly reversible, she said. Less than 20% discontinued the drug.

The JC virus (JCV), which lies dormant in about 80% of adults whether they have MS or not, causes PML. When Dr. Bozic examined data from 2,370 MS patients who had undergone JCV testing, 5 had detectable plasma levels of JCV, including 3 from the placebo group.

At the time of the presentation, 2,752

physicians were registered with TOUCH and 17,863 patients were receiving natalizumab. About 18% previously had been treated with natalizumab, with a median of seven infusions. About 5,600 patients were treated for at least 1 year. Four percent were treatment naive, 65% switched from another disease-modifying therapy, 13% switched from other therapies, and a few were “returning quitters.”

As of February 2008, about 2,100 patients were enrolled in the TYGRIS study. The incidence of serious adverse events was 2.6%. The most frequent adverse events were hypersensitivity reactions (0.6%) and infections (0.6%), the latter being “garden variety” upper respiratory infections, she said. There were no reports of PML. Two deaths unrelated to treatment were documented.

Thirty-six pregnant patients were enrolled in the pregnancy registry, with 20 ongoing pregnancies. There were no reports of adverse pregnancy outcomes.

A second presentation focused on the experiences of patients with MS who resumed natalizumab after voluntary discontinuation. While the overall incidence



JCV testing of more than 6,000 plasma samples resulted in less than 1% with detectable JCV DNA.

DR. O'CONNOR

of hypersensitivity reactions or infusion reactions was low, the risks were elevated for patients who had only one or two prior infusions, said Dr. Paul W. O'Connor of St. Michael's Hospital, Toronto.

Dr. O'Connor scrutinized the records of 1,089 MS patients who had completed natalizumab pivotal clinical trials but stopped and restarted treatment. Of this group, 384 had formerly received placebo and 705 had been treated with natalizumab. All had been treated for about a year and a half, had received a median of seven infusions, and had MS for about 8 years.

Most (87%) had one or more AEs. About 55 (5%) had a serious AE, most commonly an MS relapse (2%). Overall rates of infusion reactions (5%) and hypersensitivity reactions (less than 1%) were low, and there were no opportunistic infections.

When the group was stratified by the number of prior infusions, the risk of infusion reactions or hypersensitivity reactions jumped to 24.1% and 7.4%, respectively, for those who had only one or two previous treatments.

Testing of over 6,000 plasma samples resulted in less than 1% (6/1,089 samples) with detectable JCV DNA, and these findings were not associated with PML, said Dr. O'Connor. Of the six positive samples, five had become JCV positive while on natalizumab and one was positive at baseline and became negative upon retesting.

Dr. Bozic is an employee of Biogen Idec and holds stock options in the company. Dr. O'Connor has received compensation for activities related to Biogen Idec and research support from them.

CARBATROL® (carbamazepine) Extended-Release Capsules 100 mg • 200 mg • 300 mg Brief Summary Prescribing Information Rx Only

WARNING
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 OCCUR 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 OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH CARBATROL. PATIENTS TESTING POSITIVE FOR HLA-B*1502 SHOULD NOT BE TREATED WITH CARBATROL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE WARNINGS AND PRECAUTIONS/LABORATORY TESTS).
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 HEMATOLOGIC 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.

INDICATIONS AND USAGE

Epilepsy

Carbatrol 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 patients with the following seizure types:

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

Carbatrol 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 and nortriptyline. Likewise, on theoretical grounds its use with monoamine oxidase 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.

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. Carbatrol 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

Retrospective 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 variations exist in the prevalence of HLA-B*1502. Greater than 15% of the population is reported positive in Hong Kong, Thailand, 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 <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, Hispanics, and Native Americans). Prior to initiating Carbatrol therapy, testing for HLA-B*1502 should be performed in patients with ancestry in populations in which HLA-B*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 guide. Keep 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 of mixed ancestry. Carbatrol 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 WARNINGS 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 Carbatrol. The HLA-B*1502 allele has not been found to predict risk of less severe adverse cutaneous reactions from carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption [MPE]). 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 anti-epileptic drugs associated with SJS/TEN. 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.

Application of HLA-B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502-positive Asian patients treated with carbamazepine will not develop SJS/TEN, and these reactions can still occur infrequently in HLA-B*1502-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

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

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 carbamazepine during pregnancy and congenital malformations, including spina bifida. The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

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

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

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum 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 litters the maximum number of offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (left palate, 1 tailpiece, 1 anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be 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 developing embryo or fetus.

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

General

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

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

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

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

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

PRECAUTIONS

General

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

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

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

Information for Patients

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

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

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

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

Laboratory Tests

For genetically at-risk patients [See WARNINGS], high-resolution HLA-B*1502 typing is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected.

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, 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.

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. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

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.

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

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

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

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

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

Interference with some pregnancy tests has been reported.

Drug Interactions

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

Agents Highly Bound to Plasma Protein: Carbamazepine is not highly bound to plasma proteins; therefore, administration of Carbatrol® to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

Agents that Inhibit Cytochrome P450 Isoenzymes and/or Epoxide Hydrolase: Carbamazepine is metabolized mainly by cytochrome P450 (CYP) 3A4 to the active carbamazepine 10,11-epoxide, which is further metabolized to the trans-diol by epoxide hydrolase. Therefore, the potential exists for interaction between carbamazepine and any agent that inhibits CYP3A4 and/or epoxide hydrolase. Agents that are CYP3A4 inhibitors that have been found, or are expected, to increase plasma levels of Carbatrol® are the following:

Acetazolamide, azole antifungals, cimetidine, clarithromycin, dalopristin, danazol, delavirdine, diltiazem, erythromycin, fluoxetine, fluvastatin, grapefruit juice, isoniazid, itraconazole, ketoconazole, lorazepam, nefazodone, nifedipine, nizatidine, nicotinic acid, protease inhibitors, propoxyphene, quinine, quinupristin, troloandomycin, valproate, verapamil, zileuton.

Also inhibits epoxide hydrolase resulting in increased levels of the active metabolite carbamazepine 10, 11-epoxide.

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 hydrolase inhibitors, it is reasonable to expect that a dose reduction for Carbatrol® may be necessary.

Agents that Induce Cytochrome P450 Isoenzymes: Carbamazepine is metabolized by CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent that induces CYP3A4. Agents that are CYP inducers that have been found, or are expected, to decrease plasma levels of Carbatrol® are the following:

Cisplatin, dexamethasone, rifampin, phenobarbital, phenytoin, primidone, methsulfonamide, and theophylline.

Phenoin plasma levels have also been reported to increase and decrease in the presence of carbamazepine, see below.

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 inducers, it is reasonable to expect that a dose increase for Carbatrol® may be necessary.

Agents with Decreased Levels in the Presence of Carbamazepine due to Induction of Cytochrome P450 Enzymes: Carbamazepine is known to induce CYP1A2 and CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent metabolized by one (or more) of these enzymes. Agents that have been found, or are expected to have decreased plasma levels in the presence of Carbatrol® due to induction of CYP enzymes are the following:

Acetaminophen, alprazolam, amitriptyline, bupropion, buspirone, citalopram, clobazam, clonazepam, clozapine, cyclosporin, delavirdine, desipramine, diazepam, dicumarol, doxycycline, ethosuximide, felbamate, felodipine, gluccorticoids, haloperidol, itraconazole, lamotrigine, levofloxacin, lorazepam, methadone, midazolam, mirtazapine, nortriptyline, olanzapine, oral contraceptives, oxcarbazepine, phenytoin, praziquantel, protease inhibitors, quetiapine, risperidone, theophylline, topiramate, tiagabine, tramadol, trazodone, valproate, warfarin, ziprasidone, and zonisamide.

Break through bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Phenoin has also been reported to increase in the presence of carbamazepine. Careful monitoring of phenoin plasma levels following co-medication with carbamazepine is advised.

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

Warfarin's anticoagulant effect can be reduced in the presence of carbamazepine.

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®, it is reasonable to expect that a dose increase for the concomitant agent may be necessary.

Agents with Increased Levels in the Presence of Carbamazepine: Carbatrol® increases the plasma levels of the following agents:

Clomipramine HCl, phenytoin, and primidone.

Administration of Carbamazepine to Sprague-Dawley rats for two years in the presence of carbamazepine. Careful monitoring of phenoin plasma levels following co-medication with carbamazepine is advised.

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®, it is reasonable to expect that a dose decrease for the concomitant agent may be necessary.

Pharmacological/Pharmacodynamic Interactions with Carbamazepine

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

The following additional adverse reactions were previously reported with carbamazepine:

Anticonvulsants: Additionally, anti-malarial drugs, such as chloroquine and mefloquine, may antagonize the activity of carbamazepine. 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®, it is reasonable to expect that a dose adjustment may be necessary.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 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 tumors in females and of benign intestinal adenomas in the testes of males.

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

Use in Pregnancy Pregnancy Category D (See WARNINGS)

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

Nursing Mothers Carbamazepine and its epoxide metabolite are transferred to breast milk and during lactation. The concentrations of carbamazepine and its epoxide metabolite are approximately 50% of the maternal plasma concentration. 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 account the importance of the drug to the mother.

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

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

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

Geriatric Use No systematic studies in geriatric patients have been conducted.

ADVERSE REACTIONS

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

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

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

The following additional adverse reactions were previously reported with carbamazepine:

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

Skin: Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) (see BOXED WARNING), pruritic and erythematous rashes, urticaria, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

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

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

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

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

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

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

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

Eyes: Scattered punctate cortical lens opacities, 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.

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

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

Other: 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 taking anticonvulsants.

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 dechallenge, and the meningitis reappeared upon rechallenge with carbamazepine.

Manufactured for: Shire US Inc., 725 Chesterbrook Blvd., Wayne PA