

# PPAC Offers Plan for Physician Reimbursement

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WASHINGTON — Physicians should be reimbursed retroactively for any payment miscalculations that occurred under Medicare’s new system to reimburse for in-office infusions, the Practicing Physicians Advisory Council recommended.

The “average sales price” (ASP) is something federal regulators “are concocting, and they don’t know how accurate it’s go-

ing to be,” said PPAC member Barbara L. McAneny, M.D., an oncologist from Albuquerque, N.M., who drew up the recommendation.

For that reason, the Centers for Medicare and Medicaid Services should establish a correction factor for each quarter it updates pricing on the ASP, to prevent physicians from treating patients at a loss or being put in the position of denying treatment, she said.

PPAC is an independent panel that ad-

vises CMS on physician payment issues.

The ASP was authorized by the Medicare Modernization Act of 2003, replacing the former system of overpayments for drugs and underpayments for their administration. The intent was to make fair payments for both services.

This year and next, Medicare will pay physicians the ASP plus 6%. But next year, physicians will have the option of obtaining the drugs directly from a supplier selected by Medicare through a competitive

bidding process. CMS officials told the panel that the agency would update pricing for the ASP on a quarterly basis.

Dr. McAneny countered that this wouldn’t allow for any mistakes in pricing made along the way.

“Suppose the ASP is set at \$60 for a drug, but you can only purchase that drug for \$100,” she later said in an interview. This means physicians would be getting paid only \$60 for that drug from January through April—and losing \$40 every time they administer the drug.

CMS might be able to correct the price on April 1, but that doesn’t compensate for the losses physicians incurred over the first quarter of the year, Dr. McAneny said.

As a result, the agency might end up getting complaints from half the physicians in the country about the cost of a drug.

By putting in a correction mechanism, the agency can make the change retroactive, she recommended.

A report from the Government Accountability Office indicated that physi-

cians may not get short-changed under the ASP. Medicare payments for cancer drugs may decline next year, but payments are actually expected to exceed physicians’ costs by 6% on average, the GAO found.

The American Society of Clinical Oncology responded that the study underreported some costs and the report’s methodology was flawed.

“GAO has always said that everything’s going to be fine” with the ASP, Dr. McAneny said.

Nevertheless, “we need a plan B in case they’re wrong.”

The ASP replaces the average wholesale price, a number that drug makers had been giving to the government for each drug administered.

Medicare in the past paid physicians 95% of the average wholesale price for in-office administration of a drug to a Medicare beneficiary; however, the physician was not paid an administration fee.

The ASP system comes with mixed benefits: Physicians now will get paid an administration fee but they won’t be getting paid as much for the drugs themselves as they were under the average wholesale price system.

PPAC also requested that physicians be allowed Internet access to a list of drugs that CMS compiled by manufacturer to determine ASP.

“This will be very helpful to the physician community—not just oncology—but for everybody who wants to purchase drugs ... under the average selling price, and [to] know who they can purchase these drugs from,” Dr. McAneny said. ■

**EQUETRO™** (carbamazepine) extended-release capsules  
100 mg, 200 mg and 300 mg

**Brief Summary Prescribing Information**

**WARNING** APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE-CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW. APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA. ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS. BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON CARBAMAZEPINE ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

**Rx only**

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

**INDICATIONS AND USAGE**

EQUETRO™ is indicated for the treatment of acute manic and mixed episodes associated with Bipolar I Disorder. The efficacy of EQUETRO™ in acute mania was established in 2 placebo-controlled, double-blind, 3-week studies in patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode. The effectiveness of EQUETRO™ for longer-term use and for prophylactic use in mania has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use EQUETRO™ for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

**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**

Patients should be made aware that EQUETRO™ 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 a human daily dosage of 1200 mg on a mg/kg basis or 1.5-4 times the human daily dosage on a mg/m<sup>2</sup> basis. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In 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. 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. Severe dermatologic reactions, including toxic epidermal necrolysis (Lyll's syndrome) and Stevens-Johnson syndrome have been reported with carbamazepine. These reactions have been extremely rare. However, a few fatalities have been reported.

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 the class of non-nucleoside reverse transcriptase inhibitors.

**PRECAUTIONS**

**General**

Before initiating therapy, a detailed history and physical examination should be made. Therapy should be prescribed only after critical benefit-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.

**Suicide:** The possibility of suicide attempt is inherent in Bipolar Disorder and close supervision of high risk patients should accompany drug therapy. Prescriptions for EQUETRO™ should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose.

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

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 (please see full prescribing information) may be useful for verification of drug compliance, assessing safety and determining the cause of toxicity including when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with carbamazepine administered alone. Hyponatremia 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 meaningful 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 EQUETRO™ 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. CYP3A4 inhibitors have been found, or are expected, to increase plasma levels of EQUETRO™. Commonly used agents that inhibit CYP3A4 are: azole antifungals (such as ketoconazole and itraconazole, calcium channel blockers (such as diltiazem and verapamil), macrolide antibiotics (such as erythromycin, clarithromycin, and troleandomycin), grapefruit juice, and other drugs. Please see full prescribing information.

Thus, if a patient has been titrated to a stable dosage of EQUETRO™, 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 EQUETRO™ 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. CYP3A4 inducers have been found, or are expected, to decrease plasma levels of EQUETRO™. Commonly used agents that induce CYP3A4 are: phenytoin, primidone, theophylline, anticancer agents, and other drugs. Please see full prescribing information. Thus, if a patient has been titrated to a stable dosage on EQUETRO™, and then begins a course of treatment with one of these CYP3A4 inducers, it is reasonable to expect that a dose increase for EQUETRO™ 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. These agents have been found, or are expected to have decreased plasma levels in the presence of EQUETRO™ due to induction of CYP enzymes. Commonly used agents that induce CYP enzymes are: acetaminophen, benzodiazepines (such as alprazolam, diazepam, lorazepam, midazolam, and triazolam), protease inhibitors, oral contraceptives, antidepressants (tricyclics and SSRIs), phenytoin, and other drugs. Please see full prescribing information.

Break through bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected. 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 EQUETRO™, 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:** EQUETRO™ increases the plasma levels of clobampramine HCl and primidone.

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

Phenytoin has been reported to decrease or increase in the presence of carbamazepine. Careful monitoring of phenytoin plasma levels following co-medication with carbamazepine is advised.

**Pharmacological/Pharmacodynamic Interactions with Carbamazepine**

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

Given the anticonvulsant properties of carbamazepine, EQUETRO™ may reduce the thyroid function as has been reported with other 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 EQUETRO™, it is reasonable to expect that a dose adjustment may be necessary.

Because of its primary CNS effect, caution should be used when EQUETRO™ 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 human daily dose of 1200 mg on a mg/m<sup>2</sup> basis), resulted in a dose-related increase in the incidence of hepatocellular tumors 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 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.

**Usage 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. 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**

The safety and effectiveness of EQUETRO™ in pediatric and adolescent patients have not been established.

**Geriatric Use**

No systematic studies in geriatric patients have been conducted.

**ADVERSE REACTIONS**

**General:** The most severe adverse reactions previously observed with carbamazepine were reported in the hemopoietic system (see BOX WARNING), the skin, 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 most commonly observed adverse experiences (5% and at least twice placebo) seen in association with the use of EQUETRO™ (400 to 1600 mg/day, dose adjusted in 200 mg daily increments in week 1 in Bipolar I Disorder in the double-blind, placebo-controlled trials of 3 weeks' duration are: dizziness, somnolence, nausea, vomiting, ataxia, pruritus, dry mouth, amblyopia, and speech disorder.

EQUETRO™ and placebo-treated patients from the two double-blind, placebo-controlled studies were enrolled in a 6-month open-label study. The most common adverse events with an incidence of 5% or more are: headache, dizziness, rash, infection, pain, somnolence, diarrhea, dyspepsia, nausea, asthenia, amnesia<sup>1</sup>, accidental injury, anxiety, depression<sup>1</sup>, manic depressive reaction, chest pain, back pain, constipation, ataxia, and pruritus.

<sup>1</sup>Amnesia includes poor memory, forgetful and memory disturbance  
<sup>2</sup>Depression includes suicidal ideation

Other significant adverse events seen in less than 5% of patients include: suicide attempt, manic reaction, insomnia, nervousness, depersonalization and extrapyramidal symptoms, infections (fungal, viral, bacterial), pharyngitis, rhinitis, sinusitis, bronchitis, urinary tract infection, leukopenia and lymphadenopathy liver function tests abnormal, edema, peripheral edema, allergic reaction, photosensitivity reaction, alopecia, diplopia and ear pain.

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:** Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyll's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), 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.

**Genitourinary System:** Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported. Testicular atrophy occurred in rats receiving carbamazepine orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats receiving carbamazepine in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg/day and higher. Relevance of these findings to humans is unknown.

**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 pharynx, 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 carbamazepine have been reported.

**Other:** Inbred carrier state 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 dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

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