

Topiramate Approval Reignites Generic Debate

BY MICHELE G. SULLIVAN

Although generic versions of Topamax will soon be available, some neurologists are concerned the new formulations may endanger patients at high risk of seizure complications.

The Food and Drug Administration approved the marketing of generic topiramate for seizure disorders in April, and maintains that generic formulations of

any drug must be bioequivalent to the brand formulation. But the agency's accepted bioequivalence range of 80%-125% could put some patients at risk for breakthrough seizures or increased side effects, Dr. Michael Privitera said.

"The FDA's bioequivalence requirements are not based on any strong evidence," said Dr. Privitera, professor of neurology at the University of Cincinnati. "There are no studies that say peo-

ple with epilepsy will do well within that range. The FDA could be correct in saying that generic formulations will fall within that range, but there is no way of knowing if that that range is good for our patients."

Dr. Stuart Black, medical director of the Dallas Headache Association, agreed that the lack of evidence clouds the issue of which patients might experience problems if switched to a generic formulation.

"We don't have any data at all on the similar comparison of using a generic antiepileptic for migraine as opposed to a nongeneric," said Dr. Black, who is also the medical director of neurology and codirector of the Neuroscience Center at Baylor University Medical Center, Dallas.

The American Epilepsy Society recommends that generics should not be substituted for a brand formulation without physician and patient approval. ■

moxatag[™] (amoxicillin extended-release tablets) 775 mg

The following is a brief summary only; see full Prescribing Information for complete product information.

RX ONLY

INDICATIONS AND USAGE

MOXATAG is a once-daily amoxicillin product indicated for the treatment of tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes* (*S. pyogenes*), more commonly referred to as 'strep throat', in adults and pediatric patients 12 years or older.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MOXATAG and other antibacterial drugs, MOXATAG should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

DOSAGE AND ADMINISTRATION

The recommended dose of MOXATAG is 775 mg once daily taken within 1 hour of finishing a meal for 10 days. MOXATAG should be taken approximately the same time every day. The full 10-day course of therapy should be completed for effective treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes*.

Do not chew or crush tablet.

CONTRAINDICATIONS

MOXATAG is contraindicated in patients with known serious hypersensitivity to amoxicillin or to other drugs in the same class or patients who have demonstrated anaphylactic reactions to beta-lactams.

WARNINGS AND PRECAUTIONS

Anaphylaxis and Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Before initiating therapy with MOXATAG, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, MOXATAG should be discontinued and appropriate therapy instituted.

Clostridium difficile Associated Diarrhea (CDAD)

Clostridium difficile Associated Diarrhea (CDAD) has been reported with nearly all antibacterial agents, including amoxicillin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued.

Superinfections

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, amoxicillin should be discontinued and appropriate therapy instituted.

Mononucleosis Rash

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

Development of Drug-Resistant Bacteria

Prescribing amoxicillin in the absence of proven or strongly suspected bacterial infection or treating prophylactically is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

False-Positive Urinary Glucose Tests

High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinistix[®], Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix[®]) be used.

ADVERSE REACTIONS

In a controlled Phase 3 trial, 302 adult and pediatric patients (≥12 years) were treated with MOXATAG 775 mg once-daily for 10 days. The most frequently reported adverse reactions (>1%) which were suspected or probably drug-related are vaginal yeast infection (2.0%), diarrhea (1.7%), nausea (1.3%) and headache (1.0%).

DRUG INTERACTIONS

Probenecid

Probenecid decreases the renal tubular secretion of amoxicillin.

Concurrent use of MOXATAG and probenecid may result in increased and prolonged blood levels of amoxicillin.

Other Antibiotics

Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with the bacterial effects of penicillin. This has been demonstrated *in vitro*; however, the clinical significance of this interaction is not well documented.

Oral Contraceptives

As with other antibiotics, amoxicillin may affect the gut flora, leading to lower estrogen reabsorption and potentially resulting in reduced efficacy of combined oral estrogen/progesterone contraceptives.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects. Pregnancy Category B.

Reproduction studies have been performed in mice and rats at doses up to 2000 mg/kg (12.5 and 25 times the human dose in mg/m²) and have revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

It is not known whether use of amoxicillin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers

Penicillins have been shown to be excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of MOXATAG in pediatric patients 12 years of age and older have been established based on results of a clinical trial that included adults and pediatric patients (12 years or older). The safety and effectiveness of MOXATAG in pediatric patients younger than 12 years has not been established.

Geriatric Use

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Renal Impairment

MOXATAG has not been studied in patients with renal impairment; however, a reduction of amoxicillin dose is generally recommended for patients with severe renal impairment. Therefore, MOXATAG is not recommended for use in patients with severe renal impairment (CrCl <30 mL/min) or patients on hemodialysis.

OVERDOSAGE

In case of overdose, discontinue medication, treat symptomatically, and institute supportive measures as required. If the overdose is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed.

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin.

Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdosage in adult and pediatric patients.

Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of amoxicillin.

For additional information about overdose treatment, call a poison control center (1-800-222-1222).

HOW SUPPLIED/STORAGE AND HANDLING

MOXATAG tablets for oral administration are provided as blue film-coated, oval-shaped tablets that contain 775 mg of amoxicillin. The tablets are printed with "MB-111" on one side in black edible ink. MOXATAG is packaged in bottles as follows:

Presentation	NDC Code
Bottles of 30	11042-142-03

Storage

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

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PHARMACEUTICALS[®]

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Oral Cladribine Efficacious for MS Treatment

SEATTLE — Oral cladribine reduced the annualized rate of relapse in patients with the relapsing-remitting form of multiple sclerosis by over half in a phase III trial presented at the annual meeting of the American Academy of Neurology.

Cladribine, an antineoplastic used primarily to treat hairy cell leukemia, has several properties relevant to the treatment of multiple sclerosis (MS): It produces a sustained reduction in numbers of CD4 and CD8 T cells and of B cells, decreases levels of proinflammatory chemokines, and crosses the blood-brain barrier, according to lead investigator Dr. Gavin Giovannoni, a neurologist at Barts and The London School of Medicine and Dentistry, London.

He and his coinvestigators enrolled patients who had definite, active relapsing-remitting MS and an Expanded Disability Status Scale (EDSS) score of 5.5 or less.

Of those patients, 433 received a lower total dose of cladribine (3.5 mg/kg), 456 received a higher total dose of cladribine (5.25 mg/kg), and 437 got a placebo. Medication was taken for only 4-5 days a month in 2-4 months a year.

"We were quite surprised," Dr. Giovannoni said of the trial's results for the primary end point, the annualized relapse rate after 96 weeks of treatment. "Despite having a relatively low event rate in the placebo arm, there was a robust and highly significant impact on relapse rate in both [experimental] study arms."

Specifically, in intention-to-treat analyses, annualized relapse rates were 0.14 and 0.15 in the lower- and higher-dose cladribine groups, respectively, compared with 0.33 in the placebo group. The differences corresponded to statistically significant 58% and 55% relative reductions.

Compared with their counterparts in the placebo group, patients in the lower- and higher-dose cladribine groups were significantly less likely to experience a relapse (relative risks, 0.52 and 0.54) or progression (hazard ratios, 0.67 and 0.69).

Dr. Giovannoni reported that he has received personal compensation from Merck-Serono.

The study was supported by Merck Serono S.A., Geneva, an affiliate of Merck KGaA, Darmstadt, Germany.

—Susan London