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 people 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. ■

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