Drug Monitor

FDA Approves Rivastigmine Patch—But Rebukes Misleading Marketing of Oral Form

In July, the FDA approved the rivastigmine transdermal system (Exelon Patch, Novartis, Basel, Switzerland), the first skin patch to treat mild to moderate Alzheimer disease (AD). Rivastigmine, a cholinesterase inhibitor, has been available in oral form since 2000. Both oral and transdermal rivastigmine also are indicated to treat mild to moderate dementia associated with Parkinson disease.

According to Novartis, the patch was designed to increase adherence and maximize convenience for patients and caregivers. It is applied daily to the back, chest, or upper arm, beginning with the 4.6-mg/24 hr dosage strength. If the patch is well tolerated for at least four weeks, the dosage can be increased to the target level of 9.5 mg/24 hr. In the Investigation of Transdermal Exelon in Alzheimer's Disease (IDEAL) trial, which involved nearly 1,200 patients with AD, the rivastigmine patch significantly improved memory and the ability to perform everyday activities compared with placebo and showed similar efficacy to high dose oral therapy.

Both formulations of rivastigmine have been associated most commonly with nausea, vomiting, and diarrhea—although the patch appears to lessen these effects compared with the oral capsules. Other reported adverse effects include depression, headache, anxiety, anorexia, and weight loss. Clinicians should monitor patients' weight during therapy and take special caution with patients who weigh less than 50 kg. Patients and caregivers should be advised to alternate the patch site and avoid exposing the patch to external heat for long periods of time. The patch is contraindicated in patients with known sensitivities to rivastigmine, other carbamate derivatives, or other components of the formulation.

About a month after the patch was approved, the FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) issued a warning letter to Novartis regarding a professional file card on oral rivastigmine that the company was disseminating to health care professionals. According to the letter, the card "makes unsubstantiated superiority claims for Exelon, overstates the efficacy of Exelon, includes misleading risk presentations, and recommends or suggests a combination use of Exelon that has not been approved by [the] FDA." The DDMAC requested that Novartis immediately cease distributing promotional material for rivastigmine that contains the information detailed in the warning letter and submit to the agency a plan for correcting the error.

Sources: Novartis news release. July 9, 2007.

FDA warning letter. August 14, 2007.

Exelon [prescribing information]. Basel, Switzerland: Novartis; 2007.

What's the Best Treatment for Diabetic Neuropathy?

Painful neuropathy continues to be problematic for many patients with diabetes, despite the use of various analgesics. To help understand which agents work best, researchers from United Christian Hospital and Hong Kong Polytechnic University, both in Hong Kong, performed a systematic review of randomized, controlled trial reports comparing both topically applied and orally administered drugs with placebo. They found that, for short-term pain relief, oral tricyclic antidepressants and traditional anticonvulsants were more effective than newer anticonvulsants.

Of the 1,231 reports screened, 25 met the inclusion criteria. Drugs evaluated in the trials were various anticonvulsants, antidepressants, and opioids; the ion channel blocker mexiletine; the *N*-methyl-D-aspartate (NMDA) antagonist dextromethorphan; the selective serotonin-norepinephrine reuptake inhibitor duloxetine; capsaicin cream; and isosorbide dinitrate spray. Only 17 of the reports, however, had data suitable for the efficacy analysis.

The pooled odds ratio for the primary outcome (50% pain relief, defined as "moderate," "good," or "notable" improvement in global assessment of treatment or at least moderate pain relief on a suitable categorical scale) was 5.33 for traditional anticonvulsants, 3.25 for the newer anticonvulsants, and 22.24 for tricyclic antidepressants. The odds ratio for patient withdrawal due to adverse events was 1.51 for traditional anticonvulsants, 2.98 for the newer anticonvulsants, and 2.32 for tricyclic antidepressants.

The researchers caution that, since all the trials analyzed had durations of less than six months, further evidence on the long-term effects of oral antidepressants and anticonvulsants is needed. Additionally, they call for more studies on opioids, NMDA antagonists (only one trial was reported, involving 14 patients), and ion channel blockers (three trials reported contradictory results) and for more investigation of nonpharmacologic strategies. ●

Source: *BMJ.* 2007;335(7610):87. doi:10.1136/bmj.39213.565972.AE.