Review Limited to One Study

Parkinson's *from page 1*

astigmine, at a dose of 3-12 mg per day, was safe in this population. The panel voted 7-0 with one abstention that, based on its results, the study did not need to be replicated for the FDA to approve the new indication.

"What convinces me that one study is enough" is the amount of safety data available for its use in Alzheimer's disease and "robust finding[s] on all secondary end points" for Parkinson's dementia, which were congruous with findings on the primary end points, said panel member Dr. Ralph L. Sacco, professor of neurology and epidemiology at the Neurological Institute of New York at Columbia University.

Novartis markets rivastigmine as Exelon, which was approved in the United States in 2000 for mild to moderate dementia of the Alzheimer's type. It was approved for the Parkinson's indication in the European Union earlier this year, but there are no treatments currently approved for this indication in the United States. The FDA usually follows the recommendations of its advisory panels.

There are emerging data that Alzheimer's and Parkinson's share a cholinergic deficit that presents a common treatment target.

The EXPRESS study compared the impact of rivastigmine with that of placebo over 24 weeks in 541 patients with mild to moderate dementia (362 on treatment, 179 on placebo) with a mean age of 72 years. They had been diagnosed with Parkinson's a mean of about 9 years earlier, and a mean of about 7 years had elapsed between their diagnosis and the appearance of the first dementia symptoms.

At 24 weeks, changes from baseline in the primary efficacy outcome end points, two subscales of the Alzheimer Disease Assessment Scale (ADAS) that assessed cognition and overall dementia, significantly favored those treated with rivastigmine. The secondary outcome measures of activities of daily living, executive function, attention, and behavior at 24 weeks were also significantly improved among the treated patients.

Among those on rivastigmine, 27% discontinued treatment, compared with 18% of those in the placebo group; in both groups, most discontinued because of an adverse event. During the study and an extension study that followed patients for another 48 weeks, the most frequent side effects among treated patients were cholinergic, including nausea (29%), vomiting (17%), and worsening tremor (10%), which in most cases were mild to moderate and infrequently resulted in discontinuing treatment, according to Novartis.

Speaking on behalf of Novartis at the meeting, Dr. Clive Ballard, professor of age-related diseases at the Institute of Psychiatry, King's College, London, described Parkinson's dementia as a distinct dementia syndrome that can be "unambiguously diagnosed in routine clinical practice" by using three principles: The patient has an established diagnosis of idiopathic Parkinson's disease, develops dementia at least 1-2 years after the onset of PD, and has had other causes of dementia excluded. Autopsy studies indicate that these criteria accurately diagnose 90% of cases, he said, adding that there is emerging evidence that a cholinergic deficit, shared by PD and Alzheimer's, is associated with many of the key cognitive deficits and neuropsychiatric symptoms and "presents a common treatment target."

In a unanimous vote, the panel agreed that there was a separate form of dementia associated with Parkinson's that is distinct from Alzheimer's disease, and that there are operational criteria that could be used for making the diagnosis clinically. Dr. Russell Katz, director of the FDA's division of neurology products, explained that FDA reviewers had wanted to know whether the panel believed that the average practicing neurologist could reliably diagnose dementia in these patients and distinguish it from Alzheimer's dementia using the algorithm described by the company.

Panel member Dr. J. Eric Ahlskog, professor of neurology at the Mayo Clinic, Rochester, Minn., said that although clinicians in a busy clinic may not be good at sorting out specific changes such as changes in executive function, "we are pretty good as neurologists in saying yes, this person is demented." He agreed that the type of dementia could be ascertained by the two-step process of determining whether a patient has Parkinson's and whether he or she has developed dementia after an interval of time.

Panel member Dr. Irene Litvan, director of the movement disorders program at the University of Louisville (Kentucky), said she agreed that Parkinson's disease dementia is "a clear neurological entity." While criteria for making the clinical diagnosis of dementia associated with Parkinson's are needed, Dr. Litvan, who is Raymond Lee Lebby professor of Parkinson's disease research at the university, said that for now, she "believe[s] that a neurologist will be able to apply the simple criteria and make a diagnosis of Parkinson's disease dementia and be able to treat it." She emphasized the importance of ruling out other treatable causes of dementia.

Speaking during the open public session of the meeting, Dr. Peter Lurie, of Public Citizen's Health Research Group, a health advocacy group, said that the organization opposed approval of the new indication because it did not meet the minimum criteria for approval; the criteria include the disease being clearly defined and distinct clinically, and the undertaking of a second trial that replicates the findings for efficacy. The drug has "debatable efficacy for a condition that may not exist as a unique entity," he said. ■

FDA Approves Use of MAO Inhibitor for Parkinson's

BY ELIZABETH MECHCATIE
Senior Writer

The recent approval of an irreversible monoamine oxidase inhibitor for treating Parkinson's disease includes an indication for patients with early disease as well as for those with more advanced disease who are already on levodopa.

The Food and Drug Administration approved rasagiline for treating the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy to levodopa. Rasagiline, which will be marketed under the trade name Azilect by the Israel-based company Teva Pharmaceutical Industries Ltd., will be available sometime in July, according to the company. The recommended monotherapy dose is 1 mg once daily; for adjunctive therapy, the recommended starting dose is 0.5 mg once daily, increasing to 1 mg once daily if the clinical response is not adequate.

Even before approval, the American Academy of Neurology had assigned the drug the highest level of evidence for having a significant beneficial effect.

The approval comes with a warning about the need to restrict dietary tyramine and amines contained in medications in order to avoid the risk of a hypertensive crisis, as well as a precaution about monitoring patients for melanoma.

Rasagiline—a new molecular entity that was approved in Europe and Israel last year—inhibits monoamine oxidase type B (MAO-B). Whether it is selective for and inhibits only MAO-B and not MAO-A in humans has not been adequately studied yet, according to the drug's label. The label also states that its precise mechanism of action is unknown, but is believed to be "related to inhibition of MAO-B," which results in increased extracellular levels of dopamine in the striatum.

FDA approval was based on three 18- to 26-week, randomized, placebo-controlled studies. In the monotherapy study of 404 patients with early Parkinson's disease, those treated with rasagiline experienced significantly less worsening in the total score of the Unified Parkinson's Disease Rating Scale (UPDRS) at 6 months, when compared with those on placebo. The two other studies assessed the drug in more than 1,100 patients with more advanced disease. Study participants had had Parkinson's for an average of 9 years, were on chronic levodopa therapy, and were having motor fluctuations. Compared with those on placebo, subjects who received rasagiline had significantly less daily "off" time when their function and mobility were relatively poor.

Dr. Irene Litvan, the Raymond Lee Lebby Professor of Parkinson Disease Research at the University of Louisville (Ky.), described the approval as "great news" because the drug can be used both as monotherapy early in the course of the disease as well as an adjunct agent later in the disease's progression. In addition, the drug causes few side effects, is taken once a day, and does not need to be titrated.

Rasagiline is "an important new treatment … that can not only improve some of the symptoms of Parkinson's disease, but has the potential to slow the progression of the disease," she said in an interview. This potential neuroprotective effect of the drug is the most exciting aspect of the approval and is what many patients have been waiting for, she added, noting that animal and in vitro data and some clinical evidence suggest rasagiline has some neuroprotective benefits.

Teva is currently recruiting patients with early idiopathic Parkinson's disease for a multinational trial to evaluate the effects of rasagiline on slowing the progression of the disease.

Even before approval, the 2006 American Academy of Neurology practice parameters had assigned the drug the highest level of evidence for having a significant beneficial effect, Dr. Litvan pointed out.

The FDA and the label warn that rasagiline may be associated with hypertensive crisis if patients consume tyramine-rich foods and beverages, such as aged cheese, tap beer, and red wine; dietary supplements; or amines contained in cough and cold medicines. A table of tyramine-rich food and beverages to avoid, as well as acceptable foods containing little or no tyramine, is included in the product label.

Dr. Litvan said she was surprised about the recommendation to restrict tyramine because of the selectivity of the drug. Rasagiline is more selective than selegiline (Eldepryl), which inhibits MAO-A in addition to MAO-B, she noted.

Rasagiline's label states that the drug's selectivity for inhibiting only MAO-B—not MAO-A—in humans, and a sensitivity to tyramine during treatment with rasagiline at any dose have "not been sufficiently characterized to avoid restriction of dietary tyramine and amines contained in medications."

Dr. Litvan was not involved in clinical trials of the drug, and has no ties to the manufacturer, other than having received an education grant. Several of her patients who acquired the drug in Europe or Israel have done well on it, she said.

The FDA is also recommending that patients on the drug be checked regularly for signs of melanoma because people treated with rasagiline during its development were diagnosed with melanoma at a rate greater than that seen in the general population. However, the risk was comparable to that seen in some epidemiologic studies of Parkinson's disease patients; at this point, whether the greater melanoma rate is a result of the disease or the drug treatment is unclear. Teva will evaluate the relative risk of melanoma in a 6-month postmarketing study of rasagiline added to standard treatment, in about 5,000 patients. ■