Xadago (Safinamide), an Oral MAO-B Inhibitor, FDA Approved as Adjunctive Treatment for Patients with Parkinson’s Disease

By Loretta Fala, Medical Writer

Parkinson’s disease, a neurodegenerative disorder, is characterized by low brain dopamine concentrations and progressive brain-cell destruction that affects the body’s motor system.\(^1,2\) An estimated 1 million people in the United States have Parkinson’s disease, and 60,000 new cases are diagnosed annually.\(^3\)

Although the incidence of Parkinson’s disease increases with age, approximately 5% to 10% of people are diagnosed with the disease before age 50 years.\(^3\) Men are 1.5 times more likely than women to have Parkinson’s disease.\(^3\) Accurate diagnosis of Parkinson’s disease is challenging, and generally requires a medical history, neurologic examination, and laboratory tests to rule out other disorders.\(^3\)

Symptoms associated with Parkinson’s disease include tremor, rigidity or stiffness, bradykinesia, and impaired balance. This disease can also cause difficulty swallowing, speaking, and writing, and it can have a substantial negative impact on the patient’s quality of life and daily activities.\(^1\)

Treatments for Parkinson’s disease include levodopa plus carbidopa (oral and gel infusion), dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT), anticholinergics, and amantadine.\(^2\) Levodopa continues to be a cornerstone treatment for Parkinson’s disease.\(^4,5\)

Patients with Parkinson’s disease have an “off” episode when medications are not working well, resulting in increasing symptoms such as tremor and difficulty walking.\(^6\) Conversely, an “on” episode indicates that the patient’s symptoms are under control.\(^6\)

Xadago New Option Approved for Parkinson’s Disease

On March 21, 2017, the US Food and Drug Administration (FDA) approved safinamide (Xadago; Newron Pharmaceuticals/US WorldMeds), an oral MAO-B inhibitor, as an adjunctive treatment to levodopa plus carbidopa for patients with Parkinson’s disease who are having “off” episodes.\(^6,7\) The effectiveness of safinamide as monotherapy in Parkinson’s disease has not been established.\(^6,7\)

“Parkinson’s is a relentless disease without a cure. We are committed to helping make additional treatments for Parkinson’s disease available to patients,” said Eric Bastings, MD, Deputy Director of the FDA’s Division of Neurology Products,\(^6\) commenting on the approval of safinamide.

Mechanism of Action

Safinamide inhibits MAO-B by blocking the catabolism of dopamine, a process believed to increase dopamine levels and dopaminergic activity in the brain; however, the exact mechanism of action of safinamide remains unknown.\(^7\)

Dosing and Administration

Safinamide is available in 2 tablet doses: 50 mg and 100 mg.\(^7\) The recommended starting dose is 50 mg, taken orally once daily at the same time of day, with no regard to food. After 2 weeks, the dose can be increased to 100 mg once daily, depending on need and tolerability. Patients with moderate hepatic impairment should not exceed the 50-mg once-daily dose. Safinamide should be discontinued in patients whose hepatic impairment becomes severe after taking safinamide 50 mg.

The 2 Pivotal Clinical Trials

Two double-blind, placebo-controlled, 24-week studies evaluated the efficacy and safety of safinamide as adjunctive treatment in patients with Parkinson’s disease experiencing “off” time while taking a stable dose of levodopa and other Parkinson’s disease drugs.\(^4,7,8\)

Study 1 included 645 patients with Parkinson’s disease (mean disease duration, 8 years) who were randomized to receive safinamide 50 mg daily, safinamide 100 mg daily, or placebo. Patients had at least 1 post-baseline assessment of “on” time.

Adjunctive treatment with safinamide in patients with Parkinson’s disease who were taking a stable dose of levodopa significantly increased “on” time, without
Table 1: Study 1: Change in Mean Total Daily “On” Time\(^a\) with Safinamide as Adjunctive Therapy in Parkinson’s Disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients, N</th>
<th>Baseline, hrs, mean ± SD</th>
<th>Change from baseline to end point, least squares difference(^b) vs placebo</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>212</td>
<td>9.3 ± 2.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Safinamide 50 mg once daily</td>
<td>217</td>
<td>9.4 ± 2.2</td>
<td>0.50 (95% CI, 0.03-0.96)</td>
<td>.0356</td>
</tr>
<tr>
<td>Safinamide 100 mg once daily</td>
<td>216</td>
<td>9.6 ± 2.5</td>
<td>0.53 (95% CI, 0.07-1.00)</td>
<td>.0238</td>
</tr>
</tbody>
</table>

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Table 2: Study 2: Change in Mean Total Daily “On” Time\(^a\) with Safinamide as Adjunctive Therapy in Parkinson’s Disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients, N</th>
<th>Baseline, hrs, mean ± SD</th>
<th>Change from baseline to end point, least squares difference(^b) vs placebo</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>273</td>
<td>9.1 ± 2.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Safinamide 100 mg once daily</td>
<td>270</td>
<td>9.3 ± 2.4</td>
<td>0.99 (95% CI, 0.58-1.39)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

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Adverse Reactions

The most common (incidence with safinamide 100 mg ≥2% than with placebo) adverse reactions were dyskinesia (17%), fall (6%), nausea (6%), and insomnia (4%).7 The incidence of patients discontinuing treatment in Study 1 and 2 for any adverse events was 5% with safinamide 50 mg, 6% for safinamide 100 mg, and 4% for placebo.

The most common adverse event causing study discontinuation was dyskinesia, which was 1% with safinamide 50 mg daily; 1% with safinamide 100 mg daily; and 0% with placebo.7

Contraindications

Safinamide is contraindicated for use concomitantly with other MAO inhibitors or other potent inhibitors of MAO (eg, linezolid).7 In addition, safinamide is contraindicated in patients using opioids; selective norepinephrine reuptake inhibitors; tricyclic or tetracyclic antidepressants; and their derivatives; or St John’s wort. Safinamide is also contraindicated in patients taking dextromethorphan, those with a history of hypersensitivity to safinamide, and patients with severe hepatic impairment.7

Drug Interactions

Patients receiving safinamide concomitantly with selective serotonin reuptake inhibitors should be monitored for serotonin syndrome.7 Patients using safinamide concomitantly with prescription or nonprescription sympathomimetic drugs (ie, nasal, oral, or ophthalmic decongestants and cold remedies) should be monitored for hypertension, and patients using safinamide should avoid foods containing high levels of tyramine, because of increased risk for hypertension.7

Safinamide may inhibit intestinal substrates of breast cancer resistance protein (BCRP), which could increase the plasma concentrations of BCRP substrate drugs. Patients who receive safinamide concomitantly with BCRP substrates should be monitored for pharmacologic or adverse effects.7

Dopamine agonists (eg, antipsychotics or metoclopramide) may diminish the effectiveness of safinamide and exacerbate the symptoms of Parkinson’s disease.7

Use in Specific Populations

During pregnancy, safinamide should only be used if its potential benefit justifies the potential risk to the fetus.7

Safinamide may cause serious side effects in nursing infants; consider whether nursing or the drug should be discontinued based on the importance of the drug to the mother’s health.7

No significant differences in the safety or effectiveness of safinamide were seen between patients younger and older than age 65 years; however, some older patients may have increased sensitivity to safinamide.7

Safinamide plasma concentrations are increased in patients with hepatic impairment; the drug is contraindicated in patients with severe hepatic impairment.7

Warnings and Precautions

Safinamide may cause or exacerbate hypertension.7
Serotonin syndrome may occur when safinamide is used with MAO inhibitors, antidepressants, or opioids.  
Safinamide 100 mg daily has been associated with sleep attacks or a sudden onset of sleep while engaging in daily activity.  
Safinamide may cause or exacerbate dyskinesia. Reducing the levodopa dose or the dose of another dopaminergic drug may reduce dyskinesia.  
Patients with a major psychotic disorder should generally avoid safinamide. Consider dose reduction or discontinuation if a patient has hallucinations or psychoticlike behaviors while taking safinamide.  
Patients taking safinamide can have intense impulsive or compulsive behaviors. If these behaviors occur, consider a dose reduction or treatment discontinuation.  
Hyperpyrexia and confusion have been associated with rapid dose reduction, withdrawal, or changes in safinamide or other drugs that increase central dopaminergic tone.  

**Conclusion**  
The FDA approval of safinamide provides a new once-daily oral treatment option as an adjunct to levodopa plus carbidopa for patients with Parkinson’s disease who have “off” episodes. Safinamide can be taken with or without meals. In 2 clinical trials with more than 1100 patients with Parkinson’s disease, treatment with safinamide significantly increased “on” time, without troublesome dyskinesia, and reduced “off” time, when added to stable doses of levodopa.  

**References**  

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