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SAFINAMIDE

▼XADAGO® FOR ADVANCED PARKINSON´S DISEASE

dtbn
DRUG ASSESSMENT REPORT
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ON Symptoms / LOW Evidence / OFF Medication

Indications

Safinamide is indicated for the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products in mid- to late-stage fluctuating patients.

Mechanism of action and pharmacokinetics

Safinamide is a selective reversible inhibitor of monoamine oxidase B (MAO-B) inhibitor that induces an increase of striatal extracellular dopamine levels. Safinamide blocks sodium voltage-dependent channels, modulates calcium release, and inhibits glutamate release.

It is taken orally and does not interact with food. Its binding to plasma proteins is 88-90%. Safinamide is almost exclusively cleared by hepatic metabolism and is predominantly mediated by high-capacity amylases without dependence on cytochrome P450 enzymes.

Dosage and administration

The initial oral dose is 50mg/d, which can be increased to 100mg/d according to patient's requirements. A dose of 50mg/d is recommended in patients with moderate liver disease.

Clinical efficacy

Safinamide has been tested in two randomized placebo-controlled clinical trials and an extension study. In the 016 and SETTLE studies, safinamide was found to be superior to placebo in the mean ON-time without troublesome dyskinesia at 24 weeks of treatment (primary endpoint). The study 016 revealed a 31 min.-difference (CI95% 4-56 min) with safinamide 50 mg and a difference of 33 min (CI95% 7-59 min) with safinamide 100 mg. The SETTLE study reported a 58 min.-difference between safinamide 50-100 vs. placebo (CI95% 34-82 min). These results demonstrate a slight improvement with safinamide, although its clinical relevance is uncertain.

No statistically significant differences were observed in the 018 trial, an 18-month extension study of the 016 trial.

Safinamide is not an option as a complementary treatment for advanced Parkinson's disease

Safety

Adverse reactions

The most common adverse effects of safinamide include: CNS (dyskinesia, headache, drowsiness, etc.), gastrointestinal (nausea and vomiting), musculoskeletal and vision (cataract, retinopathy) problems. Unlike most adverse effects, orthostatic hypotension tended to increase with higher doses of safinamide. Mortality with safinamide was 2.6% (1.7 per 100 persons-year) vs. 1.2% (1.3 per 100 persons-year) with placebo p=0.02. The most frequent causes of death were heart disease, general disorders and infections. Notably, patients with severe liver, renal or cardiovascular disease were excluded from the study.

The EMA remarked the elevated risk of dyskinesia associated with safinamide (which is generally mild or moderate), since 1.1% of patients treated with safinamide had dyskinesia, as compared to 0.2% of patients treated with placebo.

ABSTRACT

Safinamide is a new selective monoamine oxidase B (MAO-B) inhibitor indicated for idiopatic Parkinson's disease as a complementary treatment of levodopa alone or in combination with other drugs for Parkinson's disease in patients with mid- or advanced-stage disease with fluctuations.

Safinamide has been proven to be moderately superior to placebo in the mean daily time ON without dyskinesia. However, this drug has not been compared with other options such as selegiline or rasagiline.

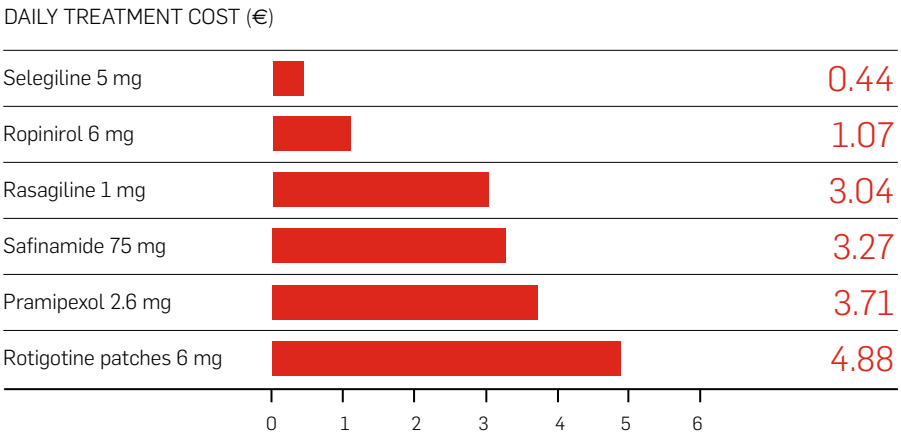
The mortality rate was significantly higher for patients receiving treatment with safinamide vs. placebo. Safinamide is contraindicated in patients with retinopathy and severe hepatic dysfunction.

The effectiveness of safinamide cannot be determined due to the lack of data on the use of this drug for Parkinson's disease. The benefit/risk balance of this drug has not been determined yet, since it has not been compared with other more widely used drugs.

CLASSIFICATION

4	IMPORTANT THERAPEUTIC INNOVATION
3	MODEST THERAPEUTIC INNOVATION
2	SOME ADDED VALUE IN SPECIFIC SITUATIONS
1	NO THERAPEUTIC INNOVATION
0	**INSUFFICIENT EVIDENCE**

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.



Warnings and precautions

Due to the risk of serotonergic symptoms associated with the use of selective inhibitors of serotonin reuptake (SSRIs), safinamide should be administered with caution at the minimum effective dose.

Safinamide should not be administered to patients with a history of ophthalmological problems at risk of retinal damage (e.g. albine patients, family history of hereditary retinal disorder, retinitis pigmentosa, any active retinopathy or uveitis).

The appearance of impulse control disorder (ICD) has been associated with the use of MAO-B inhibitors, but not with the administration of safinamide. Patients and carers should be warned on the potential occurrence of ICD symptoms, which include compulsive behaviors, obsessive thoughts, compulsive gambling, increased libido, hypersexuality, impulsive behavior, and compulsive shopping and spending.

The adverse effects of levodopa can be exacerbated with the use of safinamide and existing dyskinesia can worsen, which may require a reduction of levodopa dose.

Usage in special situations

Pediatric population: no studies available. Women of childbearing age: the use of contraceptives is required. Pregnancy and lactation: animal testing suggest the occurrence of adverse events (do not administrate). Patients >65 years: dose change is not required, there is limited experience in patients > 75 years. Liver failure: start with 50mg/d in patients with moderate liver failure, discontinue in case of progression.

Drug interactions

Do not administrate in combination with other MAO inhibitors (including moclobemide) due to risk of non-selective inhibition of MAO resulting in an hypertensive crisis.

Concomitant use of pethidine has been associated with the occurrence of severe adverse events. If needed, pethidine can be administered at least 7 days after safinamide therapy has been interrupted.

Concomitant use with sympathomimetics such as those present in nasal and oral decongestants or cold medications containing ephedrine or pseudoephedrine should be cautious.

Concomitant use of dextromethorphan, fluoxetine or fluvoxamine requires close monitoring due to the potential appearance of severe adverse events (serotonin syndrome). In case concomitant use of SSRIs is required, they should be administered at the minimum effective dose and waiting a default period of five half-lives after last SSRI dose. Adverse events have been reported to be associated with the concomitant use of serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic and tetracyclic antidepressants. In sum, SNRIs can be administered but at the minimum effective dose.

As to tyramine-rich diets (fermented cheese, red wine, cured dry sausages, etc.), no restrictions are applicable.

Contraindications

- Concomitant use with other MAO inhibitors.
- Concomitant use with pethidine.
- Patients with severe liver failure.
- Patients with albinism, retinal degeneration, uveitis, hereditary retinopathy or severe proliferative diabetic retinopathy.

Place in therapeutics

Safinamide has been shown to be slightly –although statistically significantly– superior to placebo. Yet, this difference has not been proven to be clinically relevant to treat motor fluctuations as a complementary treatment of levodopa in patients with mid- or advanced-stage Parkinson's disease.

No comparative studies have been performed of safinamide with other options such as other MAOIs-B (selegiline, rasagiline). Therefore, the advantages or disadvantages of this drug over other drugs cannot be determined.

Considering the above, the effectiveness of safinamide in the treatment of Parkinson's disease cannot be determined due to the lack of data. Its moderate therapeutic effect when compared with placebo and the lack of comparative studies make it impossible to determine the safety and effectiveness of safinamide as compared to other more widely used drug options.

Presentation

Xadago® (Zambon) 50 mg 30 tablets (131.13€), 100 mg 30 tablets (131.13€).

Reference

Based on the Therapeutic Positioning Report.

Servicio Navarro de Salud
Osasunbidea

INTERNATIONAL SOCIETY OF DRUG BULLETINS

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