SYNAPSES:
Real world data evaluating the drug safety and efficacy in Parkinson's disease

WEBINAR SUMMARY

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Parkinson's Academy

Sponsored by Zambon

Safinamide

Safinamide is a monoamine oxidase inhibitor, meaning it prevents the degradation of dopamine, and also has an effect on non-dopaminergic pathways. In clinical practice, it is started at 50mg, and can be increased to 100mg if needed.

"In my clinical experience, it's usually easily well tolerated, but there are recognised side effects," said Dr Emily Henderson, Academic Consultant Geriatrician at Royal United Hospitals in Bath.

The most common side effects are dyskinesia, somnolence, nausea, orthostatic hypotension (OH), and headaches, she added.

"It was released onto the market in 2015 and at the time it was really exciting because there had not been new drugs in Parkinson's for at least a decade", Emily explained.

The SYNAPSES trial [1]

The SYNAPES trial was published in 2021. The study was conducted in response to a request from the European Medicines Agency to provide real world data on the efficacy of safinamide in groups that had been underrepresented in the clinical trials. These included:

People over 75 years

People with concomitant psychiatric conditions

People with relevant comorbidities

"As a geriatrician, this was music to my ears. Many trials, understandably, tend to enrol younger people who have very few comorbidities and certainly don't have neuropsychiatric symptoms or conditions like cognitive impairment or dementia," said Emily, describing it as a "real step forward".

A European Observational Study to Evaluate the Safety and the Effectiveness of Safinamide in Routine Clinical Practice: The SYNAPSES Trial, was a multi-centre, retrospective/prospective cohort study. It aimed to observe the drug's safety profile and pattern of use in clinical practice in the first year after commercialisation.

The main study objectives were, firstly, to describe the occurrence of adverse events (AE) to see if the side effects reported in the pivotal clinical trials were reflective of those found in clinical practice; secondly, it looked at the experience of people in the 3 subgroups identified by the EMA.

It was retrospective and prospective, meaning patients could be enrolled at the start of safinamide treatment, or within 2 or 4 months. Participants were followed up at month 4, 8, and 12.

Participants

A total of 1,610 patients were enrolled across 128 sites. Of the 1,558 evaluable patients, data was collected on 1,373 at four-month follow up, 1,323 at eight months, and 1,326 at the end of the year.

25% (391) of the patients were older than 75, 42% (661) had psychiatric conditions, and 71% (1,103) had relevant co-morbidities, the most common being hypertension and heart disease (37.8%), metabolic disorder (22.5%), and joint, bone, and pain disorders (13.5%).

The majority of participants, 99%, had idiopathic PD, and the average time between diagnosis and enrolment was 7 or 8 years. "You would expect people to have Hoehn and Yahr stage 2 or 3 Parkinson's disease at this point," said Emily, adding that this correlated to moderate to complex phase disease.

Findings

Emily summarised some of the key findings from the study. In terms of dose alterations, 58% of patients saw their dose increased from 50mg/d to 100mg/d over the course of the study; the dose was de-escalated, from 100mg/d to 50mg/d, in 6%.

Dose increases

58% of patients had a dose increase from 50mg/d to 100mg/d

Dose decreases

6% of patients had a dose decrease from 100mg/d to 50mg/d

Just under half, 46%, of patients experienced at least one adverse event (AE), but only 10% of these were severe. I addition, just 2% of people experienced a serious adverse drug reaction. The percentage of patients experiencing AEs under real life conditions was 30% lower than those seen in the 6-month pivotal trials.

Of all AEs, 52% were judged to be unrelated to safinamide. In 13%, the researchers said it was "probable" that the drug had caused the AE, and in 23%, they said it was "possible". Two per cent were labelled as "definitely" related to the treatment.

Emily said: "We can be very reassured by these data in terms of the side effect profile of the drug."

Overall Unified Parkinson's Disease Rating Scale (UPDRS) scores, and scores across all four domains, remained "relatively stable" across the 12-month follow up period.

In addition, 39% of people saw an overall UPDRS score improvement of higher that the clinically significant threshold of 4.3 points; 45% recorded a UPDRS III score improvement of over the clinically significant threshold of 2.5 points.

Subgroup analysis

In patients over the age of 75 years, there was no relevant difference in AE frequency, severity or action taken, when compared to younger people. However, 13.6% of over 75s experienced a serious adverse event (SAE) compared to 7.7% of younger people.

Just under half, 49.1%, of people with relevant comorbidities experienced AEs and 11.1% SAEs, compared to 37.8% and 4.6%, respectively, of those without.

There were no relevant differences in the rate of AEs and SAEs in terms of frequency, severity and action taken between psychiatric conditions and the non-psychiatric condition groups.

"Not only is safinamide well tolerated and safe, but motor complications and motor scores improved," said Emily, before thanking the EMA for "recognising the need" for the data.

To hear the full discussion, watch the webinar:

https://zresource.co.uk/safinamide/

Reference:

1. Abbruzzese, G., Kulisevsky, J., Bergmans, B., Gomez-Esteban, J. C., Kägi, G., Raw, J., ... & Jost, W. H. (2021). A European observational study to evaluate the safety and the effectiveness of safinamide in routine clinical practice: the SYNAPSES trial. Journal of Parkinson's disease, 11(1), 187-198.

Prescribing Information

Xadago 50 and 100 mg film-coated tablets. Consult Summary of Product Characteristics before prescribing.
Legal Category: POM
Marketing Authorisation number and basic NHS cost: PLGB 31654/0012 and PLGB 31654/0011 £69 for 30 tablets.
Presentation:
Each film-coated tablet contains safinamide methansulfonate equivalent to 50 or 100mg safinamide.
Uses:
Xadago 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.
Dosage and administration:
Treatment with safinamide should be started at 50 mg per day. This daily dose may be increased to 100 mg/day on the basis of individual clinical need. If a dose is missed the next dose should be taken at the usual time the next day.
Method of administration:
Xadago is for oral administration. It should be taken with water. It may be taken with or without food.
Special populations:
Paediatric population: The safety and efficacy of safinamide in children and adolescents under 18 years of age have not been established.
Elderly: No change in dose is required for elderly patients. Experience of use of safinamide in patients over 75 years of age is limited.
Hepatic impairment: Caution should be exercised when initiating treatment with safinamide in patients with moderate hepatic impairment. The lower dose of 50 mg/day is recommended for patients with moderate hepatic impairment. It is contraindicated in severe hepatic impairment.
Renal impairment: No change in dose is required for patients with renal impairment.
Women of childbearing potential: Safinamide should not be given to women of childbearing potential unless adequate contraception is practiced.
Pregnancy: There are no or limited amount of data from the use of safinamide in pregnant women. Xadago should not be given during pregnancy.
Breast-feeding: Available pharmacodynamic/toxicological data in animals have shown excretion of safinamide in milk. A risk for the breast-fed child cannot be excluded. Xadago should not be used during breast-feeding.
Contraindications:
Hypersensitivity to the active substance or to any of the excipients. Concomitant treatment with other monoamine oxidase (MAO) inhibitors or with pethidine. Xadago should not be used in patients with severe hepatic impairment nor in patients with albinism, retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy.
Warnings and Precautions:
Xadago may be used with selective serotonin re-uptake inhibitors (SSRIs) at the lowest effective dose, with caution for serotoninergic symptoms. The concomitant use of Xadago and fluoxetine or fluvoxamine should be avoided, or if concomitant treatment is necessary these medicinal products should be used at low doses. A washout period corresponding to 5 half-lives of the SSRI used previously should be considered prior to initiating treatment with Xadago. At least 7 days must elapse between discontinuation of Xadago and initiation of treatment with MAO inhibitors or pethidine. When safinamide is co-administered with products that are BCRP substrates, please refer to the SmPC for that particular medicinal product. Impulse control disorders can occur in patients treated with dopamine agonists and/or dopaminergic treatments. Patients and carers should be made aware of the behavioural symptoms of ICDs that were observed in patients treated with MAO-inhibitors, including cases of compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying.
Safinamide used as an adjunct to levodopa may potentiate the side effects of levodopa, and preexisting dyskinesia may be exacerbated, requiring a decrease of levodopa.
Somnolence and dizziness may occur during safinamide treatment, therefore patients should be cautioned about using hazardous machines, including motor vehicles, until they are reasonably certain that safinamide does not affect them adversely.
Interactions:
Safinamide must not be administered along with other MAO inhibitors (including moclobemide) as there may be a risk of non-selective MAO inhibition that may lead to a hypertensive crisis. Serious adverse reactions have been reported with the concomitant use of pethidine and MAO inhibitors. Concomitant administration of dextromethorphan or sympathomimetics such as ephedrine or pseudoephedrine, requires caution.
Serious adverse reactions have been reported with the concomitant use of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic/tetracyclic antidepressants and MAO inhibitors. In view of the selective and reversible MAO-B inhibitory activity of safinamide, antidepressants may be administered but used at the lowest doses necessary. Safinamide may transiently inhibit BCRP, a weak interaction was observed with rosuvastatin. It is recommended to monitor patients when safinamide is taken with medicinal products that are BCRP substrates (e.g., rosuvastatin, pitavastatin, pravastatin, ciprofloxacin, methotrexate, topotecan, diclofenac or glyburide) and to refer to their SmPCs to determine if a dose adjustment is needed.
Side Effects:
Consult the summary of product characteristics for other side effects.
Serious adverse reactions are known to occur with the concomitant use of SSRIs, SNRIs,
tricyclic/tetracyclic antidepressants and MAO inhibitors, such as hypertensive crisis, neuroleptic malignant syndrome, serotonin syndrome, and hypotension.
Other serious adverse reactions include bronchopneumonia, pyoderma, basal cell carcinoma, leukopenia, cachexia, hyperkalaemia, delirium, suicidal ideation, Parkinson's disease, syncope, cataract, glaucoma, diabetic retinopathy, eye haemorrhage, papilloedema, arrhythmia, myocardial infarction, hypertensive crisis, peptic ulcer, upper gastrointestinal haemorrhage, hyperbilirubinaemia, ankylosing spondylitis, prolonged QT on ECG, and fat embolism. Common undesirable effects include insomnia, dyskinesia, somnolence, dizziness, headache, Parkinson's Disease, cataract, orthostatic hypotension, nausea and fall.
Further information is available from: Zambon UK Limited, Ground Floor, Suite F, Breakspear Park, Breakspear Way, Hemel Hempstead, HP2 4TZ, United Kingdom
Email: infoUK@ZambonGroup.com
Tel: +44 (0)800 0288 942
Prescribing Information drawn up: July 2022

Adverse event reporting
Adverse reactions should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse reactions should also be reported to Zambon UK Limited. at drugsafetyUK@ZambonGroup.com or telephone: +44 (0) 800 0288 942