Real World Evidence with Xadago (safinamide)

XADAGO (safinamide)

The SYNAPSES Trial: European, multicenter, retrospective-prospective cohort StudY to observe safiNAmide safety profile and pattern of use in clinical Practice during the firSt post commErcialization phaSe

The study was set-up due to a recommendation from the EMA to establish data in the following subsets:

Patients **> 75 years old** (**25.1%** of evaluable patients)

Patients with **psychiatric conditions** (**42.4%** of evaluable patients)

Patients with **relevant comorbidities** (**70.8%** of evaluable patients)

The study had broad and comprehensive inclusion criteria in order to reflect clinical practice and observe a broad audience with Parkinson's Disease. Patients were eligible if they were at least 18 years of age, had started treatment within the past 4 months and had provided signed informed consent and privacy consent.

Patient recruitment

- Study conducted in 6 countries (UK, ES, IT, DE, BE, CH)
- 1610 patients enrolled across 128 sites

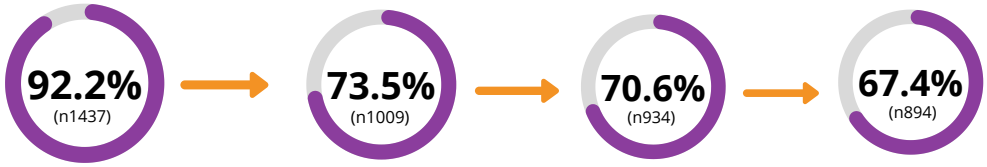
12 months

85.1% of patients completed 12 month observational period

1558 evaluable patients
1373 at 4 month follow-up
1323 at 6 month follow-up
1326 at 12 month follow-up

The number of patients with motor fluctuations* decreased during the study with safinamide treatment

All observable motor complications* decreased by 38% during the study



Full analysis set

Total evaluable patients at **4 months**

Total evaluable patients at **8 months**

Total evaluable patients at **12 months**

Descriptive data: Fluctuations at the start of treatment and during follow-up

Adapted from Abbruzzese et al. (2020) [1]

*Wearing off, Dyskinesia, Early morning fluctuations, Unpredictable fluctuations, Delayed on, Other

Clinically significant improvements were also seen in the UPDRS motor score and in the UPDRS total score in ≥40% of patients, according to the criteria developed by Shulman et al.

Real World Safety Evidence

During observation 46% patients experienced adverse events, 28% patients had adverse drug reactions and 9% patients had serious adverse events.

The adverse events were those already described in the patients' information leaflet. The majority were mild or moderate and completely resolved and no differences were detected between the subgroup of patients.

Safety results by patient subgroup compared to study patients not in subgroup

Subgroups	Adverse Event (AE)	Adverse Drug Reaction (ADR)	Serious Adverse Event (SAE)	Serious Adverse Drug Reaction (SADR)
>75 years	Similar	Similar	Higher	Similar
Comorbidities	Higher	Similar	Higher	Similar
Psychiatric	Similar	Similar	Similar	Similar

Adapted from Abbruzzese et al. (2020) [1]

Summary

The SYNAPSES study reinforces the previously documented safety profile of safinamide in a real world setting, even in special groups of patients. Motor complications and motor scores improved with clinically significant results in the UPDRS motor and total scores.

1. Abbruzzese et al., 2021: A European Observational Study to Evaluate the Safety and the Effectiveness of Safinamide in Routine Clinical Practice: The SYNAPSES Trial. Journal of Parkinsons Disease. 2021;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: Profile Pharma Ltd, Bicentennial Building, Southern Gate, Chichester, West Sussex, P019 8EZ,
United Kingdom.
Email: infoUK@ZambonGroup.com
Tel: +44 (0)800 0288 942

Prescribing Information drawn up: February 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