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Summary of the risk management plan (RMP) for Xadago (safinamide)

This is a summary of the risk management plan (RMP) for Xadago, which details the measures to be taken in order to ensure that Xadago is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Xadago, which can be found on Xadago's EPAR page.

Overview of disease epidemiology

Xadago is a medicine used to treat Parkinson's disease.

Parkinson's disease is a progressive brain disorder that causes shaking, slow movement and muscle stiffness. The rate of progression of Parkinson's disease, as well as the array of parkinsonian signs and symptoms, differs widely among individual patients.

The disease affects about 1% of the population over the age of 55 years, with a male-to-female ratio of 3:2.

Risk factors for Parkinson's disease include a family history, male gender, head injury, exposure to pesticides, consumption of well water and rural living.

Summary of treatment benefits

Xadago contains the active substance safinamide, a 'monoamine oxidase-B (MAO-B) inhibitor'. It blocks the enzyme monoamine oxidase type B which breaks down dopamine, thereby helping to restore dopamine levels in the brain and improving the patient's symptoms. Xadago is used in addition to levodopa (a medicine commonly used to treat the symptoms of Parkinson's disease) either alone or in combination with other Parkinson's medicines, in patients with mid- to late-stage Parkinson's disease who are having 'motor fluctuations'. These fluctuations occur when the effect of levodopa wears off and the patient suddenly switches from being 'on' and able to move about to being 'off' and having difficulty moving about.

Xadago, as an add-on treatment to levodopa with or without other medicines for Parkinson's disease, has been compared with placebo (a dummy treatment) in two main studies involving 1,218 patients with late stage Parkinson's disease who experienced fluctuations. In both studies, 6 months treatment with Xadago increased the time during the day during which patients were 'on' and able to move by 30-60 minutes when compared with placebo. Another study showed maintenance of this effect for 24 months.

Xadago was also investigated as an add-on to treatment in 2 studies in patients with early Parkinson's disease without fluctuations, but these studies did not show a clear benefit and the company did not pursue this use as part of the application.

Unknowns relating to treatment benefits

Limited information about the benefits of Xadago is available for patients:

- aged below 30 and above 75 years;
- treated for longer than 3 years;
- with severe, disabling peak-dose or biphasic dyskinesia (difficulty controlling movement), or with unpredictable or widely swinging fluctuations;
- who have undergone stereotactic surgery (a surgical procedure where tissue is removed with guidance of imaging techniques, such as MRI);
- with psychiatric illnesses, specifically psychosis, bipolar disorder or severe depression.

Xadago has not been studied in women not using birth control methods, children below 18 years, patients with severe liver impairment, and patients with a history of eye disorders that put the retina at risk.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Unintended and uncontrollable movements (dyskinesia)	Dyskinesia is reported as the most common side effect in mid/late Parkinson's disease patients treated with levodopa alone or in combination with other dopaminergic medicines (i.e. medications that increase the level and promote the action of dopamine). An increased incidence of side effects relating to dyskinesia in mid- to late- stage Parkinson's disease patients on levodopa was observed in patients treated with Xadago. It was reported in 25.1% of Xadago-treated patients compared with 13.9% with placebo.	The doctor should consider adjusting the patient's medication, using different combinations to see if there is a reduction in dyskinesia.
Risk of congenital malformations (teratogenicity)	No clinical data is available on the use of Xadago during pregnancy. However, fetal malformations were seen in animal studies. Xadago, given alone or even more when given in combination with other dopaminergic medicines is thought to increase the risk of congenital malformations.	Xadago should not be taken during pregnancy or given to women of childbearing potential who are not using adequate contraception.

Important potential risks

Risk	What is known
Risk of retinal deterioration	Retinal deterioration was observed in toxicity studies in rats but not in

Risk	What is known
(degeneration of the layer at the back of the eye responsible for sight)	monkeys. The effects of Xadago on the eye have been comprehensively evaluated in humans using an ophthalmological (eye) examination in around 2,000 patients in therapeutic studies. There was no difference in the incidence of adverse events relating to the lens or the retina in Xadago-treated patients compared with placebo. Although not evident in the clinical data, retinal deterioration is considered an important potential risk in patients with Parkinson's disease treated with Xadago.
Use in patients with severe reduction of liver function (hepatic impairment)	Blood levels of Xadago increase slightly in patients with moderate liver disease and are expected to be much higher in patients with severe liver disease. Xadago must not be used in patients with severely reduced liver function, and a lower dose is recommended in patients with moderately reduced liver function.
Temptation to carry out certain activities such as addictive gambling, excessive spending, and impulsive behaviour and an abnormally high sex drive (impulse control disorders)	Impulse control disorders can occur in patients treated with medications that increase the level and promote the action of dopamine. Some reports of impulse control disorders have also been observed with other medicines of the class MAO-B inhibitors. Treatment with Xadago has not been associated with any increase in the appearance of impulse control disorders.
Concomitant use of medicines blocking the enzyme monoamine oxidase (MAO), or medicines that increase the level and promote the action of the neurotransmitter serotonin (serotoninergic medicines) and/or pethidine	There is a risk of interaction between these medicinal products, based on their common mechanism of action. Serious adverse events have been reported with the combined use of MAO inhibitors and pethidine. As this may be an effect of this class of medicines, the use of Xadago with pethidine is contraindicated. Xadago must not be given with other MAO inhibitors, as concomitant use may lead to a hypertensive crisis (extremely high blood pressure).

Missing information

Risk	What is known
Safety in patients with retinal disease or a history of retinal disease	Since patients with a history of retinal disease, including inherited conditions, were excluded from clinical studies with Xadago, no information is available about the risk of retinal deterioration in this population.
Use of safinamide in patients aged below 30 years and above 75 years	Use in these patients has not been sufficiently investigated. Data will be collected and evaluated in a post-authorisation study.

Risk	What is known
Effects of overdose	Reports of overdose with safinamide have been rare. The expected pattern of events or symptoms following intentional or accidental overdose with Xadago would be those related to its mechanism of action. The effects of excessive inhibition of monoamine oxidase (leading to an increase in dopamine level) could include increase of blood pressure (hypertension), dizziness on standing (postural hypotension), seeing things that are not there (hallucinations), agitation, nausea (feeling sick), vomiting, and dyskinesia (uncontrollable movements).
Use in patients with severe, disabling dyskinesia [which occurs when blood levels of levodopa are rising or falling (biphasic dyskinesia) or when levodopa reaches its peak of effectiveness and dopamine levels are at their highest (peak-dose dyskinesia)], or with unpredictable or widely swinging fluctuations	There is no information in these patient populations.
Use in patients who have undergone stereotactic surgery as a treatment for Parkinson's disease	There is no information in this patient population.
Use in patients with psychiatric illnesses, specifically psychosis, bipolar disorder or severe depression	No information was obtained in patients with mental disorders, except for mild depression and anxiety. No increase in psychiatric disorders was noted in patients treated with safinamide.
Long term use (for longer than 3 years)	734 patients with mid- to late-stage Parkinson's disease received Xadago for over one year while 414 and 222 received treatment for over 2 or 3 years respectively. 169 patients were exposed to Xadago for over 4 years.
Use of Xadago concomitantly with medicines which are taken up by BCRP (a protein that exchanges a wide range of substances across biological membranes)	Xadago may transiently block BCRP. A post-authorisation study will be carried out; until such results are available, a time interval of 5 hours should be kept between dosing of Xadago and medicines that are rapidly (Tmax ≤2 hours) taken up by BCRP.
Whether specific substances blocking amidases (amidase inhibitors) involved in the metabolism of safinamide may increase the blood levels of Xadago	Xadago is broken down to its major metabolite by enzymes called amidases. Many, as yet unidentified, amidases appear to be involved in this activity. An amidase inhibitor may increase the level of Xadago. However, this is unlikely as many amidases are involved in its metabolism.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Xadago can be found on Xadago's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	**Objectives**	**Safety concerns / efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
Drug utilisation study	To investigate how safinamide is prescribed and used in routine clinical practice.	To confirm the risk/benefit profile of safinamide in patients aged >75 years and patients who are concomitantly suffering from psychiatric conditions (specifically psychosis, bipolar disorder or severe depression).	Planned	July 2019
BCRP interaction study	To investigate if safinamide-induced BCRP inhibition increases the exposure of BCRP substrates.	To determine if safinamide's blocking of BCRP increases exposure/side effects of BCRP substrates with Tmax <2 hours.	Planned	July 2015
In vitro amidase study	To identify specific substances blocking amidases (amidase inhibitors) involved in the	To assess if inhibitors of amidases would increase the exposure of safinamide by	Planned	July 2015

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	metabolism of safinamide	blocking its metabolism.		

Studies which are a condition of the marketing authorisation

None.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 01-2015.