Summary of Risk Management Plan for Xadago® (safinamide)

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Xadago is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Xadago in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Zambon Svizzera SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of Xadago.

PART VI.: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR XADAGO (SAFINAMIDE)

This is a summary of the risk management plan (RMP) for Xadago. The RMP details important risks of Xadago, how these risks can be minimised, and how more information will be obtained about safinamide's risks and uncertainties (missing information).

Xadago's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how safinamide should be used.

This summary of the RMP for Xadago should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Xadago's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Xadago is authorised for the treatment of patients with idiopathic Parkinson disease, in mid-to late-stage fluctuating patients receiving a stable dose of L-dopa alone or in combination with other Parkinson disease medications (see SmPC for the full indication). It contains safinamide as the active substance and it is given by oral route of administration as 50 or 100 mg tablets.

Further information about the evaluation of Xadago's benefits can be found in Xadago's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to the EPAR summary landing page:

https://www.ema.europa.eu/en/medicines/human/EPAR/xadago

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Xadago, together with measures to minimise such risks and the proposed studies for learning more about Xadago's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of safinamide is not yet available, it is listed under 'missing information' below.

II.A. List of important risks and missing information

Important risks of Xadago are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered or taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Xadago. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Summary of safety concerns	
Important identified risk:	• Dyskinesia • Teratogenicity
Important Potential Risks:	• Retinal degeneration in patients with Parkinson disease treated with safinamide • Use in severe hepatic impairment. • Impulse control disorders (ICDs) • Concomitant use of MAOIs, serotonergic drugs, and/or pethidine.
Missing information:	• Use in patients with history and/or presence of retinal disease • Use of safinamide in patients aged<30 years • Long term use >3 years • Whether specific inhibitors of the amidases involved in the metabolism of safinamide to NW-1153, may increase the exposure of safinamide

II.B. Summary of important risks

Important identified risks: Dyskinesia	
Evidence for linking the risk to the medicine	Risk identified during clinical development (clinical trials NW-1015/016/III/2006, NW-1015/018/III/2006, 27919 (SETTLE) and Open-label Extension (28850)).

	Known drug class effect (L-dopa, MAO-B inhibitors, any agent with dopaminergic properties) (selegiline, rasagiline; Thomson Reuters Healthcare, Drug Summary Information).
Risk factors and risk groups	Patients on L-dopa alone, or in combination with other dopaminergic treatments are at risk for developing dyskinesia.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4, 4.8 and 4.9 PL sections 2, 3 and 4Routine

Important identified risks: Teratogenicity	
Evidence for linking the risk to the medicine	A comprehensive reproductive toxicity study programme indicates that Safinamide when given alone, or even more so when given in combination with dopaminergic drugs, is predicted to increase the risk of adverse developmental and perhaps reproductive outcomes in humans when used in accordance with the dosing information in the product label.
Risk factors and risk groups	Women of childbearing potential.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.6 PL section 2

Important potential risks: Retinal degeneration in patients with Parkinson disease treated Safinamide	
Evidence for linking the risk to the medicine	Retinal degeneration was observed in rat repeated-dose toxicity studies but not in monkey studies. The ocular effects of safinamide have been comprehensively evaluated using an ophthalmological examination in ~2000 patients in therapeutic studies, including the measurements of retinal change using Ocular Coherence Tomography (OCT) in over 300 patients on safinamide, and retinal function using electro-retinogram (ERG) in a single center in a limited number of patients. Review of the data, and detailed statistical analyses did not detect any systematic difference in the incidence of newly abnormal, or worsening ocular function in safinamide treated patients compared to placebo. There was no difference in the incidence of adverse events relating to the lens or the retina in safinamide treated patients compared to 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. Since patients with history of retinal disease, including inherited conditions, were excluded from the studies, use of safinamide in these patients is contraindicated. However, as patients with history of retinal disease, including inherited conditions were excluded from the studies, use of safinamide in these patients is considered a potential risk.
Risk factors and risk groups	Patients with Parkinson's disease treated with Xadago. Patients with history of retinal disease, including inherited conditions.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3, 4.4 and 5.3 PL section 2

Important potential risks: Use in severe hepatic impairment	
Evidence for linking the risk to the medicine	Patients with severe hepatic impairment were not eligible for safinamide clinical studies, and therefore data in this patient population are not available. Results from a study performed in patients with mild and moderate hepatic dysfunction (Study 28696) indicated higher exposures of safinamide, but without any clinically important changes in liver enzymes. In patients with mild hepatic impairment, the increase in exposure does not require dose adjustment. In patients with moderate hepatic impairment, the lower dose of 50 mg/day is recommended.
Risk factors and risk groups	Patients with mild, moderate or severe hepatic impairment.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.3 and 4.4 PL section 2

Important potential risks: Impulse control disorders (ICDs)	
Evidence for linking the risk to the medicine	ICDs can occur in patients treated with dopamine agonists and/or dopaminergic treatments. Some reports of ICDs have also been observed with other MAO-inhibitors. No increase in incidence of ICD assessed using the QUIP in safinamide treated patients compared to placebo.
Risk factors and risk groups	Patients with a medical history of impulse control disorders or concomitantly on other MAO-inhibitors.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 and 4.8

	PL section 2 and 4

Important potential risks: Concomitant use of MAOIs, serotonergic drugs, and/or pethidine	
Evidence for linking the risk to the medicine	Serious adverse events, including serotonin syndrome, have been reported with the concomitant use of MAOIs, serotonergic drugs, and/or pethidine. These patients were not included in safinamide clinical studies. As this may be a class effect, it has been considered an important potential risk.
Risk factors and risk groups	Patients concomitantly on MAO-inhibitors, serotonergic drugs and/or pethidine.
Risk minimisation measures	Routine risk minimisation measures SmPC Sections 4.3, 4.4 and 4.5 PL section 2

Missing information: Use in patients with history and/or presence of retinal disease	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3 and 4.4 PL section 2

Missing information: Use of safinamide in patients aged<30 years	
Risk minimisation measures	Routine risk minimisation measures None

Missing information: Long term use >3 years	
Risk minimisation measures	Routine risk minimisation measures None

Missing information: Whether specific inhibitors of the amidases involved in the metabolism of safinamide to NW-1153, may increase the exposure of safinamide	
Risk minimisation measures	SmPC sections 4.5 and 5.2
Additional pharmacovigilance activities	In vitro investigation if applicable in future. See section II.C of this summary for an overview of the post-authorisation development plan.

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Xadago.

II.C.2. Other studies in post-authorisation development plan

None