EU RISK MANAGEMENT PLAN FOR XADAGO (SAFINAMIDE METHANSULFONATE)

RMP version to be assessed as part of this application:

RMP Version number: 7.0

Data lock point for this RMP: 31-Jan-2020

Date of final sign off: 19-October 2020

Rationale for submitting an updated RMP: submission of Drug Utilization Study Z219N02 final report.

Summary of significant changes in this RMP:
Submission of Z219N02 final report and closure of relevant commitment
-deletion of the following missing information:

- Use of safinamide in patients aged >75 years
- Use in patients with psychiatric illness, specifically psychosis, bipolar disorder, or severe depression

Other RMP versions under evaluation: None
RMP Version number: Not applicable
Submitted on: Not applicable
Procedure number: Not applicable

Details of the currently approved RMP:

Version number: 6.1

Approved with procedure: EMEA/H/C/002396/II/0031

Date of approval (opinion date): 5 September 2019

QPPV name: Dr. Maria Luisa Bonura

QPPV signature: [redacted]

[redacted]

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LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AUC	Area Under the Curve
BCRP	Breast Cancer Resistant Protein
BID	Bis in die (Twice a day)
CI	Confidence Interval
Cmax	Maximum concentration
COMT	Catechol-O-methyltransferase
COPD	Chronic Obstructive Pulmonary Disease
ERG	Electro-Retinogram
EMA	European Medicines Agency
ESPD	Early-Stage PD
EPAR	European Public Assessment Report
EU	European Union
GLP	Good laboratory practice
ICD	Impulse Control Disorder
IPD	Idiopathic PD
LSPD	Late-Stage PD
MAH	Marketing Authorisation Holder
MAO	Monoamine Oxidase
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum-tolerated dose
NDA	New Drug Application
NOAEL	No-adverse-effect level
OCT	Ocular Coherence Tomography
PD	Parkinson disease
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
PT	Preferred Term
RMP	Risk Management Plan
RNA	RiboNucleic Acid
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
WHO	World Health Organisation
WOCBP	Women of childbearing potential

PART I. PRODUCT(S) OVERVIEW

Table Part I–1 – Product Overview

Active substance(s) (INN or common name)	Safinamide methansulfonate
Pharmacotherapeutic group(s) (ATC Code)	NO4BD03
Marketing Authorisation Holder	Zambon SpA
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	XADAGO®
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	Chemical class: Safinamide, (S)-(+)-2-[4-(3-fluorobenzyl) oxybenzyl] aminopropanamide methanesulfonate is an alpha-aminoamide derivative with combined dopaminergic and glutamatergic activity.
	Summary of mode of action: Safinamide acts through both dopaminergic and non-dopaminergic mechanisms of action. Safinamide is a highly selective and reversible MAO-B inhibitor causing an increase in extracellular levels of dopamine in the striatum. Its non-dopaminergic mechanism results from state-dependent inhibition of voltage-gated sodium (Na+) channels, and modulation of stimulated release of glutamate.
	Important information about its composition: Safinamide is provided as 50 mg and 100 mg film-coated tablets. The tablets consist of safinamide methanesulfonate combined with the following inactive ingredients: microcrystalline cellulose, crospovidone, colloidal silicone dioxide, magnesium stearate, and for the coating hypromellose and polyethyleneglycole. Candurin® pigments are included for tablet colouring.
Hyperlink to the Product Information	*ema-combined-h2396-en*
Indication(s) in the EEA	Current: Safinamide is indicated as add-on therapy for the treatment of patients with idiopathic PD, in mid-to late-stage fluctuating patients receiving a stable dose of L-dopa alone or in combination with other PD medications.
	Proposed: Not applicable
Dosage in the EEA	Current: Dosing: Treatment with safinamide should be started with a dose of 50 mg once per day. The dose may be increased to 100 mg/day on the basis of individual clinical need. Route of Administration: Safinamide is administered orally

	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Safinamide tablets are orange to copper, round, biconcave, (film-coated tablet with metallic gloss), embossed with the strength “50” or “100” on one side of the tablet.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

PART II. SAFETY SPECIFICATION

PART II: MODULE SI. - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Epidemiology of the disease

Incidence

It is generally accepted that PD is under-diagnosed; therefore the epidemiological studies best designed to estimate its prevalence use a two-step screening method in community-based studies. The first step usually consists of a door-to-door survey aimed at identifying all potential cases of PD. The second step consists of a detailed examination of all potential cases to diagnose definite cases of Parkinsonism. There is no reliable diagnostic test or marker for PD available yet, thus the diagnosis of PD is primarily based on clinical symptoms. The most commonly used criteria for the diagnosis of Parkinsonism in prevalence studies include the presence of at least two of the four following cardinal signs: resting tremors, bradykinesia, rigidity or postural imbalance; or at least one sign in a patient specifically treated.

The diagnosis of idiopathic PD (IPD) is then made once all other possible causes have been eliminated. These other potential causes include:

1. Drug-induced Parkinsonism. Parkinsonism after the use of anti-dopaminergic drugs in the six months preceding onset of symptoms and with no previous history of Parkinsonism.
2. Vascular Parkinsonism. There is a clear temporal relation between a cerebrovascular event and onset of atypical Parkinsonism.
3. Parkinsonism with associated features (Parkinson-plus syndromes) or due to other causes (dementia, head trauma, brain tumour, nervous system infection).
4. Unspecified Parkinsonism; this includes patients with no clear relation between Parkinsonism and a possible cause and patients with parkinsonian features who show no progression or are not responsive to anti-parkinsonian drugs.

Few studies report on incidence rate of PD and they rely on diverse methods. Since PD is a progressive condition with an insidious onset, the point from which people will be considered as definitely suffering from the disease may be blurry and the identification of definite new cases may be difficult.

Some studies conducted to estimate the incidence of PD rely on the identification of cases through a two-step screening method in community-based studies and on the identification of two out of four cardinal signs for the diagnosis of Parkinsonism (Benito-Leon et al., 2004; Wang et al., 1991; de Lau et al., 2004). The cohort of people surveyed is then followed over a certain time, and incident cases are identified. Estimation of crude annual incidence rate in these studies was 13-187/100,000 person-years (p-y) in people older than 65 years old. The incidence increased with the age group and was about 5-11/100,000 p-y in people younger than 55 years, about 30/100,000 in people aged 55 to 64 years old, about 55/100,000 in people aged between 65 and 74 years old, 140/100,000 in people aged 75-84 years old and 46-

181/100,000 in people older than 85 years. However, it should be noted, however, that the number of new cases identified in these studies was generally low and the size of the population considered was also restricted. Thus, the estimates were made sometimes based on a single case identified.

Other methods used the identification of cases through patients' registries, hospital databases or general practitioners. It is likely that studies conducted using those methods would lead to lower estimates than studies conducted using the two-step methods, as they do not include cases who have not sought medical attention.

Another set of criteria for the diagnosis of PD quite commonly used is that of the UK Parkinson's disease Society Brain Bank. For Parkinsonism to be diagnosed according to these criteria, patients must have bradykinesia plus at least one additional feature between rigidity, tremor or postural instability. Idiopathic PD is then identified by ruling out all other possible cause for the disease. Since this diagnosis technique relies on stricter criteria than the methods which consist of identifying two cardinal signs, it is likely that the estimates of disease occurrence will be lower. Studies relying on these methods (Bower et al., 1999; Driver et al., 2009; Winter et al., 2010; Linder et al., 2010) reported estimates of incidence rates between 9.95-19.7/100,000 p-y in the overall general population and about 156/100,000 p-y for people older than 65 years.

Prevalence

Community-based studies using a two-step screening method reported prevalence rates of 345-1267/100,000 persons for people over 40 years of age and of 1400-1600/100,000 persons for people 65 years of age and older (Bergareche et al., 2003; Margante et al., 1992; Schoneberg et al., 1988; Claveria et al., 2002; de Rijk et al., 1995). Prevalence estimates also increased with age, being typically 300-800, 1600-3000 and 3000-15,000/100,000 persons for people 65-69 years of age, 70-80 years of age, and older than 80 years of age, respectively. The response rate in these studies was between 68 and 97%.

The method using the two-step screening in a community probably provides the better estimates.

Other studies used the identification of cases through patients' registries, hospital databases, and general practitioners (Masahla et al., 2010; Chen et al., 2009). Some studies relied on the UK Parkinson's disease Society Brain Bank criteria for PD diagnosis.

Demographics of the population in the authorized indication – age, sex, race/ethnic origin and risk factors for the disease

The occurrence of PD is generally higher in men than women. Reported estimations of the male:female ratio ranged from 1.2 to 2.5 (Linder et al., 2010; Winter et al., 2010; Benito-Leon et al., 2004; Wang et al., 1991). In contrast, analysis of data from the Rotterdam study showed no difference of PD occurrence in men and women (de Rijk et al., 1997).

The cause of PD is unknown. Many researchers believe that a combination of several factors is involved in the development of PD. These factors include free radicals, accelerated aging, environmental toxins, and genetic predisposition.

It may be that free radicals, unstable and potentially damaging molecules that lack an electron, are involved in the degeneration of dopamine producing cells. Free radicals add an electron by reacting with nearby molecules in a process called oxidation. This process can damage nerve cells. Chemicals called antioxidants normally protect cells from oxidative stress and damage. If antioxidative action fails to protect dopamine-producing nerve cells, these cells may be damaged, resulting in PD. Dysfunctional antioxidative mechanisms are associated with older age, which suggests that the acceleration of age-related changes in dopamine production also may be a factor in PD. Exposure to an environmental toxin, such as a pesticide, that inhibits dopamine production and produces free radicals and oxidation damage may be involved in PD development. In some cases, the use of certain drugs can produce parkinsonian symptoms, referred to as drug-induced Parkinsonism. These drugs include chlorpromazine and haloperidol, which are prescribed for psychiatric patients, and metoclopramide, which often is used to treat stomach disorders. Changing the medication or adjusting the dosage of the drug moderates or eliminates Parkinson's symptoms in many cases.

Roughly one-fifth of PD patients have at least one relative with parkinsonian symptoms, suggesting that a genetic factor may be involved in the disorder. Several genes that cause symptoms in younger patients have been identified. However, most cases are not thought to be caused by genetic factors alone.

The main existing treatment options

There is no known cure for Parkinson's disease. The goal of treatment is to control and treat movement-related symptoms of Parkinson's disease, including the use of the following medications:

- Levodopa (L-dopa); L-dopa and dopa (e.g. Sinemet, Atamet); L-dopa and benserazide (e.g. Madopar), Stalevo (e.g. carbidopa, L-dopa and entacapone)
- Dopamine agonists: pramipexole (Mirapex), ropinirole (Requip), bromocriptine (Parlodel)
- Monoamine Oxidase (MAO) inhibitors: selegiline (Eldepryl, Deprenyl), rasagiline (Azilect), safinamide (Xadago)
- Amantadine or anticholinergic medications to reduce early or mild tremors, and/or dyskinesia and rigidity
- Catechol-O-methyltransferase (COMT) inhibitors: entacapone and opicapone as an adjunct to Levodopa

Other medications may include:

- Memantine, donepezil, rivastigmine, galantamine (for cognitive difficulties)
- Antidepressants (for mood disorders)
- Gabapentin, duloxetine (for pain)
- Fludrocortisone, midodrine, botox, sildenafil (for autonomic dysfunction)

- Armodafinil, clonazepam, zolpidem (for sleep disorders)
- Laxatives (for constipation)

Natural history of the indicated condition in the population, including mortality and morbidity:

Studies on PD mortality are sparse. A case-control study including 15,304 subjects with PD was based on administrative data in Canada (Guttman et al., 2001). The odds ratio of deaths in the PD group versus the control group was 2.5. Another study including the identification of cases through hospitalization records, medical records and death certificates yielded a similar estimate (Morens et al., 1996). Two smaller studies relied on general practitioners for the identification of PD cases. These studies reported Standardized Mortality Ratios (SMR) for PD patients of about 1.5. Finally, two additional studies identified cases using the two-step process, including a door-to-door survey. In both studies, the presence of PD was associated with an approximate two-fold increased risk of dying (de Lau et al., 2005; Morgante et al., 2000).

Important co-morbidities:

Based on clinical trials data main expected co-morbilities in the target population included: hypertension, depression, insomnia, constipation, hypercholesterolemia and benign prostatic hyperplasia.

Main expected co-medications included antihypertensive drugs, NSAIDs and anxiolytics.

PART II: MODULE SII. - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Non-Clinical Summary

Safinamide acts through multiple mechanisms of action including, reversible and selective Monoamine Oxidase B (MAO-B) inhibition, state-dependent blockade of voltage gated sodium channels and inhibition of excessive release of glutamate. Therapeutic activity of safinamide in humans is achieved at doses from 50 – 100 mg/day and mediated through MAO-B inhibition (90% inhibition at >30 mg/day), sodium channel blockade (100 mg/day) and glutamate release inhibition (100 mg/day). All of the therapeutic effects were achieved at exposures in humans which were lower than those in the animal studies at the respective NOAELs. In rat and monkey, safinamide absorption is rapid (tmax 1-2 h), the absolute bioavailability is high (rat 92%; monkey 80%) and the plasma elimination half-life is short in rat (1-2 h) and longer in monkey (8-11 h). The plasma protein binding of safinamide and its major metabolite NW-1689 is comparable across species (85% - 89% and ≥97.5%, respectively). The clearance of safinamide is based almost completely on metabolism and it is transformed via the same metabolic pathways in human and toxicology species.

An extensive and complete nonclinical safety program including safety pharmacology studies and its combinations with other drugs commonly used to treat Parkinson's disease. As with any large and comprehensive safety program with a new active pharmaceutical substance, a number of issues have emerged during the course of the studies i.e. CNS effects, changes in some clinical chemistry parameters, minor hepatic changes in rats and mice but not in monkeys, phospholipidosis, adrenal changes, retinal degeneration in rodents but not monkeys and teratogenicity. Of these issues/risks identified in the preclinical studies, none have been confirmed as being associated with safinamide in clinical trials.

Key safety findings from non-clinical studies and relevance to human dosage

Single and Repeat-dose Toxicity

Adverse CNS effects, including tremors, abnormal coordination, clonic contractions and convulsions leading to death were seen at high doses in toxicity studies. Convulsions were encountered in monkeys (≥70 mg/kg/day, 39-wk), rabbits (50 mg/kg/day, embryo-foetal), rats (100 mg/kg/day, carcinogenicity) and mice (≥ 200 mg/kg/day, 4-wk & carcinogenicity). Various CNS signs (tremors, abnormal coordination etc.) were usually prodromal events to convulsions. These convulsions occurred at exposures which were greater than human exposure at 100 mg/day i.e., in monkeys x12.8 (AUC) and x16.8 (C_{max}), in rabbits x3.2 (AUC) and x7.7 (C_{max}), in rats x1.6 (AUC) and x3.9 (C_{max}), and in mice x2.8 (AUC) and x4.9 (C_{max}).

Relevance to human usage: None. No pattern of treatment related seizures, seizure-like events or adverse CNS events has been reported in over 2000 PD patients, with over 1000 subjects receiving safinamide treatment for 1 year or more.

Reversible changes in some clinical chemistry parameters (i.e., increases in alkaline phosphatase, ALT, urea, creatinine, cholesterol, triglycerides and decreased glucose, levels) were observed at doses as low as 30 mg/kg/day in rats and 50 mg/kg/day in monkey.

Relevance to human usage: None.
These changes were not associated with target organ toxicity and have not been observed in clinical trials.

Phospholipidosis was seen in rats at exposures similar to human clinical exposure and in monkeys at greater than 12.8 times human clinical exposure, based on plasma AUC. It was identified inconsistently in rats and with a lower incidence in monkeys but was not associated with increased mortality and not progressive. In rats minimal to moderate foamy macrophage infiltration was seen in repeat dose toxicity studies at doses ⩾ 60 mg/kg/day, while no effects were seen in 13- and 26-week toxicity studies at doses up to 50 mg/kg/day. Generally, foamy macrophages were limited to the lungs, although in a 4-week toxicity study similar cells were seen in the thymus, liver, uterus and vagina. In monkeys, infiltration with foamy macrophages was seen in lymph nodes, thymus and spleen at doses of 80 and 120 mg/kg/day in a 4-week repeat dose toxicity study. No effects were seen in subsequent monkey studies up to 39 weeks of duration at doses up to 70 mg/kg/day. In the second 26-week rat study, EM examinations at 180 mg/kg/day showed that the alveolar macrophages contained concentric multi-lamellar, myeloid body-like inclusions in the cytoplasm which were considered indicative of a phospholipidosis condition. No related functional changes were observed in the affected organs; therefore, these findings are unlikely to be of clinical significance in humans.

Relevance to human usage: None.
No evidence of phospholipidosis has been observed in clinical trials.

Adrenal gland changes were noted in both monkeys and rats. Increased weight and adrenal cortical hypertrophy occurred in different studies in rats at doses > 50 mg/kg/day. Similar effects were seen in the 4-week monkey studies at doses > 40 mg/kg/day, but not in the subsequent sub-chronic and chronic toxicity studies at doses up to 70 mg/kg/day. Inconsistent results were obtained from the serum cortisol and ACTH level measurements performed in monkeys of two 4-week studies and one 39-week study. There were no adrenal cortical changes in mice. Adrenal changes were shown to be reversible following an adequate withdrawal period. There was no evidence of altered adrenal function in clinical studies.

Relevance to human usage: None.
No evidence of adverse effects on the adrenal function has been observed in clinical trials.

Retinal degeneration was observed in rat repeated-dose toxicity studies but not in monkey studies. The species most affected was the rat, in which a time and dose-dependent retinal atrophy was observed both in pigmented and non-pigmented animals. The lowest dose producing retinal atrophy was 15 mg/kg/day. Only mild retinal atrophy occurred in mice after life-time treatment in the carcinogenicity study at the highest dose tested (200 mg/kg/day).

Monkeys were not affected by retinal changes (at doses up to 70 mg/kg/day for 39 weeks); this was confirmed by an independent Pathology Working Group. In addition, no retinal

changes were induced in monkeys treated for 13 weeks with combination of safinamide and L-dopa/carbidopa. Similarly, retinal atrophy was not detected in another 13-week monkey combination study with safinamide and pramipexole either by light or by electron microscopic examination.

In rats, the retinal changes were: time and dose dependent, occur in pigmented and albino strains, exacerbated by high light intensity levels, not exacerbated by combination treatment with L-dopa/carbidopa but slightly exacerbated by pramipexole combination treatment, not associated with melanin binding or undue sensitivity to UV light, correlate with changes in electro-retinogram (ERG) and SD-OCT, apparent early photoreceptor changes at 24 hours after start of treatment by EM examination and reversible after 3 days of treatment. Overall mechanistic studies, including *in vivo* and *in vitro* studies performed to date, did not identify a mechanism underlying the pathogenesis of rodent retinal atrophy, however, the Sponsor continues to evaluate new research.

Relevance to human usage: Important potential risk
In the clinical trial program, the ocular effects of safinamide have been comprehensively evaluated using an ophthalmological examination that included assessment of visual acuity, colour vision, visual fields, intra-ocular pressure, lenticular evaluations, and fundus examination including photo micrographs of the retina in ~2000 patients in therapeutic studies.
Ocular coherence tomography (OCT) was assessed longitudinally in over 300 patients on safinamide, and ERG in a single center in a limited number of patients. All results were reviewed by an independent rater blinded to the treatment condition.
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. These conclusions were based on >1000 patients treated with safinamide who had ocular assessments at 6 months, >600 patients with at least 12 months, and >400 patients with over 2 years ocular assessment in double-blind, placebo-controlled studies, and >200 patients for 3 years, and >130 for 4 years in open label extension studies.
Studies performed to date indicate that retinal degeneration is limited to rodents (it is not seen in monkeys alone, or in combination with pramipexole and levodopa). The results of ophthalmologic monitoring in ~2000 patients in therapeutic studies, indicate there is no increase in incidence of retinal degeneration compared to placebo. Therefore, no special monitoring procedures are required in PD patients receiving safinamide.
Although not evident in the clinical data to date, retinal degeneration is considered an important potential risk in patients with PD treated with safinamide. Since patients with history of retinal disease, including inherited conditions, were excluded from the studies, use of safinamide in these patients is contraindicated.

Reproductive and developmental toxicity

No adverse effects of safinamide were seen on rat male fertility indices despite a marginal increase in morphological sperm abnormalities (mostly at 150 mg/kg/day): the numbers were small and within background data ranges for control animals, A minor reduction in average

path velocity (VAP) and straight line velocity (VSL) at > 100 mg/kg/day was note: VAP was marginally lower than the background range for historical control data and showed no dose-related response (60.0 and 60.3 µm/s at 100 and 150 mg/kg/day, respectively). VSL was well within the range and close to the mean for the historical control data. Importantly, sperm motility was unaffected in spite of the minimal reductions in VAP and perhaps VSL. The small, isolated and changes seen at the mid (100 mg/kg/day) and high dose (150 mg/kg/day) levels are unlikely to signify any adverse effects in men. This is supported by safety margins (AUC based, study ONP005) at these doses i.e. exposure at 100 mg/kg/day in rats exceeded human exposure (100 mg/day) by a factor of 2.8 and at 150 mg/kg/day by a factor of 4.1. The study considered 150 mg/kg/day - the highest dose tested, to constitute the NOAEL for male fertility.
High dose females (150 mg/kg/day) had a slightly lower mean number of corpora lutea. No histopathological changes have been observed in the reproductive organs of either sex including testes and ovaries in the numerous repeat-dose toxicity studies in rats and monkeys. Dose-related foetal abnormalities of ectopic testes and urinary system changes were induced in an oral embryo-foetal development study in the rat. Similar findings as well as an increase of skeletal abnormalities were observed in a subsequent study in combination with L-dopa/carbidopa. L-dopa /carbidopa alone also induced an increased incidence of skeletal abnormalities. In an embryo-foetal development study in rabbits, no abnormalities were recorded. An increase in skeletal variations was considered due to slight maternal toxicity. In a subsequent rabbit embryo-foetal toxicity study in combination with L-dopa/carbidopa, the group receiving safinamide alone showed an increased incidence of minor skeletal abnormalities while L-dopa/carbidopa alone was associated with an increased incidence of major cardiovascular abnormalities. Combination treatment of safinamide and L-dopa/ carbidopa was associated with additional cardiovascular findings and increased foetal deaths. These findings suggest that the combination treatment increases the risk of inducing foetal abnormalities, compared to either compound alone, especially of the cardiovascular system.
In a rat pre- and post-natal development study, there was increased gestational length and pup mortality. The pups had distended abdomens, elevated bilirubin plasma concentrations, were tinged yellow and showed multifocal liver necrosis. Surviving pups had normal liver pathology by postpartum day 21.

Relevance to human usage: Important potential risk
The findings encountered in the comprehensive reproductive toxicity study programme suggest that safinamide when given alone or in combination with dopaminergic co-medications is predicted to increase the risk of adverse developmental and perhaps reproductive outcomes in humans.
Safinamide therefore should not be given during pregnancy, to lactating women, or to women of childbearing potential not practicing adequate contraception. Women of child bearing potential women should be advised not to become pregnant during safinamide therapy.

Nephrotoxicity

No safety findings

Relevance to human usage: None

Hepatotoxicity

There were liver changes in rats and mice but not in monkeys. At 4 weeks in rats, there was fatty change at ⩾ 50 mg/kg/day, increased weight at ⩾ 60 mg/kg/day, centrilobular hypertrophy and increased serum enzymes at ⩾ 200 mg/kg/day. At 13 weeks, there was increased alkaline phosphatase at 80 mg/kg/day, increased liver weight was seen at ⩾ 30 mg/kg/day. These changes were reversible during a recovery period. There were no changes in the 26 week study (high dose, 45 mg/kg/day = NOAEL). In the 13-week pre-carcinogenicity studies, there was hypertrophy (rats and mice ⩾ 100 mg/kg/day) and fatty change (mice 375/250 mg/kg/day). In the carcinogenicity studies, there was hypertrophy (rats & mice ⩾ 50 mg/kg/day) and vacuolation (mice ⩾100 mg/kg/day). Hepatocyte necrosis was not recorded in any of these studies. In the monkey, no liver changes were recorded even at the highest dose in the long-term study (70 mg/kg/day, 39 weeks). This high dose exceeded the human systemic exposure by a factor of x12.8 (AUC based)
In view of: the lack of liver change in the non-human primate, the nonspecific and adaptive nature of the rat and mouse liver changes together with the lack of morphological features of hepatotoxicity (liver cell necrosis, fibrosis, inflammation) and the complete reversibility of all changes, preclinical data indicate a lack of hepatic risk for patients.

Relevance to human usage: None
The absence of adverse hepatic changes in monkeys suggests the effects with safinamide on the liver are rodent-specific. Data from therapeutic clinical studies in over 2000 patients did not detect any evidence of adverse change in liver function tests (LFTs)
The evidence from long-term clinical trials in PD patients of whom >1400 patients were treated for 6 months or more, >1000 patients treated for longer than 1 year, >500 patients treated for longer than 2 years, >200 treated for longer than 3 years, and >160 for more than 4 years, and who were receiving multiple treatments concomitantly to safinamide, confirms that the liver is not a target organ with safinamide treatment. Based on this evidence, no liver function monitoring is required.
Treatment with safinamide should be restricted to a dose of 50mg/ day based on evidence of reduced clearance in patients with moderate hepatic disease (Study 28696). Consequently, treatment with safinamide is contraindicated in patients with severe hepatic impairment.

Genotoxicity

Safinamide was tested in a series of in vitro and in vivo studies to assess its genotoxic potential. No mutagenic or clastogenic activity was shown in any in vitro assay. An increase in micronucleated polychromatic erythrocytes (PCEs) was seen in male mice in an in vivo micronucleus test following a single oral administration of safinamide at a dose of 1000 mg/kg at the 48-hour sampling time, but not at the 24-hour sampling time. This effect was not reproduced in a subsequent experiment using a larger number of animals and was therefore considered not biologically relevant.
In conclusion, safinamide is considered to have no genotoxic potential.

Relevance to human usage: None

Carcinogenicity

The carcinogenic potential of safinamide was studied in two life-span oral studies in mice and rats. These studies indicate that safinamide has no carcinogenic potential.

Relevance to human usage: None

General safety pharmacology:

- **Cardiovascular (including potential for QT interval prolongation)**

In three different studies, both under Good Laboratory Practice (GLP) or non-GLP conditions, safinamide showed a low inhibition of the Kv11.1 (hERG) channel function with IC50s of 28.3 µM, 27 µM and 37.7 µM, respectively. These values are > 70-times above the mean unbound plasma level in humans of approximately 0.4 µM after repeated oral dosing of 100 mg/patient. Also, the three main human metabolites showed no relevant effect on Kv11.1 channel function. Thus, the risk of safinamide causing Torsade de Pointes arrhythmias is considered to be low, as is also shown in in vitro studies on isolated guinea pig papillary muscles and canine Purkinje fibers. In addition, safinamide is not expected to provoke any adverse effects due to interactions with other major cardiac ion channels.
Results from in vivo studies in rat and dog showed no apparent safety concerns with respect to the function of the cardiovascular system. Safinamide was well tolerated in rats at acute dose of up to 50 mg/kg i.v. and 100 mg/kg p.o., with no significant effect on mean arterial blood pressure and ECG rhythm in conscious and anesthetized rats. Neither potentiation of the tyramine pressure effect nor modifications of the pressure response curve to noradrenaline were observed (at 20 mg/kg and 50 mg/kg, respectively).
No relevant effects on blood pressure and heart ECG parameters were observed in dogs after single administration beside a dose-dependent reduction in the action potential duration and QT interval starting from 15 mg/kg, in line with the sodium channel blockade mechanism. ECG evaluations were normal in monkeys treated with safinamide up to 70 mg/kg/day for 39 weeks. A decrease in heart rate was seen when 50 mg/kg/day safinamide was given alone or in combination with levodopa/carbidopa for 13 weeks and in male monkeys given daily doses of 80 or 120 mg/kg/day for 4 weeks.

Relevance to human usage: None

- **Nervous system**

With respect to the central nervous system, safinamide caused a transient and dose-dependent depressive effect (including reduced spontaneous activity and activity, ataxia, hypothermia) after single oral administrations of 100 to 1000 mg/kg in mice, and 30 to 200 mg/kg in rats. This effect was consistent with CNS effects seen in monkeys after repeated oral treatment with 50 mg/kg or higher doses of safinamide. This dose is >16-fold higher than the minimal effective dose in the MPTP primate model of L-dopa induced dyskinesia.

Relevance to human usage: None

- **Respiratory, renal and gastrointestinal systems**

In vivo results showed no significant interference with the respiratory, renal and gastrointestinal systems.

Relevance to human usage: None

Mechanisms for potential Drug-Drug Interactions (DDI)

Inhibition of the drug metabolizing Cytochrome P450s (CYPs) and MAO-A by safinamide and its main human metabolites NW 1153, NW 1689 and NW 1689 AG has been tested by in vitro studies. CYP1A2 inhibition, including a competitive inhibition component (Ki = 54 μM) and a mechanism-based inhibition (MBI) component (KI = 33.5 μM, kinact = 0.075 min 1) was observed in vitro; in light of the CYP1A2 induction by safinamide (see below), MBI of CYP1A2 appears the dominant mechanism in vivo, with potential clinical relevance towards CYP1A2 substrates. Increased plasma exposure of the probe caffeine was observed when administered together with single or multiple doses of safinamide (100 mg) in a clinical Phase I study. The single dose effect was more pronounced, with an increase in AUC0-t of 30%, compared to a 13% increase after 14 days of safinamide 100 mg o.d. administration. The single dose effect suggests that safinamide is a weak CYP1A2 inhibitor, whereas lower increased caffeine exposure after multiple doses of safinamide indicates an additional weak CYP1A2 induction effect. Overall, the observed effect is considered not clinically relevant.
The high IC50's observed for the in vitro inhibition of other metabolizing enzymes indicate an unlikely risk, as these concentrations cannot be reached in man.
Drug metabolizing enzymes involved in the metabolism of safinamide are amidase(s), CYP3A4, MAO-A, several aldehyde dehydrogenases (ALDHs) and UDP glucuronosyl transferase (UGT). The clinical relevance of CYP3A4 has been shown to be low during a clinical inhibition trial with ketoconazole. Inhibition of MAO-A and ALDHs by co-administered drugs is considered of remote relevance for safinamide clearance, as those enzymes catalyze secondary and tertiary metabolic steps and are not rate limiting for the overall metabolism. The amidase(s) are the important enzyme(s) responsible for the overall clearance of parent drug. It has been demonstrated that the formation of NW-1153 is catalysed by non-specific cytosolic amidases. Human fatty acid amide hydrolase (FAAH) was identified as one potential enzyme that contributes to the metabolic pathway of safinamide to NW-1153. Additional investigation on other amidases potentially responsible for the formation of NW1153 did not evidence the involvement of N-Acylethanolamine Amidase (NAAA) and Acid Ceramidase (ASAH1) in safinamide metabolism. Accordingly, NW-1153 was never observed in HLM incubations with safinamide, but only in hepatocytes. The amidases leading to NW-1153 are considered to be high capacity enzymes and therefore, relevant inhibition by other drugs is considered unlikely.
The amidases leading to NW 1153 are considered to be high capacity enzymes. However, not all amidases involved in the metabolism are elucidated. Moreover, there are currently no marketed drugs known to cause clinically significant drug-drug interactions through inhibition or induction of amidase enzymes. Because in the future relevant inhibitors or inducers of such amidases may become known, it is considered important to identify this specific amidase, when new techniques will became available.

Induction of the major nuclear receptors AhR, CAR and PXR by safinamide has been studied in human hepatocyte cultures. CYP3A4 in vitro induction was observed at high concentrations (30-100 µM), which was not confirmed during a clinical study based on the unchanged hydroxycortisol / cortisol ratio in urine at the 100 mg and 350 mg dose level. A 20% decrease in exposure of midazolam was observed when administered together with safinamide 100 mg after 14 days of o.d. dosing in a clinical Phase I study. Accordingly, this suggests that safinamide is a weak 3A4 inducer. Compared to other known CYP3A4 inducers, this effect can be considered small and overall not clinically relevant. Considerable CYP2B6 induction was found during in vitro studies indicating potential clinical relevance, while co-induced UGT1A1 and SULT2A1 activities and mRNA were not changed to a clinically relevant extent. However, the maximum unbound concentration of safinamide in plasma is more than 100× lower than the EC50 of CYP2B6. Therefore, DDI via this mechanism is considered extremely unlikely and it is not considered necessary to perform a clinical follow up to evaluate a possible induction of CYP2B6 by safinamide. NW 1689 acyl glucuronide (AG) has been identified as a circulating metabolite of safinamide in humans and in animals. Since some acyl glucuronides are known to be reactive towards cellular macromolecules, which may finally lead to idiosyncratic drug toxicity, the reactivity of NW 1689 AG towards proteins was investigated in vitro. According to the rating scale introduced by Boelsterli et al., NW 1689 AG would be classified as low to medium reactive in vitro. Considering a more recent approach by Sawamura et al., which recognizes that the chemical stability of acyl glucuronides correlates with the risk of idiosyncratic drug toxicity, NW 1689 AG can be classified as a “safe” acyl glucuronide. This is also in agreement with the generally known low reactivity of benzylic acyl glucuronides, of which NW 1689 AG is a derivative. From both human and animal in vivo trials administering 14C safinamide, there was no indication of covalent binding of drug-related material to plasma proteins. In addition, there were no indications of NW-1689 AG related toxicity or adverse effects from in vivo trials – neither in humans nor in animals. Moreover, NW 1689 AG has been shown to be not genotoxic in two in vitro test systems. Finally, NW 1689 AG did not exhibit any relevant primary and safety pharmacological activity or DDI-relevant effects in vitro. In conclusion, the low reactivity of NW 1689 AG towards proteins observed in vitro is considered not to be of clinical relevance.

Relevance to human usage: Missing information.
Amidases involved in the metabolism of safinamide

- **Pharmacokinetic drug-interaction potential due to effects on transporters**:

Inhibition by safinamide and its main human metabolites NW 1153, NW 1689 and NW 1689 AG has been tested in in vitro studies for the kidney transporters OAT1, 3 and 4, as well as for most transporters considered relevant in the recently published ITC white paper. Among all results, only inhibition of BCRP (Breast Cancer Resistant Protein) by safinamide ($IC50,app \approx 43 \pm 23$ µM) may indicate some intestinal BCRP inhibition in vivo. However, safinamide is highly permeable and its absorption from the intestine is very rapid. Thus, any potential inhibition of intestinal BCRP is considered to be of transient duration and therefore of minor clinical relevance. Safinamide, NW-1153, NW-1689 and NW-1689 AG are not inhibitors of P-glycoprotein (P-gp) at clinically relevant concentrations. Therefore, no clinically relevant DDI potential at the P-gp transporter is expected from safinamide and its main metabolites.

Recent additional data on the interaction in vitro of safinamide and NW-1153 with the human ABC (efflux) transporter (BCRP) and the human SLC (uptake) transporters showed that:

- safinamide is not a substrate of BCRP efflux transporter.
- safinamide is not a substrate of the investigated organic anion uptake transporters (OATP1B1, OATP1B3, OATP1A2 and OATP2B1).
- safinamide is not a potent inhibitor of OATP1A2, OATP2B1, OCT1, MATE1 and MATE2-K at clinically relevant concentrations.
- NW-1153 is not a substrate of the OAT1 and OCT2 renal uptake transporters, while it is a substrate of OAT3.
- NW-1153, at a clinically relevant range, is neither an inhibitor of OCT2, MATE1 nor MATE2-K as it did not inhibit these transporters up to 5 µM (approximately 50-fold of the unbound Cmax).

High renal clearance of the main metabolites NW 1153 (CLR = 13.9 L/h) and NW 1689 AG (CLR = 6.2 L/h) is indicated by clinical data, pointing to some contribution of active secretion in the elimination process (OAT3). Since neither metabolite is pharmacologically active and has shown no DDI potential, reduced renal excretion by transport inhibition is considered to be of low clinical relevance.

Relevance to human usage: None
Safinamide may transiently inhibit BCRP in vitro. In drug-drug interaction studies in human, a weak interaction was observed with rosuvastatin (AUC increase between 1.25 and 2.00 fold) but no significant interaction was found with diclofenac.
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.

- **DME Inhibition Perpetrator**

Mechanism-based inhibition of CYP1A2: This has been evaluated in a Phase III study (ropinirole PK) and a Phase I trial (cocktail DDI study). The results of these studies did not indicate any evidence of clinically relevant effect of safinamide on the plasma levels of ropinirole.

Relevance to human usage: None

- **DME Inhibition – Victim**

Overall clearance of safinamide is considered to be mainly driven by unidentified amidase(s). Although there are currently no marketed drugs known to cause clinically significant drug-drug interactions through inhibition or induction of amidase enzymes. it is considered important to identify this specific amidase, because in the future relevant inhibitors or inducers of such amidases may become known,
The safinamide metabolite, NW-1689 AG is formed by an UGT1A1, UGT1A3, UGT1A7, UGT1A9, and UGT2B15. DDI due to inhibition of this pathway appears unlikely due to redundancy of responsible isoenzymes. Moreover, NW-1689 has been demonstrated to have a very low potential for acute toxicity, even lower than the parent drug itself

Relevance to human usage: None

- **DME Induction**

Potentially clinical relevant CYP3A4 induction was indicated by in vitro experiments in human liver microsomes, which was not confirmed during a clinical study based on the unchanged hydroxycortisol / cortisol ratio in urine. A dedicated cocktail study using a validated CYP3A4 probe substrate (midazolam) has been performed and indicated that safinamide does not influence the plasma levels of midazolam, thus ruling out any induction of CYP3A4.
Potentially relevant CYP2B6 induction was indicated by in vitro experiments in human hepatocyte cultures. However, the maximum unbound concentration in plasma is more than 100 times lower than the EC50 of CYP2B6. Potentially co-induced drug metabolizing phase-II enzymes UGT1A1 and SULT2A1 have been shown to be hardly induced in vitro.

Relevance to human usage: None

- **Transporter Inhibition – Perpetrator**

BCRP inhibition by safinamide has been found (IC50,app $\approx 43 \pm 23$ µM); however, systemic plasma concentrations of safinamide are too low to exhibit relevant inhibition. In the gastrointestinal tract only a temporary higher concentration may be achieved during the fast absorption process, thus the clinical relevance is considered low. Potential P-gp inhibition by NW 1689 AG is considered highly unlikely.

Relevance to human usage: None

- **Transporter Inhibition – Victim**

Potential active renal secretion by transporters is indicated by CLR data for NW 1153 (OAT3) and NW 1689 AG. Since both metabolites are not pharmacologically active, potentially reduced renal excretion by transport inhibition is considered to be of low clinical relevance. A renal impairment study in patients did not detect any meaningful effect of renal function on the exposure to safinamide.

Relevance to human usage: None

- **Transporter Induction**

Since CYP3A4 is known to be significantly induced by safinamide in vitro, potential co-induction of P-gp needs to be considered. However, a clinical study (QT) showed that the urinary ratio of 6 hydroxycortisol/cortisol is not impacted by safinamide; therefore, an in vivo induction of CYP3A4 appears unlikely. This has been confirmed in another DDI cocktail trial using substrates of CYP1A2 (caffeine) and CYP3A4 (midazolam). It can be concluded that P-gp is not induced either, as induction would occur via the same nuclear receptor.

Relevance to human usage: None

Other toxicity-related information or data

Abuse liability

The following animal behavioral studies were performed by the Sponsor:

Study Type	Study Number	Safinamide Dose	Active Control/ Comparator	Species
Drug discrimination	RS1414	50 and 100 mg/kg PO	D-amphetamine: 0.5 mg/kg IP (training discriminative cue) D-amphetamine: 0.125, 0.5, and 1.0 mg/kg PO phentermine 1.0, 2.0 and 3.0 mg/kg PO	30 female Lister Hooded rats
	RS1426	50 and 100 mg/kg PO	Midazolam: 0.2 -0.5 mg/kg IP (training discriminative cue) Midazolam: 0.5, 1.0, 1.5 mg/kg PO Alprazolam: 0.25, 0.50, 1.0 and 1.50 mg/kg PO	30 female Lister Hooded rats
Self-administration	RS1417	0.3, 1.0, and 1.5 mg/kg/IV injection	Cocaine 0.032 mg/kg/IV injection	4 Rhesus monkeys (2 males and 2 females)
Tolerance and dependence	RS1415	50 and 100 mg/kg/day PO for 28 days	Morphine 60 mg/kg/day PO for 28 days	58 male Sprague Dawley rats
	RS1425	50 and 100 mg/kg/day PO for 28 days	Morphine 60 mg/kg/day PO for 28 days	58 female Sprague Dawley rats

- **Drug discrimination in Rats (Studies RS1414 and RS1426)**

Two studies were performed in Lister hooded rats (50 or 100 mg/kg/day): the first study (RS1414) evaluated discrimination of safinamide and phentermine in rats trained to discriminate d-amphetamine from saline, the second study (RS1426) evaluated the discrimination of safinamide and alprazolam in rats trained to discriminate midazolam from saline.
Data for each drug were expressed as a percent generalization to d-amphetamine IP/ midazolam (% generalization = number of d-amphetamine or midazolam lever presses / total number of lever presses).
The highest test doses of oral d-amphetamine (1.0 mg/kg), and phentermine (3.0 mg/kg) fully generalized to the d-amphetamine IP cue with a mean (±SD) of 77.0±25.9% and 79.8 ± 12.7%, respectively, confirming the validity of the study. Both the 50 and 100 mg/kg PO doses of safinamide generalized to the saline cue, with a mean of only 8.9% and 18% of safinamide generalized to the amphetamine IP cue, respectively.
In the same way, the highest dose of oral midazolam (1.5 mg/kg) and of alprazolam (1.5 mg/kg) fully generalized to the midazolam cue (63.5 ± 39.1% and 85.2 ± 34.6%, respectively) and both the 50 and 100 mg/kg PO doses of safinamide generalized to the saline cue and were not associated with any midazolam–like psychoactive effects.

In conclusion, considering that mean plasma safinamide Cmax values were 2730 and 6750 ng/ml at 50 and 100 mg/kg doses, respectively, i.e. ~2.2x and ~5.5x the human Cmax (1234 ng/ml) at the therapeutic dose of 100 mg, these data suggest that safinamide is unlikely to be associated with any d-amphetamine–like psychoactive effects and that it will not have benzodiazepine-type recreational abuse potential in humans.

- **Self-administration in Monkeys (Study RS1417)**

Study RS1417 evaluated the reinforcing potential of safinamide (0.3, 1.0 or 1.5 mg/kg/iv injection) in cocaine-maintained Rhesus monkeys (cocaine was used as the training drug). Four adult Rhesus monkeys (2 males, 2 females) were trained to respond to a fixed ratio (FR) 30 schedule of drug reinforcement to intravenously self-administer a low dose of cocaine (0.032 mg/kg/injection); and the monkeys were then tested on the same FR 30 schedule across a range of safinamide doses. Pharmacokinetics of safinamide were measured in the plasma after IV dosing. Cocaine (0.032 mg/kg/injection) maintained high rates of self-administration in all 4 monkeys, both before and after testing with safinamide, and saline maintained low rates of self-administration in the monkeys, both before and after testing with safinamide, thus validating the study.
The pharmacokinetic results of the study indicated that a wide range of plasma safinamide concentrations were associated with the doses administered, including multiples of the maximum clinical exposure in humans at therapeutic dose of 100 mg/day, i.e. up to 6.7x (male monkeys) and 4.0x (female monkeys), thus providing a reliable safety margin for the self-administration results.
Results for safinamide-treated monkeys indicated that none of the safinamide doses maintained rates of self-administration at a level significantly greater than self-administration of saline. The relative reinforcing strength of safinamide in monkeys under the conditions of this study indicate that safinamide did not act as a positive reinforcer at exposures many fold higher than at human therapeutic doses, and therefore is unlikely to pose any a meaningful risk for recreational abuse in humans.

- **Tolerance and Dependence in Rats (Studies RS1415 and RS1425)**

Two studies were conducted in Sprague Dawley rats to evaluate the potential of safinamide to produce effects related to physical drug tolerance and dependence after 28 days of once–daily oral administration of safinamide compared to a positive control (morphine) in male (RS1415) and female (RS1425) rats. The studies were comprised of a 28 consecutive days of dosing (drug administration period) and 7 days of observation following abrupt drug withdrawal and the treatments were administered at sufficiently high doses (50 mg/kg and 100 mg/kg po; Cmax at 100mg/kg/day >3x human Cmax at 100mg). Morphine (30 mg/kg po, twice a day) was used as the positive control because of its ability to induce rapid tolerance and dependence with a pronounced withdrawal syndrome in both humans and animals. Any unusual physical or behavioural signs and any signs of tolerance or dependence in the rats in the treatment groups were recorded and scored.
In both studies rapid tolerance developed in morphine-treated (30 mg/kg BID) rats after 3 consecutive days of treatment. The initial subdued behaviour and decreased locomotor activity were replaced by increased locomotor activity, rearing, jumping, escape attempts from cages, increased reactivity to sound and increased body tone, which persisted for the remainder of the drug administration period. Also the reported behavioural and physical

effects of morphine withdrawal were consistent with previous results from nonclinical studies of morphine to induce withdrawal dependence in rats, and therefore, the methodology used in both studies was considered valid.
Both doses of safinamide were devoid of an effect on physiological measures (e.g. body weight, food and water intake). There were no consistent signals of tolerance or sensitization to safinamide oral administration (50 or 100 mg/kg/day) during the drug administration period in male and female Sprague Dawley rats. In both studies, after abrupt discontinuation of safinamide dosing, the behavioral and physical effects observed during the drug administration period reduced markedly or were no longer apparent within 7 days after the final dose. Importantly, no new behaviours or physical signs were observed during the withdrawal period in either study.

Relevance to human usage: None
A review of all data for safinamide related to abuse liability, dependence and withdrawal, based on non-clinical studies specifically evaluating abuse liability (Report n. RS1414, RS1415, RS14,17, RS1425), PD patient data from the clinical program and reports from post-marketing surveillance in Europe did not detect any systematic pattern of symptoms suggestive of abuse potential with safinamide usage.

PART II: MODULE SIII. - CLINICAL TRIAL EXPOSURE

SIII.1 Clinical Trial exposure

Safinamide has been investigated in a series of clinical studies (therapeutic and non-therapeutic) with 3216 subjects exposed to safinamide or placebo (or other comparators) (3221 randomized/enrolled) (see Table 1). The program included 35 completed clinical studies and 4 studies that were terminated prematurely (i.e. Motion Extension, OLE, DAT, 024 Cognition studies).

A total of 2515 subjects have received at least one dose of safinamide in clinical trials. 450 subjects were enrolled in non-therapeutic trials, and 2065 patients were enrolled in therapeutic trials. The total number of patients with PD exposed to safinamide in placebo controlled clinical studies to date are summarized and categorized by duration of exposure in Table 2.

Table 1 - Subject exposure to safinamide, placebo or comparator

Investigational Arm	Safinamide	Placebo / Active [A]	Overall number of subjects [B]
PD patients in placebo-controlled studies and OLE Phase (pooled data)			
Early stage PD	**795**	**422**	**1,217**
Mid-Late stage PD on L-DOPA	**721**	**497**	**1,218**
PD patients that took safinamide for the first time in the OLE extension study	400 [B]		
TOTAL	**1,916**	**919**	**2,435**
PD patients in other studies (not pooled)			
Other therapeutic studies	69	6	75
Non therapeutic studies	28	22	29
TOTAL	**97**	**28**	**104**
Total PD patients	*2,013*	*947*	*2,539*
Other studies in non-PD subjects			
Therapeutic studies	56	2	58
Non therapeutic studies	446	210	619
TOTAL	**502**	**212**	**677**
Overall total	*2,515*	*1,159*	*3,216*

Exposure to Safinamide in Parkinson's Disease Patients

The total number of patients with PD exposed to safinamide in placebo-controlled clinical studies or in the Open-Label studies, included in the "pooled studies" for safety to date are summarized and categorized by duration of exposure in Table 2: the total of 1949 PD patients includes patients with early-stage PD (ESPD) and late-stage PD (LSPD) enrolled in placebo-controlled clinical studies, as well the OLE study. Further, 64 PD patients who received safinamide in therapeutic and non-therapeutic "non-pooled studies" are not included the summary of exposure.

Overall more than 150 were treated with safinamide for >4 years, > 200 treated for > 3 years, more than 500 treated for > 2 years, more than 1000 treated for > 1 year, and more than 1400 treated for > 6 months.

Table 2 - Summary of exposure to safinamide in all clinical trials

Exposure	Any	>6 months	>1 yr	>2 yrs	>3 yrs	>4 yrs
Number of All PD patients exposed to safinamide	1949 (a)	1440	1180	533	222	169
Number of Early PD patients exposed to safinamide	879	542	428	110	0	0
Number of Late PD patients exposed to safinamide	1036	876	734	414	222	169

(a) excluding 64 patients who received safinamide in the "not pooled" studies: 004, 012, 0023, 28780 and 28849 (DAT), and did not enter the Open Label Phase.

Source: Section 1.2.1 and 1.2.2 of Safinamide-CTD Sect. 2.7.4 "Summary of Clinical Safety".

Table 3 - Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure

[redacted]

Duration (weeks)	0 < Dose <= 5mg	5 < Dose <= 10mg	10 < Dose <= 20mg	20 < Dose <= 30mg	30 < Dose <= 50mg	50 < Dose	Total (Any Dose)	%
Early Stage PD								
0 < Dur <= 1	0	0	0	0	1	0	1	0.1
1 < Dur <= 2	0	0	0	0	2	3	5	0.6
2 < Dur <= 4	0	0	0	2	3	7	12	1.4
4 < Dur <= 12	0	0	3	15	34	62	114	13.7
12 < Dur <= 24	0	0	1	2	31	88	122	14.6
24 < Dur <= 48	0	0	0	0	36	97	133	15.9
48 < Dur <= 96	0	0	0	0	66	218	284	34.0
Dur >96	0	0	0	0	31	133	164	19.6
Total (Any Duration)	0	0	4	19	204	608	835	100.0
Percent	0.0%	0.0%	0.5%	2.3%	24.4%	72.8%	100.0%	
Late Stage PD								
0 < Dur <= 1	0	0	0	0	2	3	5	0.5
1 < Dur <= 2	0	0	0	0	3	1	4	0.4
2 < Dur <= 4	0	0	0	0	8	6	14	1.4
4 < Dur <= 12	0	0	0	1	8	25	34	3.3
12 < Dur <= 24	0	0	0	0	16	42	58	5.6
24 < Dur <= 48	0	0	0	0	32	129	161	15.6
48 < Dur <= 96	0	0	0	0	17	254	271	26.3
Dur >96	0	0	0	0	35	447	482	46.8
Total (Any Duration)	0	0	0	1	121	907	1029	100.0
Percent	0.0%	0.0%	0.0%	0.1%	11.8%	88.1%	100.0%	
Combined, All PD Subjects								
0 < Dur <= 1	0	0	0	0	3	3	6	0.3
1 < Dur <= 2	0	0	0	1	5	4	10	0.5
2 < Dur <= 4	0	0	0	3	11	13	27	1.4
4 < Dur <= 12	0	0	3	16	42	89	150	7.9
12 < Dur <= 24	0	0	1	2	47	135	185	9.7
24 < Dur <= 48	0	0	0	0	68	233	301	15.9
48 < Dur <= 96	0	0	0	0	83	477	560	29.5
Dur >96	0	0	0	0	66	593	659	34.7
Total (Any Duration)	0	0	4	22	325	1547	1898	100.0
Percent	0.0%	0.0%	0.2%	1.2%	17.1%	81.5%	100.0%	

Source: Section 1.2.2 of Safinamide-CTD Sect. 2.7.4 "Summary of Clinical Safety" and
Appendix 1 Table 1 (Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure)
Source: Safinamide-CTD Sect. 2.5 "Clinical Overview".

Further description of exposure for the population of PD patients enrolled in safinamide trials by proposed age group, gender and ethnicity

Exposure stratified by ethnic or racial origin are included in Table 4 for safinamide as an add-on to L-dopa and other concomitant anti-Parkinson's medications for treating mid- to late-stage PD.

The number of patients exposed to safinamide in the pooled placebo-controlled studies of safinamide as an add-on to L-dopa and other concomitant anti-Parkinson's medications for treating mid- to late-stage idiopathic PD patients is reported in Table 4, combining data from the following studies: Study NW-1015/016/III/2006 (referred to as Study 016) and Study 27919 (the SETTLE study). This tabulation includes also Study NW-1015/018/III/2006

(referred to as Study 018), a double-blind, placebo-controlled extension study for subjects enrolled in Study 016.

Table 4: Number of patients exposed to safinamide by age group, gender and ethnicity (safinamide as an add-on to L-dopa and other concomitant anti-Parkinson's medications for treating mid- to late-stage idiopathic PD patients)

Age Category	< 55		55-75		>= 75	
	Safinamide (N=177)	Placebo (N=116)	Safinamide (N=517)	Placebo (N=361)	Safinamide (N=27)	Placebo (N=20)
% (within each treatment group)	**24.6 %**	**23.3 %**	**71.7 %**	**72.6 %**	**3.7 %**	**4.0 %**
Age (years)						
n	177	116	517	361	27	20
Mean	48.1	48.1	64.1	64.1	77.8	77.5
S.D.	4.47	4.99	5.62	5.60	1.21	1.00
Min, Max	35.0, 54.0	30.0, 54.0	55.0, 75.0	55.0, 75.0	76.0, 80.0	76.0, 79.0
Gender	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Male	128 (72.3)	79 (68.1)	343 (66.3)	230 (63.7)	20 (74.1)	14 (70.0)
Female	49 (27.7)	37 (31.9)	174 (33.7)	131 (36.3)	7 (25.9)	6 (30.0)
Race	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Caucasian	39 (22.0)	34 (29.3)	219 (42.4)	181 (50.1)	13 (48.1)	15 (75.0)
Non-Caucasian	138 (78.0)	82 (70.7)	298 (57.6)	180 (49.9)	14 (51.9)	5 (25.0)
Ethnicity	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hispanic/Latin American	5 (2.8)	3 (2.6)	6 (1.2)	6 (1.7)	1 (3.7)	0 (0.0)
Non-Hispanic/Latin American	172 (97.2)	113 (97.4)	511 (98.8)	355 (98.3)	26 (96.3)	20 (100.0)

Source: Section 1.3.1.2 Demographic and Other Characteristics of Safinamide-CTD Sect. 2.7.4 "Summary of Clinical Safety" and Table DM01.2.09, DM01.2.10, and DM01.2.11.

Table 5: Duration of exposure to safinamide by age group and gender (by indication and totals)

Disease Stage	Age (A)	Sex	Persons	Person Time yr
All Patients	55-75	F	345	713.6
All Patients	55-75	M	703	1535.1
All Patients	<55	F	130	260.7
All Patients	<55	M	265	604.3
All Patients	>75	F	23	41.9
All Patients	>75	M	49	102.0
Early Stage PD	55-75	F	171	255.8
Early Stage PD	55-75	M	360	468.6
Early Stage PD	<55	F	81	96.9
Early Stage PD	<55	M	137	186.0
Early Stage PD	>75	F	16	25.7

Disease Stage	Age (A)	Sex	Persons	Person Time yr
Early Stage PD	>75	M	29	35.2
Late Stage PD	55-75	F	174	457.8
Late Stage PD	55-75	M	343	1066.5
Late Stage PD	<55	F	49	163.8
Late Stage PD	<55	M	128	418.3
Late Stage PD	>75	F	7	16.2
Late Stage PD	>75	M	20	66.8

(A) Baseline Demographics Characteristics of patients included in Group 1 pooled studies (OLE phase is excluded)

Source: Exposure Tables EX_Adhoc2 (Table 5 RMP)

Table 6: Duration of exposure to safinamide by ethnic or racial origin (by indication and totals)

Disease Stage	Ethnicity	Persons	Person Time yr
All Patients	Hispanic	240	387.5
All Patients	Non-Hispanic	1276	2870.3
Early Stage PD	Hispanic	228	355.7
Early Stage PD	Non-Hispanic	567	712.7
Late Stage PD	Hispanic	12	31.8
Late Stage PD	Non-Hispanic	709	2157.6

Source: Exposure Tables EX_Adhoc2 (Table 6 RMP)

Table 7: Special populations: cardiac and hepatobiliary diseases (by indication and totals)

Disease Stage	Cardiac	Persons (N)	Person Time yr
All Patients	Y	64	190.6
Early Stage PD	Y	26	45.2
Late Stage PD	Y	38	145.4
Disease Stage	**Hepatobiliary**	**Persons (N)**	**Person Time yr**
All Patients	Y	5	18.8
Early Stage PD	Y	1	4.4
Late Stage PD	Y	4	14.4

Source: Exposure Tables EX_Adhoc2

PART II: MODULE SIV. - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Patients were excluded from study enrolment if they presented with any forms of parkinsonism other than idiopathic PD, or severe, disabling peak-dose or biphasic dyskinesia and/or unpredictable or widely swinging fluctuations, or had stereotactic surgery as a treatment for PD, or were experiencing end-of-dose wearing off or on-off phenomena, or had a history of an allergic response to anticonvulsant or anti-parkinsonian agents. Patients with

Early PD were excluded if treated with a medication for PD, other than a single DA-agonist, during the weeks preceding the screening visit.

Additional exclusion criteria included: participation in a previous clinical trial with safinamide or any investigational compound within 30 days (or 5 half-lives) prior to screening; concomitant diagnosis of substance abuse (DSM-IV) or history of alcohol or drug abuse; history or concomitant presence of psychosis, dementia or cognitive dysfunction (MMSE score < 24, or a score ≥ 3 on item 1, UPDRS I), depression [GRID-HAMD (17-item scale) > 17]; neoplastic disorder, diagnosis of HIV, or tests positive for Hepatitis B or C antibodies, or Hepatitis B surface antigen (unless vaccinated); any abnormality that the investigator deemed to be clinically relevant, either on medical history, physical examination, ECG or in a diagnostic laboratory test, current clinically significant cardiac, gastrointestinal, renal, hepatic, endocrine, pulmonary or cardiovascular disease, including uncontrolled hypertension, asthma, chronic obstructive pulmonary disease (COPD), or Type I diabetes; hypersensitivity or contraindications to MAO-B inhibitors, non-compliance or uncooperativeness during the study. Patients with an ophthalmologic history of retinal disease (including progressive and/or severe diminution of visual acuity, retinitis pigmentosa, retinal pigmentation due to any cause, any active retinopathy or ocular inflammation [uveitis], or diabetic retinopathy) were excluded from the studies, as well.

Concomitant treatments with any agent known to significantly inhibit or induce drug-metabolizing enzymes (e.g., barbiturates, phenothiazines, etc.), drugs with hepatotoxic or cytotoxic potential, opioids, SNRIs, tri- or tetracyclic antidepressants, MAO inhibitors, meperidine derivatives, neuroleptics (depot or oral) were not permitted in the 4 weeks prior to the screening visit and throughout the study. Use of SSRIs was permitted, provided the dose was kept as low as possible and remained stable throughout the trial.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Based on the exclusion criteria in the Phase 2/3 clinical trial program , young and very old PD patients were not included in the studies, and patients with clinically significant and/or unstable medical conditions that could have put them at risk for taking safinamide were also excluded. Therefore, precautions should be taken if treatment with safinamide is initiated in these unstudied populations; in some of these sub-populations, safinamide treatment is contraindicated.

The main exclusion criteria across the clinical trial development program are discussed below:

Age

Reason for exclusion: Patients below the age of 30 and above the age of 80 were excluded from the studies. As Parkinson's disease is a neurodegenerative disorder that mostly affects humans after the age of 50 years, this should not be a significant issue. Use in children and adolescents, below the age of 18 will be contraindicated.

Is it considered to be included as missing information?: Yes

Rationale: (if not included as missing information)

Mental disorders

Reason for exclusion:

Patients with a history or current diagnosis of a mental disorder, defined as: psychosis (e.g. schizophrenia or psychotic depression) or a score ⩾ 3 on item 2 (thought disorder) or 3 (depression) of the UPDRS at screening; evidence of dementia or cognitive dysfunction, as indicated by a MMSE score < 24 or a score ⩾ 3 on item 1 (mentation) of the UPDRS at screening; depression, as indicated by a GRID-HAMD (17-item scale) score > 17 at screening.

were excluded from the clinical studies. Therefore, safinamide should be used with caution in patients with any of these mental disorders. In addition, use of antipsychotics and certain antidepressants (SNRIs, TCAs, MAOIs) was prohibited; therefore, these drugs should not be used concomitantly with safinamide.

Is it considered to be included as missing information?: Yes

Rationale: (if not included as missing information)

Ophthalmologic history/conditions

Reason for exclusion: Patients with eye disorders or family history that could have put them at risk for retinal effects, e.g. albino subjects, family history of hereditary retinal disease, progressive and/or severe diminution of visual acuity (i.e., 20/70), retinitis pigmentosa, retinal pigmentation due to any cause, any active retinopathy or ocular inflammation (uveitis), or diabetic retinopathy, were excluded from safinamide trials. Therefore, safinamide should not be used in patients with any of these ocular conditions or family history.

Is it considered to be included as missing information?: Yes

Rationale: (if not included as missing information)

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare (<1 in 1000)	2000 PD patients were exposed to safinamide in the clinical programme	ADRs (Adverse Drug Reaction) with a frequency greater than 1 in 2000 could be detected only if there was no background incidence
Due to prolonged exposure - Events that takes > 3years to occur	Over 200 PD patients were exposed to safinamide for more than 3 years	ADRs that appear only after 3 or more years of exposure would not have been identified in the clinical programme.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant or breastfeeding women	In women of childbearing potential, pregnancy was excluded before study entry (serum and urine pregnancy tests were performed at visits specified in the protocols) and prevented by the use of reliable contraception for four weeks prior to enrolment, throughout the treatment period, and four weeks after the last dose of the study medication. It is not known if safinamide is excreted via breast milk; therefore, breastfeeding females were not included into studies. No pregnancies were reported in any of the safinamide clinical studies.
Children	No children or adolescents, below the age of 18 were enrolled in any of the clinical trials with safinamide. The use of safinamide in these patients is contraindicated
Elderly	Experience of use in patients >75 years of age is limited, only 67 patients were enrolled in the Phase 2/3 controlled trials. There was no evidence of any effect of age on the tolerability of safinamide. The only ADR of special concern is dyskinesia.
Patients with relevant comorbidities: • Patients with hepatic impairment	Patients with severe hepatic impairment were not eligible for safinamide clinical studies, and therefore data in this patient population are not available. The use in patient with severe hepatic impairment is contraindicated.
•Patients with renal impairment	A dedicated study was performed to assess the effects of moderate and severe renal impairment on safinamide clearance. The results demonstrated that the pharmacokinetics of safinamide were not affected by impaired renal function; therefore, no change in dose is required in these patients.
• Patients with relevant co-morbidity such as, current clinically significant gastrointestinal, pulmonary or cardiovascular disease, including acute gastric ulcer,	Not included in the clinical development program, therefore, safinamide should be used with caution in patients with serious, life-threatening conditions,

hypertension that is not well controlled, asthma, chronic obstructive pulmonary disease (COPD), and Type I diabetes.	including any of these conditions.
• Patients with the following cardiac conditions/findings: second- or third-degree atrio-ventricular block or sick sinus syndrome, uncontrolled atrial fibrillation, severe or unstable angina, congestive heart failure, myocardial infarction within 3 months of the screening visit, or significant ECG abnormality, including QTc ≥ 450 msec (males) or ≥ 470 msec (females), where QTc is based on Bazett's correction method.	Not included in the clinical development program, therefore, safinamide should be used with caution in patients with serious, life-threatening conditions, including any of these conditions.
• Patients with a neoplastic disorder, which is either currently active or has been in remission for less than one year.	Not included in the clinical development program, therefore, safinamide should be used with caution in patients with serious, life-threatening conditions, including any of these conditions.
• Patients with a diagnosis of HIV, or positive test for Hepatitis C antibodies, or Hepatitis B surface antigen.	Not included in the clinical development program, therefore, safinamide should be used with caution in patients with serious, life-threatening conditions, including any of these conditions.
• Patients with signs and symptoms suggestive of transmissible spongiform encephalopathy, or family members who suffer(ed) from such.	Not included in the clinical development program, therefore, safinamide should be used with caution in patients with serious, life-threatening conditions, including any of these conditions.
• Patients with a disease severity different from the inclusion criteria in the clinical trial population	No patients were included in the clinical trials with disease severity that was different from that defined in the inclusion criteria for each study.
Sub-populations carrying known and relevant polymorphisms • Safinamide is metabolized largely through non-CYP-450 isoenzymes (amide hydrolases, MAO-A) for which there are no relevant polymorphisms, hence this is not an issue.	Not applicable

Patients of different racial and/or ethnic origin	Analyses of the safety data for safinamide by race do not indicate any differences in tolerability or response to safinamide among racial categories. Based on the metabolic pathway for safinamide, racial differences are not an issue in the metabolism of the drug. The total number of subjects exposed to safinamide in the clinical development programme categorized by racial group is as follows: • White – 1147 • Asian – 744 • Black – 9 • Other – 66

PART II: MODULE SV.- POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Xadago has been approved through centralized procedure in all European Economic Area (EEA) on 24 February 2015. The product has been approved through national procedure in Switzerland on 12 November 2015 and in the USA on 21 March 2017. As of the DLP (24 Aug 2018) of the present report, Xadago® has been launched on the market in Germany, Austria, Switzerland, Italy, Spain, Belgium, Denmark, Finland, Germany, Luxemburg, Sweden, UK, The Netherlands, Norway, Portugal, UK and USA.

Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons

No actions related to safety have been taken during the reporting interval by the marketing authorisation holder, sponsors of clinical trial(s), data monitoring committees, ethics committees or competent authorities that had either:

- a significant influence on the risk-benefit balance of the authorised safinamide-based Zambon medicinal products; and/or
- an impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme.

SV.1.1 Method used to calculate exposure

The Defined Daily Dose proposed by the WHO (i.e. 75 mg daily) has been used for the patient exposure calculation.

SV.1.2 Exposure

The number of exposed patients has been estimated based on the international ex-factory sales data that are available on monthly basis.

Considering that the treatment is expected to be chronic, it is estimated that cumulatively from 24 February 2015 through 31 August 2018, 98,178 patient-years were exposed to Xadago.

Region	Country	Medicinal Product	Total packages up to 31/08/2018	Total mg	Exposure patient-years
EEA	Belgium + Luxembourg	XADAGO® film-coated tablets	[redacted]		
	Denmark	XADAGO® film-coated tablets			
	Finland	XADAGO® film-coated tablets			
	Germany and Austria	XADAGO® film-coated tablets			
	UK	XADAGO® film-coated tablets			
	Italy	XADAGO® film-coated tablets			
	The Netherlands	XADAGO® film-coated tablets			
	Norway	XADAGO® film-coated tablets			
	Portugal	XADAGO® film-coated tablets			
	Spain	XADAGO® film-coated tablets			
	Sweden	XADAGO® film-coated tablets			
		Sub-total EEA	**867,665**	**2,408,266,800**	**87,973**
Non EEA	Switzerland	XADAGO® film-coated tablets	[redacted]		
	U.S.A.	XADAGO® film-coated tablets			
		Sub-total Non EEA			
		Total	**1,056,670**	**2,687,613,900**	**98,178**

PART II: MODULE SVI. - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Safinamide increases dopaminergic transmission by inhibition of the MAO-B enzyme. Chronic safinamide treatment (13 weeks at 10-20 mg/kg *po*; 39 weeks at 8-20 mg/kg *po*) in monkeys increased dopamine levels in the striatum, with a concomitant decrease of its metabolites.

Safinamide did not affect mechanisms that may contribute to the potential for drug abuse, or to psychostimulant-like effects in behavioural studies. In vitro studies in recombinant cell

systems showed an affinity to the DA and 5HT transporters (DAT and SERT, respectively) at concentrations of ~10 µM, i.e. > 17 fold lower than the affinity shown by cocaine, and inhibition of DA and 5HT reuptake with IC_{50s} of ~10 µM, i.e., >30 times lower potency as compared to cocaine (Study 1205014). As previously described an in vivo brain imaging study in baboons confirmed that there is no occupancy of DAT and SERT even at supra-therapeutic plasma concentrations.

In addition, safinamide increases dopamine levels in the specific brain region devoted to motor control (putamen nucleus) without affecting regions involved in reward circuits such as mesolimbic structures (nucleus accumbens), indicating it is likely to be devoid of abuse potential (0901003; Caccia, 2008 (MKS45276a_Caccia).

Safinamide does not produce an increase in locomotion, noted with psychostimulant drugs like cocaine; however, it attenuated the hyperactivity induced by cocaine in mice, with an ED_{50} of 43.7 mg/kg (Newron Study Report 1205013).

Specific animal behavioral studies were performed by the Sponsor, in accord with the 2010 draft Guidance concerning *Assessment of Abuse Potential of Drugs* and the results were as follows:

- In drug discrimination assays in Lister Hooded rats, safinamide (50 or 100 mg/kg/day) did not evoke any d-amphetamine–like or midazolam-like psychoactive effects.
- In a primate self-administration assay, safinamide (0.3, 1.0 or 1.5 mg/kg/iv injection) was associated with variable responses in 2 of 4 subjects trained to reliably self-administer low doses of cocaine (0.032 mg/kg/injection on a FR30 schedule); however, the relative reinforcing strength of safinamide in monkeys under the conditions of this study indicate that safinamide did not act as a positive reinforcer at exposures many fold higher than at human therapeutic doses, and therefore is unlikely to pose any a meaningful risk for recreational abuse in humans
- No evidence of tolerance development or physical dependence upon abrupt drug withdrawal was observed with safinamide (50 or 100 mg/kg/day po) administered for 28 consecutive days in male and female Sprague Dawley rats.

Clinical data from over 2000 subjects treated with safinamide for up to 2 years did not show any pattern of behaviour that could be considered indicative of addiction liability. Evaluations performed after abrupt premature treatment discontinuation, or following discontinuation of treatment at the end-of-study (after >2 years), did not indicate any signs of withdrawal or rebound effects on CNS symptoms.

A review of all data for safinamide related to abuse liability, dependence and withdrawal, based on these non-clinical studies specifically evaluating abuse liability, as well as PD patient data from the clinical program and reports from post-marketing surveillance in Europe did not detect any systematic pattern of symptoms suggestive of abuse potential with safinamide usage.

PART II: MODULE SVII. - IDENTIFIED AND POTENTIAL RISKS

SVII.1Identification of safety concerns in the initial RMP submission

Summary of safety concerns	
Important identified risk:	• Dyskinesia • Teratogenicity
Important Potential Risks:	• Retinal degeneration in patients with PD • 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 and >75 years • Effects of Overdose • Patients with severe, disabling peak-dose or biphasic dyskinesia, or with unpredictable or widely swinging fluctuations. • Patients who have undergone stereotactic surgery as a treatment for Parkinson's disease • Use in patients with psychiatric illness, specifically psychosis, bipolar disorder, or severe depression • 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

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

None

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk:
Dyskinesia

Risk-benefit impact: Dyskinesia was the most commonly reported AE in safinamide treated patients. Increased risk of development of dyskinesia may lead to increased morbidity and disability in the population exposed to safinamide depending on its severity and nature.

Important Identified Risk:

Teratogenicity
Risk-benefit impact: 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. Considering the potential serious outcome, the risk has been considered important.

Important Potential Risk:
Risk of retinal degeneration in patients with PD treated with safinamide

Risk-benefit impact: retinal degeneration was observed in rat repeated-dose toxicity studies but not in monkey and human studies. Patients with history of retinal disease, including inherited conditions were excluded from the studies. Consequently, the risk of retinal degeneration is considered an important potential risk.

Important Potential Risk:
Use in severe hepatic impairment.
Risk-benefit impact: results from the study performed in patients with hepatic dysfunction indicated higher exposures of safinamide, but without any clinically important changes in liver enzymes. Considering that the higher exposure of safinamide may lead to the onset of serious adverse reactions, the risk is considered an important potential one.
The product is contraindicated in patients with severe liver disease, and the maximum dose to be administered to patients with moderate liver disease is limited to 50 mg, with the provision that if the liver dysfunction progresses from moderate to severe, the patients should discontinue treatment with safinamide

Important Potential Risk:
Impulse control disorders (ICDs)
Risk-benefit impact: 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. Safinamide treatment has not been associated with any increase in the appearance of ICDs. Consequently, impulse control disorders is considered an important potential risk.

Important Potential Risk:
Concomitant use of MAOIs, serotonergic drugs, and/or pethidine.

Risk-benefit impact: serious adverse events, including serotonin syndrome, have been reported with the concomitant use of MAOIs, serotonergic drugs, and/or pethidine. There is no enough evidence that this may be a class effect. Consequently, it has been considered an important potential risk.

Missing information:
Use in patients with history and/or presence of retinal disease

Risk-benefit impact: Patients with history of retinal disease, including inherited conditions, were excluded from the studies. Since retinal degeneration was observed in rat repeated-dose toxicity studies but not in monkey and human studies, the product should not be administered to patients with ophthalmological history. However, an off-label use could not be excluded.

Missing information:
Use of safinamide in patients aged<30 years and >75 years

Risk-benefit impact: patients below the age of 30 were excluded from the studies. Experience of use in patients >75 years of age is limited. The product is not contraindicated in these populations.

Missing information:
Effects of Overdose

Risk-benefit impact: reports of overdose with safinamide have been rare. Two cases have been reported in late stage PD patients.

Missing information:
Patients with severe, disabling peak-dose or biphasic dyskinesia, or with unpredictable or widely swinging fluctuations.

Risk-benefit impact: patients were excluded from study enrolment if they presented with any forms of parkinsonism other than idiopathic PD, or severe, disabling peak-dose or biphasic dyskinesia and/or unpredictable or widely swinging fluctuations. The product is not contraindicated in this population.

Missing information:
Patients who have undergone stereotactic surgery as a treatment for Parkinson's disease

Risk-benefit impact: patients who have undergone stereotactic surgery as a treatment for Parkinson's disease were excluded from study enrolment. The product is not contraindicated in this population.

Missing information:
Use in patients with psychiatric illness, specifically psychosis, bipolar disorder, or severe depression.

Risk-benefit impact: No information was obtained in patients with psychosis, bipolar disorder, or severe depression since not included in clinical studies. No increase in psychiatric disorders was noted in patients treated with safinamide. The product is not contraindicated in this population.

Missing information: Long term use >3 years

Risk-benefit impact: Limited information for use > 3 years.

Missing information:
Whether specific inhibitors of the amidases involved in the metabolism of safinamide to NW-1153, may increase the exposure of safinamide

Risk-benefit impact: 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.
Currently no marketed medicinal products known to cause clinically significant drug-drug interactions through inhibition or induction of amidase enzymes.

SVII.2New safety concerns and reclassification with a submission of an updated RMP

The results of Study Z7219N02 (SYNAPSES) were analysed: neither age, comorbidities, nor psychiatric conditions seem to have any relevant effect on safinamide safety profile.
For this reason, it is proposed to remove the following missing information from the list of product safety concerns:

- Use of safinamide in patients aged >75 years
- Use in patients with psychiatric illness, specifically psychosis, bipolar disorder, or severe depression.

Specifically, 1610 patients have been enrolled in the SYNAPSES study, and 1558 (96.8%) were evaluable for the analysis, with more than 80% followed up prospectively for one year.
The sample was composed by the following sub-groups: 25% patients older-than-75-years, 71% patients with relevant comorbidities and 42% with psychiatric conditions.
Mean (SD) age at enrollment was 68.4 (9.7) years. Patients without relevant comorbidities were five years younger than those with comorbidities (64.6 (10.7) vs 70 (8.7) years), while no difference was observed between patients with vs without psychiatric conditions (68.3 (9.4) vs 68.5 (9.9) years). Overall, 37.1% (N=516) of patients had H&Y stage > 2, while in the subpopulations the proportions were 56.0% (patients with age > 75 years), 40.2% (patients with relevant comorbidities) and 46.2% (patients with psychiatric conditions). Lower H&Y stages were observed for younger patients (vs older ones), for patients without (vs patients with) relevant comorbidities and for patients without (vs patients with) psychiatric conditions.
Older patients showed a higher frequency of tremor, postural instability and cognitive symptoms than younger patients. No relevant differences for fluctuations were observed according to age. This reflects what is clinically expected in PD patients according to age.
Patients with comorbidities had similarities to elderly patients: they showed higher disease severity and tremor. Postural instability and non-motor symptoms were more frequent in patients with relevant comorbidities than in those without.
Patients with psychiatric conditions had higher disease severity, higher frequency of postural instability and higher frequency of non-motor symptoms than patients without psychiatric conditions.
Safinamide was administered at an initial dose of 50 mg/die to 93% of patients, and in total 336 discontinuations were observed for 22% of patients. Almost half of discontinuations occurred due to adverse reactions. During the observation period, 58% of patients had a dose increase of safinamide and 6% had a dose decrease.
Safinamide was safe and well tolerated. Dyskinesia, which was the most frequently AE reported in other studies was also the most frequent event in the SYNAPSES study, although

it occurred in a lower frequency in the SYNAPSES study (14% vs 31%). Other events occurred in less than 3% of patients in the SYNAPSES study included: fall (2.6%), headache (1.2%) and back pain (1.0%). No relevant frequency of cataract, constipation was reported. Hallucination, which could be related to other dopaminergic side effects, was observed in 2.9% of the overall sample.

No relevant differences emerged in the safinamide initial daily dose by younger and older patients: at the start of treatment, the majority of patients (93% in patients aged ≤ 75 and 93% in patients aged > 75) were administered with a daily dose of 50 mg. During study, 21% and 23% of evaluable patients aged ≤ 75 and > 75 respectively, permanently discontinued safinamide.

The proportions of patients experiencing AE were similar in the population of patients aged > 75 (47%) when compared to patients aged ≤ 75 (45%). No relevant differences emerged in severity or in action taken between the two age groups (patients aged ≤ 75 and > 75). Dyskinesia was still the most frequent AE in elderly patients (9.5%), with a lower frequency than the overall sample (13.7%). On the other hand, other AEs had higher frequency than the overall sample, namely hallucinations (5.1% in elderly patients vs 2.9% in overall sample), fall (3.5% vs 2.6%) and somnolence (2.2% vs 1.2%). Both younger and older patients had similar safinamide treatment patterns, hence the difference in frequency of adverse events does not seem related to a different safinamide dose according to age.

The safinamide initial daily dose was 50-mg daily in 94% of patients with relevant comorbidities and in 90% of patients without relevant comorbidities. No test was performed to assess significance; however, it seems reasonable to interpret this as if a higher dosage could be administered in less fragile patients (i.e. in patients without relevant comorbidities). No relevant difference was observed regarding the rate of safinamide discontinuation according to the presence or absence of concomitant conditions.

A higher occurrence of AEs was observed in patients with comorbidities (49% and 38% of patients with and without relevant comorbidities, respectively). Dyskinesia was, again, the most frequent AE in the subgroup of patients with comorbidities (12.3%), with a similar frequency as the overall sample. The distribution of the occurrence of the other AEs was quite similar in the subgroup of patients with comorbidities and the overall sample.

Finally, dyskinesia was the most frequent AE in the subgroup of patients with psychiatric conditions too (15.6%), with a slightly higher frequency than in the overall sample (13.7%). Patients with psychiatric comorbidities also showed a higher occurrence of hallucinations (4.1% plus 1.5% visual hallucinations) and falls (3.4% vs 2.6% in the overall sample). On the other hand, no relevant difference emerged in safinamide initial daily dose by patients with or without psychiatric conditions. No relevant differences as for severity and action taken for adverse events were observed in patients with or without psychiatric conditions.

A different frequency of SAEs was observed according to age and comorbidities. In particular, 13.6% of SAEs in patients aged > 75 vs 7.7% in those agred ⩽ 75. Patients aged > 75 had more SAEs not related to safinamide (85%) than patients aged ⩽75 (69%). Moreover, 11% and 4.6% of patients with and without relevant comorbidities, respectively, had at least one SAE. This is an expected phenomenon given that elderly patients and patients with other

conditions could experience more clinical events. Occurrence of SAEs in patients with and without psychiatric conditions was similar (10% and 8.4%, respectively). The most frequent SAE experienced by psychiatric patients was dyskinesia (0.8% vs 0.3% of the overall sample). In the other subgroups, lung infections were the most common SAE.
On the other hand, ADR did not occur more frequently in older patients when compared with younger patients (26.1% in patients aged > 75 vs 28.3% in patients aged ⩽ 75), nor according to the presence of comorbidities. ADR occurred in a slightly higher frequency in patients with psychiatric conditions (31.0%) vs patients without (25.3%).

SVII.3Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk
MedDRA PT Dyskinesia

Potential mechanisms:
Excess dopaminergic stimulation.

Evidence source(s) and strength of evidence:
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).

Characterisation of the risk:
During the safinamide clinical trial development program, the number and percentage of subjects with at least 1 treatment-emergent dyskinesia AE are summarized by SOC and preferred term for the pooled subject populations. Overall, the number and percentage of dyskinesia AEs reported for subjects in the Early-stage PD and Mid/Late Stage PD or OLE Phase trial populations were relatively small.

The overall incidence of dyskinesia as an adverse event in safinamide treated patients was 11.6% compared with an incidence of 7.1% in placebo treated patients.

Mid/Late Stage PD
For patients with Mid-Late Stage PD, treatment-emergent dyskinesia AEs were reported for a higher percentage of subjects in the combined safinamide group compared with the combined placebo groups (25.1% and 13.9 %; see Table 8). The most frequently reported dyskinesia AE for both the combined safinamide and combined placebo groups was dyskinesia (24.3% and

12.9%). Additionally, an AE of dystonia was reported for a similar percentage of subjects in the combined safinamide and placebo groups (1.5% and 1.0%). All other dyskinesia AEs were reported by only 1 or 2 subjects in any treatment group.

Table 8: Treatment-Emergent Dyskinesia by Treatment Group for Group 1 Mid/Late Stage PD

System Organ Class/ Preferred Term	Safinamide (mg/day)			Placebo Randomized (N=497) n (%)
	50 (N=243) n (%)	100 (N=478) n (%)	All (N=721) n (%)	
Subjects with ≥1 dyskinesia event of interest	80 (32.9)	101 (21.1)	181 (25.1)	69 (13.9)
Nervous system disorders	80 (32.9)	101 (21.1)	181 (25.1)	69 (13.9)
Dyskinesia	76 (31.3)	99 (20.7)	175 (24.3)	64 (12.9)
Dystonia	8 (3.3)	3 (0.6)	11 (1.5)	5 (1.0)
Chorea	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
Drooling	1 (0.4)	0 (0.0)	1 (0.1)	1 (0.2)
Movement disorder	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
Extrapyramidal disorder	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Spasmodic dysphonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

MedDRA dictionary (Version 13.0). A subject with multiple occurrences of an AE is counted only once in the SOC and preferred term category. Dyskinesia events of interest are based on dyskinesia, dystonia, and akathesia SMQs. (SMQ = standard MedDRA query).

SOURCE: Section 2.11.35 of Safinamide-CTD Sect. 2.7.4" Summary of Clinical Safety" and Table AE43.2 Late PD.

Dyskinesia was the most commonly reported AE in safinamide treated patients occurring with an overall incidence of 11.6% compared with an incidence of 7.1% in placebo treated patients. However, the incidence was higher in the 50 mg/day (14.5%) dose compared with an incidence of 11.1% in the 100 mg/day dose group.

SOURCE: Section 2.5.5 Common TEAEs of Safinamide-CTD Sect. 2.7.4 "Summary of Clinical Safety" Table 26 and Table AE 11.4 Early PD and Mid/Late PD.

Early-stage PD

For patients with Early-stage PD, treatment emergent dyskinesia AEs (TEAEs) were reported for a very small and similar percentage of subjects in the combined safinamide and placebo groups (1.1% and 1.2%). The most frequently reported dyskinesia AEs were motor dysfunction (0.5%) and dystonia (0.4%) for the combined safinamide group and dystonia (0.5%) for the combined placebo group. All other dyskinesia AEs were reported by only 1 or 2 subjects in any treatment group.

Regarding *seriousness*, in trial NW-1015/015/III/2003 and its extension NW-1015/017/III/2003, there was no serious TEAE dyskinesia. In trial NW-1015/016/III/2006, one subject in the safinamide 100 mg/day group experienced a serious TEAE dyskinesia. The event was of moderate severity and resolved with sequelae. In trial NW-1015/018/III/2006, there was no serious TEAE dyskinesia. In trial 27918 and its extension, 27938, no subject

experienced a serious TEAE dyskinesia. In trial 27919, no subject experienced a serious TEAE dyskinesia. In Open-label trial, 28850, 4 of 964 (0.4%) subjects experienced a serious TEAE of dyskinesia.

Regarding *severity and nature of risk*, in trial NW-1015/015/III/2003, only one subject in safinamide low dose (50-100 mg/day) group experienced a TEAE dyskinesia, which was of mild severity. NW-1015/017/III/2003, there was no TEAE dyskinesia. In trial NW-1015/016/III/2006, 4.1% (16/390) subjects experienced a TEAE of dyskinesia which were mild, 4.1% (16/390) which were moderate, and 1% (4/390) which were severe. In trial NW-1015/018/III/2006, 12.7% (24/189) of subjects in the safinamide 50 mg/day group (5.8% [11/189] mild, 5.8% [11/189] moderate, 1.1% [2/189] severe) and 13.3% (24/180) of subjects in the safinamide 100 mg/day group (8.9% [16/180] mild, 3.9% [7/180] moderate, 0.6% [1/180] severe) experienced a newly emergent TEAE of dyskinesia. In trial 27918 and its extension, 27938, no subjects experienced a TEAE dyskinesia.
In trial 27919, 14.6% (40/274) subjects in the safinamide group experienced a TEAE of dyskinesia, which was mild in 6.6% (18/274) of subjects, moderate in 8.0% (22/274) of subjects and severe in 1.8% (5/274) of subjects.
In Open- label trial, 28850, 11.2% (106/964) subjects experienced a TEAE of dyskinesia, which was mild in 6.8% (66/964) subjects, moderate in 4.5% (43/964) of subjects, and severe in 0.5% (5/964) of subjects.

Regarding *frequency* in trial NW-1015/015/III/2003, only one subject in safinamide low dose group experienced TEAE dyskinesia.
NW-1015/017/III/2003, there was no TEAE dyskinesia
In trial NW-1015/016/III/2006, TEAE dyskinesia occurred more frequently in subjects in the safinamide 50 mg group (20.6%, 46/223) compared with the safinamide 100 mg group (17.9%, 40/224).
In trial NW-1015/018/III/2006, the incidence of the newly emergent TEAE dyskinesia was 12.7% (24/189) in the safinamide 50 mg/day group and 13.3% (24/180) in the safinamide 100 mg/day group.
In trial 27918 and its extension trial27938, no subject experienced TEAE dyskinesia.
In trial 27919, the incidence of the TEAE dyskinesia was 4.6% (40/274).
In Open-label trial, 28850, 11.2% (106/964) subjects experienced a TEAE of dyskinesia.

Background incidence/prevalence
The percentage of patients with newly occurring dyskinesia in placebo-treated mid-to late stage patients in the clinical program was 13.9% (69 out of 497 patients on placebo group).

Risk factors and risk groups:
Patients on L-dopa alone, or in combination with other dopaminergic treatments are at risk for developing dyskinesia.

Preventability:
Patients to take the lowest dose of dopaminergic agents required to control PD symptoms.

Impact on the risk-benefit balance of the product:

The risk is well known and no additional activities (neither additional pharmacovigilance nor additional risk minimisation measures) are considered necessary to further characterise or minimise the risk and maintain a favourable risk-benefit profile.

Public health impact:
Increased risk of development of dyskinesia may lead to increased morbidity and disability in the population exposed to safinamide depending on its severity and nature. The limitations placed upon administration of Xadago by virtue of the warnings and/or precautions are considered adeguate.

Important Identified Risk
MedDRA PT Teratogenicity

Potential mechanisms:
The potential mechanism is unclear.

Evidence source(s) and strength of evidence:
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.

Characterisation of the risk:
No clinical data is available on the use of Xadago during pregnancy. Pregnancy was excluded before study entry and prevented by the use of reliable contraception for four weeks prior to enrolment, throughout the treatment period, and four weeks after the last dose of the study medication.

Risk factors and risk groups:
Women of childbearing potential.

Preventability:
Safinamide should not be given during pregnancy, to lactating women, or to women of childbearing potential not practicing adequate contraception. Women of child bearing potential should be advised not to become pregnant during safinamide therapy.

Impact on the risk-benefit balance of the product:
The limitation in the use of the product minimise the risk and contribute to maintain a benefit-risk profile of the product. No additional activities (neither additional pharmacovigilance nor additional risk minimisation measures) are considered necessary to further characterise or minimise the risk.

Public health impact:
No public health impact is expected in view of the limitations placed upon administration of Xadago by virtue of the warnings and/or precautions.

Important Potential Risk:
Risk of retinal degeneration in patients with PD treated with safinamide

Potential mechanisms:
The precise etiology of the retinal degeneration found in rodents following safinamide treatment remains unknown. The pathogenesis is probably multifactorial.

Evidence source(s) and strength of evidence:
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.

Characterisation of the risk:
In rats, the retinal changes were time and dose dependent, occurred in pigmented and albino strains, were exacerbated by high light intensity levels, not exacerbated by combination treatment with L-dopa/carbidopa but slightly exacerbated by pramipexole combination treatment, not associated with melanin binding or un-due sensitivity to UV light, correlated with changes in ERG and SD-OCT, with apparent early photoreceptor changes at 24 hours after start of treatment and reversible after 3 days of treatment. The lowest dose producing retinal atrophy was 15 mg/kg/day. Only mild retinal atrophy occurred in mice after life-time treatment in the car-cinogenicity study at the highest dose tested (200 mg/kg/day).
Monkeys were not affected by retinal changes (at doses up to 70 mg/kg/day for 39 weeks); this was confirmed by an independent Pathology Working Group. In addition, no retinal changes were in-duced in monkeys treated for 13 weeks with combination of safinamide and L-dopa/carbidopa. Similarly, retinal atrophy was not detected in another 13-week monkey combination study with safinamide and pramipexole either by light or by electron micro-scopic examination.

In the clinical trial program, no increase in incidence of retinal degeneration compared to placebo was identified. These conclusions were based on >1000 patients treated with safinamide who had ocular assessments at 6 months, >600 patients with at least 12 months,

and >400 patients with over 2 years ocular assessment in double-blind, placebo-controlled stud-ies, and >200 patients for 3 years, and >130 for 4 years in open label extension studies.

Risk factors and risk groups:
Patients with Parkinson's disease treated with Xadago.
Patients with history of retinal disease, including inherited conditions.

Preventability:
The product should not be administered to patients with ophthalmological history that would put them at increased risk for potential retinal effects (e.g., albino patients, family history of hereditary retinal disease, retinitis pigmentosa, any active retinopathy, or uveitis).

Impact on the risk-benefit balance of the product:
Routine PhV activities are optimised through a targeted follow-up questionnaires for all reports of retinal events to determine if these may related to retinal degeneration and may be associated with safinamide use. No additional activities (neither additional pharmacovigilance nor additional risk minimisation measures) are considered necessary to further characterise or minimise the risk and maintain a favourable risk-benefit profile.

Public health impact:
No public health impact is expected in view of the limitations placed upon administration of Xadago by virtue of the warnings and/or precautions.

Important Potential Risk
Use in severe hepatic impairment.

Potential mechanisms:
Reduced clearance of safinamide in patients with hepatic impairment.

Evidence source(s) and strength of evidence:
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.

Characterisation of the risk:
The potential influence of hepatic impairment on safinamide PK was investigated in a dedicated study [Study 28696]. This study was an open-label, parallel-group, single center, single oral dose (50 mg) study in 24 male/female subjects with different grades of hepatic function (mild, and moderate hepatic impairment) and control healthy subjects with normal hepatic function).

Results of this study showed that the PK of safinamide and its metabolites are affected by the degree of hepatic impairment. The marginal increase in exposure of safinamide

(approximately 30% increase in AUC) that was observed in subjects with mild hepatic impairment (Child-Pugh A) was considered to be within the boundaries of clinical acceptability, based on the favourable safety profile. Thus, for subjects with mild hepatic impairment no recommendation regarding dose adjustment will be given.
In subjects with moderate hepatic impairment (Child-Pugh B), exposure of safinamide increased about 80% (CI: 154-215%). Steady-state exposures in the clinical studies 015/017 after doses of 200 mg/day of safinamide were about 4-fold higher than those observed in the Child-Pugh B subjects.

These high exposures were not associated with any pattern of adverse changes, i.e., AEs, liver function tests, ECG, and vital signs.

Risk factors and risk groups:
Patients with mild, moderate or severe hepatic impairment.

Preventability:
Xadago use in patients with severe hepatic impairment is contraindicated. No dose adjustment is required in patients with mild hepatic impairment. The lower dose of 50 mg/day is recommended for patients with moderate hepatic impairment. If patients progress from moderate to severe hepatic impairment Xadago should be stopped.

Impact on the risk-benefit balance of the product:
These high exposures were not associated with any pattern of adverse changes, i.e., AEs, liver function tests, ECG, and vital signs. No additional activities (neither additional pharmacovigilance nor additional risk minimisation measures) are considered necessary to further characterise or minimise the risk and maintain a favourable risk-benefit profile.

Public health impact:
No public health impact is expected in view of the limitations placed upon administration of Xadago by virtue of the warnings and/or precautions.

Important Potential Risk:
Impulse control disorders

Potential mechanisms:
The mechanism is dopamine-related. The mesolimbic circuits are expected to be implicated in the development of ICDs in Parkinson's Disease due to stimulation by dopaminergic drugs, particularly in susceptible individuals.

Evidence source(s) and strength of evidence:
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.

Characterisation of the risk:
ICD have been evaluated in safinamide clinical study using the QUIP score by categories based on the absence of any compulsive behaviour ('none'), or the presence of 1 or $\geqslant$ 2

compulsive behaviours (‘Any 1 Compulsive Behaviour’, ‘Any ≥ 2 Compulsive Behaviour’) in the SETTLE study.

The frequencies of subjects with shifts from the ‘none’ to at least ‘1 Compulsive Behaviour’ at any time after baseline were 15 (8.8%) and 19 (10.7%) in the safinamide and placebo treatment groups, respectively.

Risk factors and risk groups:
Patients with a medical history of impulse control disorders or concomitantly on other MAO-inhibitors.

Preventability:
Patients and carers are made aware of the behavioural symptoms of impulse control disorders 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.

Impact on the risk-benefit balance of the product:
No increase in incidence of ICD assessed using the QUIP in safinamide treated patients compared to placebo was observed.
No additional activities (neither additional pharmacovigilance nor additional risk minimisation measures) are considered necessary to further characterise or minimise the risk and maintain a favourable risk-benefit profile.

Public health impact:
No public health impact is expected in view of the limitations placed upon administration of Xadago by virtue of the warnings and/or precautions.

Important Potential Risk:
Concomitant use of MAOIs, serotonergic drugs, and/or pethidine.

Potential mechanisms:
The concomitant administration of safinamide with other MAO inhibitors (including medicinal and natural products without prescription) may lead to a non-selective MAO inhibition possibly causing a hypertensive crisis.

Serious adverse events, including serotonin syndrome, have been reported with the concomitant use of MAOIs, serotonergic drugs, and/or pethidine. Serotonin syndrome is an intra-synaptic serotonin concentration-related phenomenon, due to a combination of serotonergic drugs with different mechanism of action, e.g. MAOIs combined with any serotonin reuptake inhibitor.

Some cases of opioid toxicity (respiratory depression, hypotension, coma) involving MAOIs and pethidine have been reported. Opioid toxicity is caused by CYP450 inhibition by the MAOI leading to accumulation of opioids.

Evidence source(s) and strength of evidence:

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.

Characterisation of the risk:
Patients receiving concomitant treatment with MAO-inhibitors, serotonergic drugs and/or pethidine were not included in safinamide clinical studies.

Risk factors and risk groups:
Patients conconcomitantly on MAO-inhibitors, serotonergic drugs and/or pethidine.

Preventability:
Concomitant treatment with other monoamine oxidase inhibitors and pethidine is contraindicated.

Xadago may be used with selective serotonin re-uptake inhibitors at the lowest effective dose, with caution for serotoninergic symptoms. In particular, 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.

Impact on the risk-benefit balance of the product:
No additional activities (neither additional pharmacovigilance nor additional risk minimisation measures) are considered necessary to further characterise the risk. If confirmed the risk is minimised by the information reported in current reference document.

Public health impact:
No public health impact is expected in view of the limitations placed upon administration of Xadago by virtue of the warnings and/or precautions.

SVII.3.2 Presentation of the missing information

Missing information:
Use in patients with history and/or presence of retinal disease

Evidence source
Population in need of further characterization:
Retinal degeneration was observed in rat repeated-dose toxicity studies but not in monkey and human studies.
Patients with history of retinal disease, including inherited conditions, were excluded from the studies.

Anticipated risk/consequence of the missing information:

Patients with ophthalmological history may be at increased risk for potential retinal effects (e.g., albino patients, family history of hereditary retinal disease, retinitis pigmentosa, any active retinopathy, or uveitis).
Routine PhV activities are optimised through a targeted follow-up questionnaires for all reports of retinal events to determine if these may related to retinal degeneration and may be associated with safinamide use.

Missing information:
Use of safinamide in patients aged<30 years

Evidence source
Population in need of further characterization:
Patients below the age of 30 were excluded from the studies. As Parkinson's disease is a neurodegenerative disorder that mostly affects humans after the age of 50 years, this should not be a significant issue relative to patients below the age of 30. Use in children and adolescents, below the age of 18 is contraindicated.

Anticipated risk/consequence of the missing information:
No risks are anticipated.

Missing information:
Long term use >3 years

Evidence source
Population in need of further characterization:
Limited information. 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. One hundred and sixty-nine (169) patients were exposed to Xadago for over 4 years.

Anticipated risk/consequence of the missing information:
No risks are anticipated. The missing information is investigated through routine pharmacovigilance activities.

Missing information:
Whether specific inhibitors of the amidases involved in the metabolism of safinamide to NW-1153, may increase the exposure of safinamide

Evidence source
Population in need of further characterization:
Safinamide is almost exclusively eliminated via metabolism, largely by high capacity amidases that have not yet been characterized, and there are currently no marketed medicinal products known to cause clinically significant drug-drug interactions through inhibition or induction of amidase enzymes.

Anticipated risk/consequence of the missing information:
The risk of interaction will be investigated through in vitro studies if applicable in future.

PART II: MODULE SVIII. - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1. Summary of safety concerns

Summary of safety concerns	
Important identified risk:	• Dyskinesia • Teratogenicity
Important Potential Risks:	• Risk of retinal degeneration in patients with PD 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 • 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

PART III. : PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

A full description of the Pharmacovigilance System established by Zambon S.p.A exists as a separate document, the Pharmacovigilance System Master File.

III.1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for safety concerns:

Risk of retinal degeneration in PD patients treated with safinamide (important potential risk): Routine PhV activities are optimised through a targeted follow-up questionnaire for all reports of retinal events to determine if these may relate to retinal degeneration and may be associated with safinamide use. A comprehensive list of terms (HLGT and HLT) indicative of retinal degeneration, retinal atrophy and macular degeneration is kept updated, as appropriate.

- Other forms of routine pharmacovigilance activities for safety concerns:
  Not applicable.

III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

With respect to the additional pharmacovigilance activites completed or ongoing presented in table part III.1, no further additional pharmacovigilance activities are planned for the concerned products.

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table III.3.1 : On-going and planned additional pharmcovigilance activities

None

PART IV. : PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V. : RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. ROUTINE RISK MINIMISATION MEASURES

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk: Dyskinesia	Listed in SmPC sections 4.4, 4.8 and 4.9 Listed in PL sections 2, 3 and 4 Levodopa doses may need to be reduced in con-comitant treatment as safinamide may potentiate its side effects and exacerbate pre-existing dyski-nesia (effect not seen when safinamide was used as an adjunct to dopamine agonists in early stage PD patients).
Important identified risk: Teratogenicity	Listed in SmPC section 4.6 Listed in PL section 2 Safinamide should not be given to women of child-bearing potential (unless practicing adequate contraception), during pregnancy and breast-feeding.
Important potential risk: Retinal degeneration in patients with PD treated with safinamide	Listed in SmPC sections 4.3, 4.4 and 5.3 Listed in PL section 2 Treatment should not be initiated in patients with presence/history of retinal disease.
Important potential risk: Use in severe hepatic impairment.	Listed in SmPC sections 4.2, 4.3 and 4.4 Listed in PL section 2 Use in patients with severe hepatic impairment is contraindicated. In case patients progress from moderate to severe hepatic impairment, treatment should be stopped.
Important potential risk: Impulse control disorders (ICDs)	Listed in SmPC sections 4.4 and 4.8 Listed in PL section 2 and 4. Patients and carers should be made aware of the behavioural symptoms of impulse control disorders.
Important potential risk: Concomitant use of MAOIs, serotonergic drugs, and/or pethidine	Listed in SmPC Sections 4.3, 4.4 and 4.5 Listed in PL section 2 Concomitant treatment with other monoamine oxidase (MAO) inhibitors is contraindicated. Concomitant treatment with pethidine is contraindicated. Avoid risk of interaction by ensuring adequate wash-out (7 days).
Missing information: Use in patients with history and/or presence of retinal disease	Listed in SmPC sections 4.3 and 4.4 Listed in PL section 2 Treatment should not be initiated in patients with presence/history of retinal disease.
Missing information: Use of safinamide in	None

patients aged<30 years	
Missing information: Long term use >3 years	None
Missing information: Whether specific inhibitors of the amidases involved in the metabolism of safinamide to NW-1153, may increase the exposure of safinamide	Listed in SmPC sections 4.5 and 5.2

V.2. ADDITIONAL RISK MINIMISATION MEASURES

Not applicable: routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. SUMMARY OF RISK MINIMISATION MEASURES

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Dyskinesia	SmPC sections 4.4, 4.8 and 4.9 PL sections 2, 3 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilnace activities: None
Important identified risk: Teratogenicity	SmPC section 4.6 PL section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilnace activities: None
Important potential risk: Risk of Retinal degeneration in PD patients treated with safinamide	SmPC sections 4.3, 4.4 and 5.3 PL section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaires for all spontaneous reports of retinal events to determine their potential association with

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		safinamide A comprehensive list of terms (HLGT and HLT) indicative of retinal degeneration, retinal atrophy and macular degeneration is kept updated, as appropriate. Additional pharmacovigilnace activities: None
Important potential risk: Use in severe hepatic impairment	SmPC sections 4.2, 4.3 and 4.4 PL section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilnace activities: None
Important potential risk: Impulse control disorder (ICDs)	SmPC sections 4.4 and 4.8 PL section 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilnace activities: None
Important potential risk: Concomitant Use of MAOIs, serotinergic drugs and /or pethidine	SmPC Sections 4.3, 4.4 and 4.5 PL section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilnace activities: None
Missing information: Use in patients with history and/or presence of retinal disease	SmPC sections 4.3 and 4.4 PL section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaires for all spontaneous reports of retinal events to determine their potential association with safinamide. A comprehensive list of terms (HLGT and HLT)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		indicative of retinal degeneration, retinal atrophy and macular degeneration is kept updated, as appropriate Additional pharmacovigilance activities: None
Missing information: Use in patients <30 years	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilnace activities: None
Missing information: Long term use >3 years	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilnace activities: None
Missing information: Whether specific inhibitors of the amidases involved in the metabolism of safinamide to NW-1153, may increase the exposure of safinamide	SmPC sections 4.5 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilnace activities: In vitro investigation if applicable in future

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

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

XADAGO® - TARGETED FOLLOW-UP FORM
(Retinal events)

1. GENERAL INFORMATION

CASE IDENTIFICATION NUMBER: _____

PATIENT'S INITIALS _____

PATIENT'S AGE: _____

2. DETAILS ON TREATMENT WITH XADAGO®

Daily Dose	**Start date (dd/mm/yyyy)**	**Ongoing (Yes/No)**	**Stop date (dd/mm/yyyy)**

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XADAGO® - TARGETED FOLLOW-UP FORM
(Retinal events)

3. OCULAR SYMPTOMS

Did the patient have recent experience of any of the following symptoms?

Symptom	YES	NO	From	To	Continuing (YES/NO)
Loss of visual acuity – Visual acuity is the ability to detect fine detail, for example when you read or drive					
Loss of colour vision — may be noticeable especially with whitish colours or may be noticeable with very dark colours such as differentiating a dark blue from a black coat					
Distortion of central vision – Images, writing or faces can become distorted in the centre					
Dark adaptation problems — Orientation in very dim light has become more difficult, such as discerning details when entering a long street tunnel, walking in not well illuminated streets					
Changes in the visual field - Has the field of vision become narrower? This may be noticed only indirectly by more commonly bumping into objects in the pathway, such as flower pots, dust bins, chairs or not noticing objects which come from the side such as other pedestrians, cars, bicycles, dogs etc.					
Loss of contrast sensitivity - Has it become more difficult to differentiate darker grey from lighter greyish areas in a scene such as detecting cars in front in a fog or noticing other pedestrians in a dimly illuminated area					
Increased glare — Has it become more difficult to see object if the lightening conditions change suddenly from dark to bright?					

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XADAGO® - TARGETED FOLLOW-UP FORM
(Retinal events)

4. RELEVANT MEDICAL HISTORY/CONCURRENT ILLNESS/RISK FACTORS

Date of first diagnosis of Parkinson Disease: _____

Most recent Hoehn and Yahr Staging (if known): _____

Date last visit at an eye doctor: _____

Did the eye doctor provide any diagnosis of an ophthalmological disorder, such as:

- Cataract
- Glaucoma
- Diabetic retinopathy
- Uveitis

Is the patient wearing glasses? Yes ☐ No ☐
if Yes:

- When were they prescribed last time: date:_____
- Diopters (strength of the glasses) (if known): right eye / left eye_____
- Does the patient use them only for reading Yes ☐ No ☐
- Does the patient use them only for far vision (such as driving)? Yes ☐ No ☐

Did the patient have any head or eye trauma and if so, which type?_____

Is there any family history of retinal diseases, such as retinal degeneration, night blindness, glaucoma, high myopia (short-sightedness), age-related macular diseases?

How much alcohol does the patient drink in average (e. g. 2 bottles of beer daily, half a bottle of wine daily etc.)? _____

Does or did the patient smoke regularly? Yes ☐ No ☐
If Yes: when did the patient start smoking and how much do/did he/she smoke daily in average?
_____

Does the patient has other particular diseases or common health conditions

- Diabetes mellitus
- Hypertension
- Cardiovascular diseases
- Obesitas (Please indicate size and weight) _____
- Blood disorders (anemia etc.)
- Stroke
- Other relevant health conditions and risk factors (Please specify)

_____

XADAGO® - TARGETED FOLLOW-UP FORM
(Retinal events)

5. CONCOMITANT/PREVIOUS MEDICATIONS

Which drugs does the patient **presently take** (including OTC and "natural products" ? Please indicate the name of the drug, the daily dose and the duration

Specify	From/To	Daily Dosage

Did the patient **previously** take any drugs for more than two months and if so which ones (dose, start and duration) ?

Please indicate especially:

- Antimalarial drugs
- Antirheumatic drugs
- Antiepileptic drugs
- Drugs for tuberculosis
- Drugs for cancer

Please look specifically through the following list of drugs:

	YES	NO	Specify	From/To	Dosage
Chloroquine, Hydrochloroquine					
Chlorpromazine					
Thioridazine					
Deferoxamine					
Topiramate					
Metronidazole					
Latanoprost					
Epinephrine					
Rosiglitazone					
Niacin					
Tamoxifen					
Digoxin					
Sildenafil					
Interferon					
Isoretinoin					
Antiepileptic drugs					
Anticancer drugs					

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XADAGO® - TARGETED FOLLOW-UP FORM
(Retinal events)

6. OPHTALMOLOGICAL TESTS (before and after XADAGO® intake)

Are results of the following tests available?

- Visual acuity
- Slit lamp examination
- Ophthalmoscopy and / or fundus photography
- Tonometry
- Static perimetry
- Kinetic perimetry
- Amsler grid
- Fluorescence angiography
- OCT
- Electroretinography or electrooculography
- Dark adaptation function
- Others (please specify) _____

If so please provide such results.

Date:

Filled in by:

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.