Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Safinamide

Proprietary Product Name: Xadago

Sponsor: Seqirus Pty Ltd

March 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ABPM	Ambulatory blood pressure monitoring
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse events of special interest
AMT	Active motor threshold
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
CGI	Clinical global impression
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMI	Consumer Medicine Information
COMT	Catechol-O-methyl transferase
COPD	Chronic obstructive pulmonary disease
CRO	Clinical Research Organisation
CSR	Clinical Study Report
DA	Dopamine
DC	Direct Compression
DRS	Dyskinesia Rating Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ECG	Electrocardiograph
ESPD	Early stage Parkinson's disease

Abbreviation	Meaning
ESS	Epworth Sleepiness Scale
EU	European Union
Euro-QOL	European Quality of Life scale
FDA	Food and Drug Administration
FDA-mITT	FDA-version of modified intent-to-treat population
GCP	Good Clinical Practice
GRID-HAM-D	Grid version of Hamilton rating scale for depression
HAMD	Hamilton scale for depression
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HLM	Human liver microsomes
HR	Heart rate
HRU	Health resource utilisation
HV	Healthy volunteers
HVA	Homovanillic acid
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
L-DOPA	Levodopa
LOCF	Last observation carried forward
LS	Least-squares
LTFU	Lost to follow-up
MAO	Monoamine oxidase
MAO-A	Monoamine oxidase, type A
MAO-B	Monoamine oxidase, type B
MEP	Motor evoked potential
MHPG	3-methoxy-4-hydroxy-phenilglycol

Abbreviation	Meaning
mITT	Modified intent-to-treat
MMRM	Mixed-effect model with repeated measures
OC	Observed cases
OLE	Open-label extension
PD	Parkinson's disease
PD	Pharmacodynamics
PEA	Phenylethylamine
PI	Product Information
PK	Pharmacokinetics
PP	Per Protocol
PRP	Platelet-rich plasma
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using the Fridericia formula
RC	Roller compaction
RDO	Retrieved drop out
RMP	Risk Management Plan
RMT	Resting motor threshold
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	Standard deviation
SNRI	Serotonin-norepinephrine reuptake inhibitor

Abbreviation	Meaning
SSRI	Selective serotonin reuptake inhibitor
TBM	To be marketed
TEAE	Treatment–emergent adverse event
TGA	Therapeutic Goods Administration
TLC	Thin layer chromatography
TMS	Transcranial magnetic stimulation
TSF	Tyramine sensitivity factor
UPDRS	Unified Parkinson's Disease Rating Scale
USA	United States of America
WB	Whole blood

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	30 October 2018
Date of entry onto ARTG:	2 November 2018
ARTG numbers:	292144 and 292145
, *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Active ingredient:	Safinamide
Product name:	Xadago
Sponsor's name and address:	Seqirus Pty Ltd 63 Poplar Road, Parkville, VIC 3052
Dose form:	Film-coated tablets
Strengths:	50 and 100 mg
Container:	Polyvinyl chloride (PVC)/Polyvinylidene chloride (PVDC)/Aluminium blister packs
Pack size:	30s
Approved therapeutic use:	*Xadago is indicated for the treatment of adult patients with fluctuating idiopathic Parkinson's disease (PD) as add-on therapy to a regimen that includes levodopa (L-DOPA).*
Route of administration:	Oral (PO)
Dosage:	Xadago treatment should be started at 50 mg/day. The dose may be increased to 100 mg/day after two weeks on the basis of individual clinical need. Xadago tablets are for oral use. Xadago should be taken with water. Xadago may be taken with or without food. If a dose is missed, the next dose should be taken at the usual time the next day.

Product background

This AusPAR describes the application by the sponsor to register a new chemical entity, safinamide (as mesilate) with the product name Xadago, for the treatment of idiopathic

Parkinson's disease as add-on therapy to levodopa (L-DOPA) alone or in combination with other Parkinson's disease medicinal products, at a starting dose of 50 mg/day with an optional progression to 100 mg/day, contingent on the therapeutic response and clinical need.

The submission proposes registration of the following dosage forms and strengths: 50 and 100 mg film-coated tablets.

Parkinson's disease is a major neurodegenerative disease, with an incidence that increases with age. The cause of Parkinson's disease is unclear but the primary pathology is progressive degeneration of the substantia nigra (SN), a group of dopaminergic neurons located in the brainstem with subsequent loss of dopaminergic input to the basal ganglia, a collection of deep grey matter in the brain.

L-DOPA is the most effective single therapy for Parkinson's disease. L-DOPA can cross the protective blood–brain barrier whereas dopamine itself cannot. Thus, L-DOPA is used to increase dopamine concentrations in patients with Parkinson's disease and dopamine-responsive dystonia. Once L-DOPA has entered the central nervous system, it is converted into dopamine by the enzyme aromatic L-amino acid decarboxylase, also known as DOPA decarboxylase. In clinical practice, other dopaminergic treatments are also used to reduce or delay the need for L-DOPA therapy or to improve the efficacy or moderate the side effects of L-DOPA. For example, dopamine agonists may be chosen in patients with a relatively early onset of Parkinson's disease.

Monoamine oxidase B (MAO-B) inhibition increases the levels of dopamine in the brain, including the striatum, where dopamine deficiency plays a major role in producing the deficits of Parkinson's disease. Inhibition of MAO-B increases dopamine levels in parkinsonian mice. Safinamide inhibits MAO-B and it is likely that this effect accounts for its anti-parkinsonian efficacy in humans.

During the course of Parkinson's disease motor fluctuations and dyskinesia occur. Whether this is related to long term L-DOPA use, disease progression or both remains a matter of debate. Safinamide played an anti-dyskinetic role in parkinsonian monkeys with L-DOPA induced dyskinesia.

Safinamide differs from MAO-B inhibitors currently used for PD therapy (selegiline and rasagiline) in its mode of inhibition (non-covalent and reversible for safinamide, as compared with covalent and irreversible for selegiline and rasagiline) and by its additional activity at non-MAO-B targets.

Safinamide is also associated with state-dependent inhibition of voltage-gated sodium (Na^+) channels and the consequent modulation of stimulated glutamate release, but it is unclear if this mechanism is relevant to its efficacy in Parkinson's disease.

Regulatory status

This is an application to register a new chemical entity on the Australian Register of Therapeutic Goods (ARTG).

Table 1 below depicts the current status of registration internationally. Due to limitations of the clinical data currently available to support safinamide as add-on therapy to dopamine (DA) agonist monotherapy, this indication was not approved in the European Union (EU), Switzerland or the USA. Hence TGA approval is only sought for safinamide as an add-on to L-DOPA (alone or in combination with other PD medications).

Table 1: Current Status of overseas registration

Country/ Region	Submission Date	Status	Indications:	Other Relevant Information
European Union	05-Dec-2013	Approved: 24-Feb-2015	For the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients.	Centralised Procedure: *Rapporteur:* Netherlands *Co-Rapporteur:* United Kingdom Procedure No. EMEA/H/C/00239/0000
United States of America	26-Dec-2014	Approved: 21-Mar-2017	As adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes	A New Drug Application (NDA 207145) for safinamide was submitted to the FDA on 27-May-2014. FDA assessed the NDA as materially incomplete and that sections lacked sufficient organisation to permit timely, efficient, and complete review by all relevant disciplines. FDA concerns were addressed and the NDA was resubmitted and accepted for evaluation in December 2014.
Switzerland	20-Mar-2014	Approved: 12-Nov-2015	For the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients.	National procedure
Brazil	05-Feb-2016	Submitted: *Under Evaluation*	*For the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to: A single Dopamine Agonist (DA-agonist) at a stable dose in early stage non-fluctuating patients, and A stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products in mid- to late-stage fluctuating patients.*	National procedure

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Description	Date
Submission dossier accepted and first round evaluation commenced	30 August 2017
First round evaluation completed	23 March 2018
Sponsor provides responses on questions raised in first round evaluation	29 May 2018
Second round evaluation completed	4 October 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	5 July 2018
Sponsor's pre-Advisory Committee response	19 July 2018
Advisory Committee meeting	1-2 August 2018

Description	Date
Registration decision (Outcome)	30 October 2018
Completion of administrative activities and registration on ARTG	2 November 2018
Number of working days from submission dossier acceptance to registration decision*	241

*Statutory timeframe for standard applications is 255 working days.

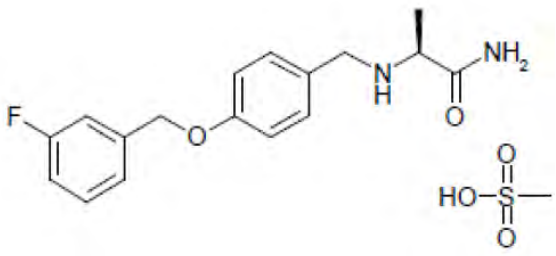
Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

III. Quality findings

Drug substance (active ingredient)

The molecular formula of safinamide mesilate is $C_{17}H_{19}FN_2O_2 \bullet CH_4O_3S$ and the molecular weight is 398.45 g/mol. There are no British Pharmacopeia (BP) or USA Pharmacopeia (USP) monographs for the drug substance safinamide mesilate or the finished product. The chemical abstracts service (CAS) registry number is 202825-46-5 and the chemical structural is described in Figure 1.

Figure 1: Chemical Structure of safinamide



There are three polymorphic forms:

- Anhydrous Form A1: most thermodynamically stable form (melting point: 216 to 217°C). The drug substance used in this product has A1 form.
- Anhydrous Form A2: A1 can convert to A2 form at <3°C (fast and reversible). Since this transition is fast and reversible, it is unlikely that both forms co-exist.
- Hemi-hydrate form H1: H1 is formed at high humidity, or where water is accessible. This converts to back to A1 at 40 to 60°C.

Drug product

Safinamide mesilate is a white to off white crystalline powder and was manufactured as polymorphic form A1. It is classified as Biopharmaceutics Classification System (BCS) class

2 (low solubility, high permeability).[1] Particle size of the drug substance has been controlled.

The excipients of the tablet core are all conventional pharmaceutical ingredients and comply with the European Pharmacopeia (Eur. Ph.)/USP NF monograph. No compatibility issues between the drug substance and each proposed excipients were noted from the compatibility studies.

Both strengths of the proposed tablets appear as orange to copper, round, biconcave tablets with metallic gloss, and embossed with '50' (for 50 mg strength) or '100' (for 100 mg strength) on one side of the tablet.

All labels are otherwise compliant with TGO91;[2] and acceptable from a TGA perspective.

Apart from the limits of the parameters water content, safinamide R-isomer, content of methanesulphonate and particle size, all other parameters in the specification are acceptable.

Method validation data were provided for assay and related Substances, residual solvent, methanesulfonic acid (MSA) ester and platinum content. Clarification from the sponsor was sought regarding the site of method validation. Confirmation on the site of method validation was provided. All methods were adequately validated. Particle size distribution method has been adequately validated.

Biopharmaceutics

The Xadago dossier included bioavailability and bioequivalence data and the findings from the following biopharmaceutic studies have been summarised below:

- Study 021: A randomised, open-label, two-period crossover bioequivalence trial of two different oral tablets of 100-mg safinamide, utilizing different manufacturing processes, in healthy volunteers (full name: Study EMR701165-021).
- Study 022: A randomised, open-label, three-way crossover trial to investigate absolute bioavailability of safinamide and to assess food effects on a single dose administration of 50 mg safinamide in healthy volunteers (full name: Study EMR701165-022).

Study 021 conclusion

The roller compaction tablets (RC yellow) manufactured by the proposed manufacturing process have shown to be bioequivalent to the direct compression tablet manufactured by the former process.

In addition, the following points are noted:

- The proposed formulation 'RC Candurin' tablet has a different film-coating to the 'RC yellow tablet' used in this bioequivalence study.
- However, the dissolution profiles of the proposed 'RC Candurin' tablet are in between dissolution profiles of the clinical formulation 'DC white tablets' and the 'RC yellow tablet' used in this bioequivalence study.

[1] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.
[2] Therapeutic Goods Order No. 91 Standard for labels of prescription and related medicines. <https://www.legislation.gov.au/Series/F2016L01285>

- Hence, the efficacies results from the pivotal clinical studies obtained with direct compression tablets (DC white) can be extended to the roller compaction tablets (RC candurin).

Study 022 conclusion

This was an absolute bioavailability/food effect study.

The absolute bioavailability of safinamide is 95%, which indicates the safinamide absorption is almost complete. First pass metabolism is negligible.

Food delays time to peak plasma concentration (T_{max}) by approximately 1 h but did not significantly affect the peak plasma concentration ($C_{max)}$ or area under the plasma concentration versus time curve (AUC) for the tablets.

Quality summary and conclusions

The registration of the proposed product is recommended from a pharmaceutical chemistry and biopharmaceutic perspective, provided that the particle size limits are amended as requested below and the revised drug substance provided for review.

The particle size limit in the drug substance specification applied by the finished product manufacturer should be tightened in line with batch data (including the clinical and biobatches).

The revised drug substance specification applied by the finished product manufacturer should be provided for review.

IV. Nonclinical findings

Introduction

General comments

The nonclinical dossier was of good overall quality, with the package of studies conducted in accordance with relevant TGA-adopted guidelines, including ICH M3 (R2).[3] All pivotal safety-related studies were conducted according to Good Laboratory Practice (GLP).

Non-human primate models were preferred in the evaluation of Parkinson's disease relevant pharmacology, since safinamide inhibits MAO-B and there is wider expression of MAO-B in human and non-human primate central nervous system (CNS) than in rodents.[4]

Pharmacology

The proposed mechanism of action for safinamide involves MAO-B inhibition, state-dependent blockade of voltage gated sodium channels, and 'inhibition of excessive release of glutamate'.

The sponsor postulated that the therapeutic effects of safinamide are mediated by dopaminergic and non-dopaminergic mechanisms of action.

[3] ICH M3 (R2): Guidance on Nonclinical Safety Studies For the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.
[4] Factor SA, Weiner WJ. Parkinson's Disease: Diagnosis and Clinical Management. 2nd ed. New York: Demos Medical Publishing; 2002.

In vitro and in vivo pharmacology studies demonstrated distinct mechanisms of actions by which safinamide extends/increases the anti-Parkinson's effects caused by L-DOPA and decrease dyskinetic episodes that often accompany L-DOPA treatment.

Primary pharmacology

Treatment of Parkinson's disease with L-DOPA may be accompanied by complications such as changes in its efficacy profile (fluctuations, wearing off), and the development of uncontrolled movements (dyskinesias) associated with its administration.

The effect of safinamide on levels of MAO-B (which is increased in Parkinson's disease and metabolises dopamine), on dopamine levels (which are decreased in Parkinson's disease), and on ion channels and glutamate release, were examined in order to establish any potential therapeutic effects on the complications associated with L-DOPA's treatment.

Safinamide reversibly and non-time dependently inhibited MAO-B (which is increased in Parkinson's disease), preventing dopamine breakdown and enhancing dopaminergic transmission in the brain. Safinamide inhibited the reuptake of dopamine and serotonin, although it is uncertain if these effects would be relevant at the concentrations of safinamide expected clinically. Safinamide did increase dopamine levels in mice and monkeys.

Safinamide reduced dyskinesias (induced by galantamine, pilocarpine or pimozide) in parkinsonian rats. In parkinsonian monkeys treated with L-DOPA, safinamide significantly reduced dyskinesias scores (including dystonic and choreic dyskinesias) and the duration and intensity of dyskinesias, as well as significantly and reversibly increased the duration (without affecting the efficacy) of the antiparkinsonian effect of L-DOPA.

Lazabemide (a MAO-B inhibitor) did not decrease L-DOPA induced dyskinesias, but did prolong the L-DOPA induced antiparkinsonian effects ('wearing off' of the effects of L-DOPA is a common treatment complication in Parkinson's disease). This suggests that safinamide's prolongation of the L-DOPA induced antiparkinsonian effects is (but the antidyskinetic effect is not) mediated via inhibition of MAO-B.

The increased duration of the antiparkinsonian effect of L-DOPA is likely due to the MAO-B activity of safinamide. The antidyskinetic activity of safinamide is likely due to other activities of this compound such as ion channel inhibition and effects of glutamate release (glutamate overactivity is observed in parkinsonian monkeys with dyskinesias and reduced with glutamatergic inhibition).

In two studies performed in a different laboratory from the other in vivo studies in parkinsonian monkeys, no effect on dyskinesia was observed after administration of safinamide. The sponsor provided a plausible argument for the lack of significant effect in these two studies. Due to low frequency sampling, information was lost on the rising phase, peak, and descending phase of dyskinesia. The higher sampling rate of the other studies provided a more sensitive evaluation of the dyskinesia severity and time course, and made the detection of the antidyskinetic effects of safinamide more reliable. Even with the different results in these two studies, other in vitro results provide a plausible explanation and mechanism of action for the decrease in dyskinesias by safinamide.

Since safinamide did not strongly inhibit N-methyl-D-aspartate receptor (NMDA) channels, its mechanism of action against LID may be due to the inhibition of presynaptic glutamate release by blockade of voltage-gated sodium channels.

In rat hippocampal neurons, safinamide inhibited tetrodotoxin sensitive fast sodium currents, veratridine induced and high potassium induced glutamate release, and high voltage-activated calcium currents. Safinamide had preferential affinity for the inactivated state of the sodium channels and no selectivity for a specific sodium channel subtype. Safinamide also weakly blocked calcium channels.

The high potassium induced release of gamma-aminobutyric acid (GABA) in the rat hippocampus (and not in the prefrontal cortex and striatum) was inhibited by safinamide.

In summary, in vitro and in vivo pharmacology studies demonstrated that safinamide extends/increases the antiparkinson's effects caused by L-DOPA and decreases dyskinetic episodes that often accompany L-DOPA treatment. These effects are achieved via a complex interaction of MAO-B inhibition and state-dependent inhibition of sodium currents and glutamate release.

These results support the potential therapeutic use of safinamide for the management of dyskinesia and wearing-off associated with L-DOPA-treatment.

Secondary pharmacodynamics and safety pharmacology

No significant effects of safinamide were observed against potassium channels or any of the following receptors: adenosine, alpha and beta adrenergic, benzodiazepine (peripheral), bradykinin, Calcitonin gene-related peptide (CGRP), cannabinoid, cholecystokinin, choline, GABA, galanin, glutamate, histamine, monoamine, muscarinic, neuropeptide Y, nicotinic ACh (central), opiate, purinergic, somatostatin, tachykinin, or vasoactive intestinal peptide (Study 0502001).

Cardiovascular system

Safinamide inhibited the potassium (Kv11.1; hERG) channel with 50% inhibitory concentrations (IC_{50}) of ≥ 27 µM, values which are > 67 times the mean unbound plasma level in humans of approximately 0.4 µM at the maximum recommended human and dose (MRHD) of 100 mg. The three main human metabolites (NW-1153, NW-1689 and NW-1689 AG) showed no relevant effect on the hERG channel.

In isolated guinea pig papillary muscles, safinamide (≥ 10 µM) shortened the APD20 (action potential duration at 20 % repolarisation) (by 9 to 16%), APD50 (by 25 to 35%) and APD90 (by 28 to 52%). At ≥ 30 µM, safinamide also reduced the action potential amplitude and the upstroke velocity.

After high doses of 100 mg/kg PO in rats, only a mild decrease in mean arterial pressure and mild to moderate decreases in heart rate were observed, without effects on the electrocardiogram (ECG) rhythm, blood gases and urinary excretion.

Bradycardia was observed in monkeys 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. However, ECG evaluations were normal in monkeys treated with safinamide up to 70 mg/kg/day for 39 weeks. Based on the concentrations at which effects on cardiac channels were observed, the risk of arrhythmia is low.

In anaesthetised monkeys, exposure to safinamide after intraduodenal and intravenous (IV) dosing did not cause hypotension. The IV infusion of safinamide also caused a slight decrease in heart rate and respiratory depression (and no effects on ECG). Hypotension was observed after intracisternal exposures (suggesting that the hypotension stems from a central mechanism) similar to that at the MRHD. Hypotension was not observed following repeated and single administration in conscious animals. In contrast to monkeys, in conscious dogs, oral administration of safinamide at 50 mg/kg PO caused an increase in diastolic blood pressure and decrease in the QT interval.[5]

[5] The QT interval is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarisation and repolarisation, effectively the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.The QT shortens at faster heart rates. An abnormally prolonged QT is associated with an increased risk of ventricular arrhythmias, especially Torsades de Pointes.

The risk of hypotension (possibly through a central mechanism) cannot be discounted, and it has been described as an uncommon side effect in the draft PI document.

Central nervous system

High doses of safinamide caused hypoactivity, inhibition of locomotor activity and loss of balance in mice, rats and monkeys. This is consistent with its known pharmacological activity.

Combination studies

Safinamide (10 mg/kg) did not interfere with the metabolism of L-DOPA or interact with AADC and catechol-O-methyltransferase (COMT) inhibitors (used in conjunction with L-DOPA to extend its duration of action) in rats, as shown by a lack of effect in plasma levels of L-DOPA and its metabolite 3-OMD, when safinamide was administered together with L-DOPA (40 mg/kg), carbidopa (10 mg/kg), or with L-DOPA (40 mg/kg), carbidopa (10 mg/kg) and entacapone (10 mg/kg). Safinamide caused hypotension and CNS symptoms (hunched back, teeth gnashing, head flicking, piloerection; Study 0405001/PR051740).

The hypertensive effect of 10 mg/kg (PO) tyramine was not potentiated by safinamide (10 or 20 mg/kg PO) in rats. Tyramine did not affect heart rate (Study 2001-42). Safinamide (at 50 mg/kg PO) did not modify the hypertensive response curve to noradrenaline in rats (2000-39).

Respiratory system

Administration of safinamide (at 30, 70, and 200 mg/kg) or R-safinamide (at 30 mg/kg) to conscious rats (Study GSP0010RF) had no effect on respiratory parameters (respiratory rate, tidal volume adjusted, minute volume adjusted, inspiration and expiration time, peak inspiratory and expiratory flow, pause or enhanced pause.

Urinary system

Conscious rats receiving a single oral dose of 30, 100 or 300 mg/kg safinamide (Study 9750236/N856-Q1519) displayed no effects on urinary volume, specific gravity, or concentrations and total excretion of electrolytes, urea and creatinine when compared with controls.

Gastrointestinal system

Conscious mice receiving a single oral dose of 30, 100 or 300 mg/kg safinamide (Study 9750274/N859-Q1520) displayed no effects on the intestinal transit of a charcoal meal when compared with controls.

Pharmacodynamic drug Interactions

Safinamide did not cause inhibition of aromatic L-amino-acid decarboxylase (AADC) or of catechol-O-methyltransferase (COMT).

These studies established that safinamide is not expected to interact with inhibitors of AADC and COMT that are used in conjunction with L-DOPA (such as carbidopa and entacapone, respectively).

The recently described congenital short QT syndrome has been found to be associated with an increased risk of paroxysmal atrial and ventricular fibrillation and sudden cardiac death.

Pharmacokinetics

Nonclinical pharmacokinetic (PK) studies were conducted in the mouse, rat and monkey, with limited studies in the rabbit, dog and mini-pig.

Oral absorption of safinamide was rapid in all species studied. Time to peak plasma concentration (T_{max}) was 1 h in mice, rats and humans, and 1 to 2 h in monkeys. Bioavailability was high after oral administration (92% in Sprague Dawley rats, 80% in monkeys, and 95% in humans). Bioavailability in Wistar rats was 49% after PO and 63% after intraperitoneal (IP) administration. Sprague Dawley rats and monkeys were used for the repeated dose toxicity studies.

The area under the plasma concentration versus time curve (AUC) was dose-dependent, dose-proportional in mice, more than dose-proportional in rats and monkeys, and less than dose-proportional in in mice. Systemic exposure to safinamide was lower in female mice, and exposure to metabolites NW-1153 and NW-1689 was generally higher in female rats. The half-life ($t_{1/2}$) was 1 to 2 h in rodents and 5 to 13 h in monkeys and 20 to 40 h in humans.

The volume of distribution was larger than the body water volume in rat, monkey and human, indicating extensive tissue distribution: safinamide-related radioactivity was distributed into tissues, as demonstrated by tissue to plasma ratios of approximately 2.0 to 3.0 in kidney, liver, lachrymal gland, spleen, lung, salivary gland, adrenals and brown fat. Distribution was also observed into the CNS, testes and bone marrow. At 24 and 168 h the radiolabel was still found in lachrymal gland, brown and white fat and bone marrow. Levels in the brain were low at 1 h, detectable 4 h post-dose and not measurable at 24 and 168 h. An investigation into the distribution of safinamide into the brain after acute administration revealed a brain: plasma ratio of 16 for rats and mice and 8.8 in monkeys.

In studies evaluating the distribution to the retina in pigmented (Lister hooded) and albino (Wistar), total safinamide concentrations were higher in pigmented retinas. NW-1689, the predominant circulating metabolite in both strains, was found in non-pigmented eyes, but not in the eyes of pigmented rats. The levels of safinamide in the aqueous or vitreous humour were not determined.

Upon administration of safinamide for 14 days, metabolite NW-1689 was not found in the retina of Lister Hooded pigmented rats, but when administered to pigmented Long Evans rats for 90 days, NW 1689 was found at low levels in the retina. It has not been determined if the difference in distribution of NW-1689 is due to duration of dosing or rat strain differences. Distribution into the retina is of toxicological significance.

The plasma protein binding of safinamide was comparable in animal species and humans (mouse 88%, rat 89%, monkey 85% and human 89%). The binding of metabolite NW-1689 was high, ≥ 97.5% in the four species.

The in vivo metabolite pattern in plasma, urine and faeces was investigated after single oral administration of radiolabelled (^{14}C)-safinamide to male and female mice, male and female rats, male mini-pigs, female dogs, male and female monkeys, and male humans. The metabolites identified were unchanged safinamide (NW-1015), the N-dealkylated acid (NW-1689), the O-debenzylated safinamide (NW-1199), the safinamide acid (NW-1153), and the acyl glucuronide of NW-1689 (NW-1689 AG). Formation of NW-1689 from the parent drug is catalysed predominantly by non-microsomal enzymes, cytosolic amidases, MAO-A and aldehyde dehydrogenase. Formation of NW-1153 is catalysed by non-specific cytosolic amidases (human fatty acid amide hydrolase, FAAH). Human liver microsomes catalyse the glucuronidation of NW-1689 to NW-1689 AG. Only a minor involvement of CYP isoenzymes was identified in the biotransformation of safinamide.

The main metabolites found in human plasma were unchanged safinamide, NW-1689, and NW-1689 AG, with 30, 30 and 18% of the AUC of total radioactivity, respectively.

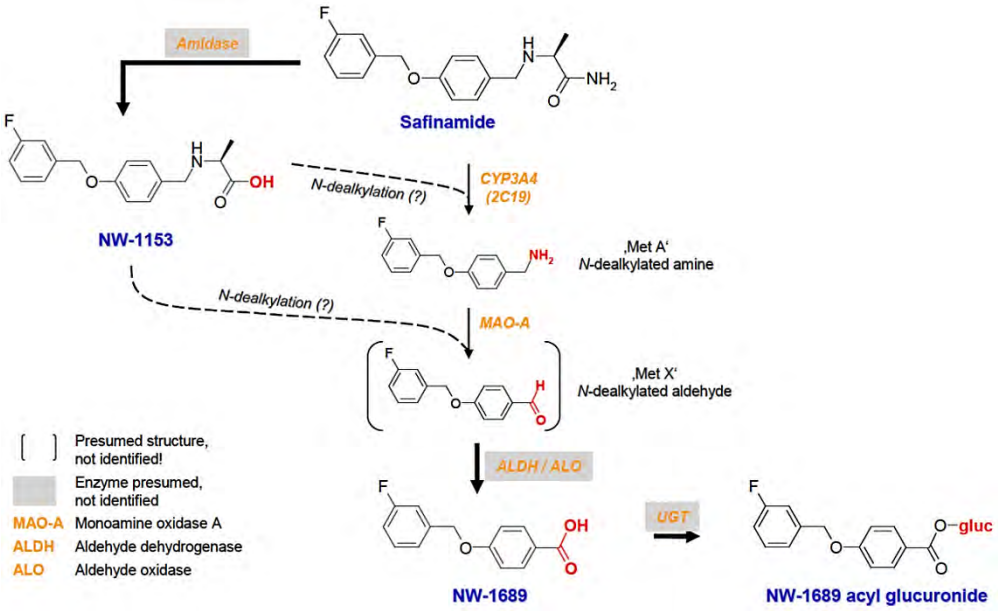
NW-1199 represented 2%, and NW-1153 represented 1% of radioactivity AUC in human plasma. NW-1689 was present at the same level as safinamide in the plasma of humans, but at higher levels than safinamide in the mouse (1 x), rat (> 50 x), mini-pig (2 x), dog (4x), and monkey (4 x). NW-1689 AG was present at 10% of the AUC of safinamide in monkeys and it was 70% higher than safinamide in dogs.

In repeat-dose studies in humans, the AUC of NW-1689 was 60% greater than safinamide, the AUC of NW-1689 AG was 25% that of safinamide, and the AUC of NW-1153 was 10% that of safinamide. In animal toxicokinetics studies, the AUC of NW-1689 was higher than safinamide in the plasma of rats (26 to 249x) and monkeys (4 to 5x), the AUC of NW-1689 AG was approximately 30% that of safinamide in monkeys, and the AUC of NW-1153 was around 30% that of safinamide in rats and approximately 5% that of safinamide in monkeys. These results indicate a high degree of systemic metabolism in the nonclinical species. All circulating metabolites in human were found in rats and monkeys.

Safinamide is cleared almost completely by metabolism, via the same metabolic pathways in human and nonclinical species. Clearance of safinamide was 1.7 to 2.8 L/h/kg in rat, and lower in monkey (0.45 L/h/kg) and humans (0.077 L/h/kg). In all nonclinical species and humans, safinamide is mainly excreted as metabolites via renal excretion (approximately 60 to 75%). The main metabolites in human urine were NW-1153, NW-1689 AG, NW-1199 and unchanged safinamide (with 14, 12, 8 and 5% of the radioactivity, respectively). Excretion via the faeces was almost absent in all species tested.

Below is a diagram with the main metabolic pathways for safinamide in humans:

Figure 2: Main metabolic pathways in humans



In rats, low levels of safinamide were seen in fetuses on Day 20 of gestation and in pups on Day 4 of lactation, therefore there is in utero exposure. Safinamide was not found in plasma from pups on Day 14 or Day 21 of lactation, although mechanistic studies suggested toxic effects in pups (neonatal hepatotoxicity) were due to exposure through lactation.

Overall, the combination of species selected for the pivotal repeat-dose toxicity studies with safinamide are adequate for evaluating possible toxic effects of safinamide in humans.

Pharmacokinetic drug interactions

Breast cancer resistant protein (BCRP) was inhibited by safinamide (IC_{50}: 43 μM) and NW-1689 (IC_{50}: 3.7 μM) at concentrations that may be achieved clinically. The possibility of interactions between safinamide and medicines that are BCRP substrates has been described in the draft PI document.

Safinamide was neither a substrate of nor an inhibitor of P-gp. NW-1689, NW-1153 and NW-1689 AG did not inhibit P-gp. Safinamide and its metabolites did not inhibit P-gp or other transporters organic cation transporter (OCT) 2, organic anion transporter protein (OATP) 1B1, OATP1B3, bile salt export pump (BSEP), OAT1/3/4. NW-1153 is an OAT3 substrate.

In human hepatocytes, safinamide was a weak inducer of cytochrome P450 (CYP) isozyme 1A2 (activity increase of > 20% compared to positive control omeprazole, at a concentration ≥ 45 μM), CYP2B6 (50% effective concentration (EC_{50}): approximately 60 μM), CYP2C9 (activity increase of 35% compared to positive control rifampicin, at a concentration of 100 μM) and CYP3A4 (activity increase of ≤ 84% compared to positive control rifampicin, at a concentration of 100 μM). In human liver microsomal preparations, safinamide inhibited (33% inhibition at 100 μM) CYP2C8, 2C19, 2D6, 2A6, 2B6, 2C9, 2E1 and 3A4/5. It also inhibited hCYP1A1/2 in a competitive manner (IC_{50}: 48 μM) and via mechanism-based inhibition (Ki = 33.5 μM). None of these effects on CYP enzymes are expected to be clinically relevant.

Metabolites NW-1153, NW-1689 and NW-1689 AG did not display clinically relevant CYP inhibition.

Toxicology

Acute toxicity

The studies presented examined the acute toxicity, following both IV and PO administration, of safinamide, using rats. Safinamide induced similar clinical signs following both IV and PO administration to rats. Rats which received ≥ 25 mg/kg IV and ≥ 500 mg/kg PO developed (from within a few hours to 5 to 10 days post-dose) dyspnoea, hypoactivity, unsteady gait, sedation and prostration. Reduced body weight and deaths were observed at ≥ 1000 mg/kg PO. The maximum non-lethal dose was 500 mg/kg PO for rats. Safinamide is of low to moderate toxicity (with LD_{50} of between 70 and 100 mg/kg IV, and ≥ 1500 mg/kg PO).

Repeat-dose toxicity

These studies were performed in CD-1 mouse (4 and 13 weeks), Sprague-Dawley rat ((4 week; 2 studies), 13 week (2 studies), and 26 week (2 studies)), and cynomolgus monkey (4, 13, 39, and 26/39 week studies). In these studies, safinamide was administered once daily by oral gavage. In addition, safinamide was tested in combination with levodopa/carbidopa (LD/CD) or pramipexole in both species. The studies' parameters such as duration, species used (rodent and non-rodent), group sizes, and use of controls, were consistent with the relevant EU guideline.[6] Mechanistic studies were performed in rats to investigate adverse findings in the preliminary peri- and postnatal studies and, to elucidate the retinal toxicity observed in rats. The pivotal toxicity studies were performed to GLP standards.

Relative exposure

As shown in the table below, relative exposures at the No NOAEL for repeat-dose toxicity studies were below unity for rats but were 4 to 11 for monkeys.

[6] CPMP/SWP/1042/99 Rev 1Guideline on repeated dose toxicity

Table 2: Relative exposure to safinamide (S) and metabolites NW-1153 and NW-1689

Study duration, route (number)	Species	Dose mg/kg/ day	$AUC_{0-24\,h}$ (µg·h/mL)			Exposure ratio[a]		
			S	NW-1153	NW-1689	S	NW-1153	NW-1689
13 weeks ONP002	**Mouse**	100	30	-	-	1.5	-	-
		200	55	-	-	2.8	-	-
		250	63	-	-	3.2	-	-
4 weeks N814-Q1505 9750253	**CD rat**	**20**	**8**	**-**	**-**	**0.4**	**-**	**-**
		60	26	-	-	1.3	-	-
		100	64	-	-	3.2	-	-
13 weeks ONP003	**CD rat**	100	31	-	-	1.6	-	-
		200	35	-	-	1.8	-	-
		250	41	-	-	2.1	-	-
13 weeks 7552	**CD rat**	**15**	**2.4**	**-**	**-**	**0.1**	**-**	**-**
		30	10	-	-	0.5	-	-
		80	50	-	-	2.5	-	-
13 weeks SOI0056	**CD rat (F)**	125	81	-	5110	4.1	-	189
	LE rat (F)	125	66	-	3130	3.3	-	115
13 weeks SOI0053	**CD rat**	25+L/C*	13	-	1285	0.7	-	47
		75+L/C*	45	-	3635	2.3	-	134
		125+L/C*	83	-	3950	4.2	-	146
		125	86	-	4250	4.3	-	157
13 weeks SOI0054	**CD rat (F)**	**5 + 25 P**	**3.8**	**1.2**	**936**	**0.2**	**0.6**	**35**
	LE rat (F)	**5 + 25 P**	**5.2**	**1.3**	**417**	**0.3**	**0.6**	**15**
	CD rat (F)	15 + 25 P	13	3.7	1550	0.7	1.8	57
	LE rat (F)	15 + 25 P	15	5.3	953	0.8	2.6	35
	CD rat (F)	50 + 25 P	37	11	3400	1.9	5.4	125
	LE rat (F)	50 + 25 P	46	14	1870	2.3	6.9	69

Study duration, route (number)	Species	Dose mg/kg/ day	$AUC_{0-24\,h}$ (µg·h/mL)			Exposure ratio[a]		
			S	NW-1153	NW-1689	S	NW-1153	NW-1689
	CD rat (F)	15	11	3.4	1020	0.6	1.7	38
	LE rat (F)	15	13	3.0	967	0.7	1.5	36
	CD rat (F)	50	56	15	4020	2.8	7.4	148
	LE rat (F)	50	56	17	3370	2.8	8.4	124
26 weeks 8724	**CD rat**	5	1.09	-	-	0.1	-	-
		15	4.1	-	-	0.2	-	-
		45	25	-	-	1.3	-	-
26 weeks RE6230 (28452)	**CD rat**	60	67	-	2100	3.4	-	77
		120	97	-	4040	4.9	-	149
		180	145	-	3557	7.3	-	131
Week 42 (/104) ONP005	**SD rat**	25	18	4.4	1884	0.9	2.2	70
		50	44	11	2858	2.2	5.4	105
		100 **Ncarc**)	69	16	3737	3.5	7.9	138
4 weeks N822-Q1509 9750107	**Monkey**	20	64	-	-	3.2	-	-
		40	**163**	**-**	**-**	**8.2**	**-**	**-**
		80	292	-	-	14.7	-	-
		120	472	-	-	23.8	-	-
13 weeks 991180	**Monkey**	10	18	-	-	0.9	-	-
		20	40	-	-	2.0	-	-
		50	**133**	**-**	**-**	**6.7**	**-**	**-**
13 weeks 22972	**Monkey**	10 + 0.4 P	27	1.3	165	1.4	0.6	6.1
		10 + 2 P	34	1.7	197	1.7	0.8	7.3
		50 + 2 P	197	10	897	9.9	4.9	33
		50	**215**	**11**	**752**	**10.9**	**5.4**	**28**
13 weeks	**Monkey**	50	225	13	600	11.4	6.4	22

Study duration, route (number)	Species	Dose mg/kg/ day	$AUC_{0-24\,h}$ (µg·h/mL)			Exposure ratio[a]		
			S	NW-1153	NW-1689	S	NW-1153	NW-1689
SOI0052		20+L/C (A)	64	3.2	234	3.2	1.6	8.6
		50+L/C (A)	182	10	650	9.2	4.9	24
39 weeks 21893 TCP (B)	**Monkey**	3.2	6.4	-	-	0.3	-	-
		8	21	-	-	1.1	-	-
		20	**77**	**-**	**-**	**3.9**	**-**	**-**
39 weeks 30939 TCP	**Monkey**	**30**	**97**	**-**	**-**	**4.9**	**-**	**-**
		50	160	-	-	8.1	-	-
		70	254	-	-	12.8	-	-
IMP28559	**Human**	100 mg/ day	19.8	2.03	27.1	-	-	-

Tabulated values refer to total (bound plus unbound) plasma concentrations of analytes; a = animal:human plasma AUC0–24 h; F: values for female animals only (all other values average of M & F); – = not determined; bolded: NOAEL; Ncarc: NOEL for carcinogenic effects (NOAEL was not established for non-neoplastic lesions); A: levodopa/carbidopa given at 40/10 mg/kg twice daily; B: AUC1–24 h; CD = Sprague Dawley (albino rat); LE = Long Evans (pigmented rat); P: pramipexole; in study RF2310, administration of 10, 30 and 50 mg/kg/day to monkeys for 2 weeks yielded a NW-1689 AG exposure 1.4, 4.5 and 10.1 times the exposure in humans.

Major toxicities

CNS

As may be expected for a CNS active drug such as safinamide, high doses elicited a number of CNS clinical signs, including lack of coordination/ataxia, staggering, tremors, clonic contractions, convulsions and even death. The CNS was consistently affected, in all species tested (mouse, rat, rabbit, and monkey), although the clinical findings did not have histological correlates. Seizures were observed in monkeys (≥80 mg/kg/day, 4 to 39 week, relative exposure (RE): approximately 15), rabbits (50 mg/kg/day, embryofetal; RE: 3), rats (45 mg/kg/day, 26 week; RE: 1.3) and mice (≥ 200 mg/kg/day, 4 week and 104 week; RE: 3). Tremors and abnormal coordination usually preceded the convulsions.

In the 4 week study in monkeys, there were deaths related to CNS toxicity at 100 mg/kg/day (1/4 animals, Day 14) and 200 mg/kg/day (4/4 animals, Days 1 to23). CNS signs and reduced food intake were also observed at 100 and 200 mg/kg/day. In a second 4 week study, similar deaths were encountered at 80 mg/kg/day (1/10 monkeys, Day 11) and 120 mg/kg/day (3/10 monkeys, Days 11 to 14). CNS signs and reduced food intake were also observed at 80 and 120 mg/kg/day. Dose-related CNS signs at ≥80 mg/kg/day included staggering, loss of balance, dysmetria, reduced activity and convulsions. Deaths occurred between Days 1 and 23, with CNS signs appearing both on the day of death or several days prior.

In the 13 week monkey study, at the high dose (HD) of 50 mg/kg/day, there were no CNS signs, but food intake was slightly reduced. In the 39 week study, monkeys receiving 70 mg/kg/day displayed 'clonic contractions', pallor of the lip mucosa, moderate hypothermia, abnormal vocalisation, lateral and ventral recumbency, mydriasis, hypoactivity, staggering gait, loss of balance, ataxia and tremors. Hypoactivity and loss of balance were observed occasionally in animals receiving 50 mg/kg/day. Histopathological examination in all species did not reveal the CNS as a target organ for toxicity, suggesting that the CNS clinical signs were due to exaggerated pharmacological activity.

Retina

The retina was identified as a target organ of toxicity in rat studies. In order to assess the risk of retinal degeneration in patients treated with safinamide, the sponsor conducted repeat dose toxicity studies (of between 2 and 39 weeks duration), combination studies, and mechanistic studies. The potential phototoxicity, melanin binding, and retinal concentrations of safinamide were also evaluated.

Retinal degeneration was not observed in any of the monkey studies, at relative exposures of up to 24 in the 4 week study, 7 to 11 in the 13 week studies, and 13 in the 39 week studies.

No retinal degeneration was detected in mice in the preliminary (13 week) carcinogenicity study (Study ONP002) at doses up to 375 mg/kg/day, or in the 104 week carcinogenicity study (Study ONP004) at a dose of 50 mg/kg/day in both sexes and 100 mg/kg/day in males. Spontaneous retinal degeneration was exacerbated in females receiving ≥ 100 mg/kg/day and males receiving 200 mg/kg/day for 104 weeks.

Retinal degeneration was observed when rats received ≥15 mg/kg/day for 13 weeks (Studies 7552 and ONP003), ≥ 45 mg/kg/day for 26 weeks (Studies 8724 and RE6230), and ≥ 25 mg/kg/day for up to 104 weeks (Study ONP005). Although administration of 20 to 500 mg/kg/day for 4 weeks (Studies N596-Q1354/9550005; N814-Q1505/9750253) showed no evidence of retinal degeneration, these studies did not appear to have been re-examined after the detection of the retinal pathology in the 13 week study. Histologically, the retinal degeneration in rats was characterised by diffuse loss of nuclei from the outer nuclear layer (ONL), associated with shortening and /or disorganization of photoreceptor segments. Effects on the pigment epithelium and inner nuclear layer (INL) were only observed in chronic studies (45 mg/kg/day for 26 weeks).

Retinal degeneration was accompanied by cataract formation in all treated groups (≥ 25 mg/kg/day) in the rat 104 week carcinogenicity study (Study ONP005). Since cataracts were observed beneath the posterior capsular of the lens, they may have been due to retinal degeneration products in the vitreous humour causing degenerative changes in lenticular fibres beneath the capsule of the lens.

Safinamide repeat-dose combination toxicity studies were performed in rats and monkeys, in combination with levodopa/carbidopa and with pramipexole.

No retinal degeneration was observed in any of the monkey combination studies, after administration for up to 13 weeks of 50 mg/kg/day safinamide, both with levodopa/carbidopa (Studies SOI0022 and SOI0052) and pramipexole (Studies IMP28941/RE8410 and 22972).

There was retinal degeneration in all rat repeat-dose (of ≥ 2 weeks duration) combination studies with safinamide. Starting at 25 mg/kg/day, safinamide in combination with levodopa/carbidopa (80/20 mg/kg/day) for 13 weeks caused retinal degeneration to albino (Sprague Dawley) rats. Safinamide alone (at 125 mg/kg/day) caused retinal degeneration but a levodopa/carbidopa combination did not (Study SOI0053). The safinamide-induced degeneration did not seem to be exacerbated by the levodopa/carbidopa combination.

In the 13 week combination study with pramipexole (Study SOI0054), pigmented (Long Evans (LE)) rats did not have retinal degeneration when receiving safinamide (50 mg/kg/day) alone, but developed it when receiving 50/25 mg/kg/day safinamide/pramipexole. Light microscopic examination revealed that albino (SD) rats developed retinal degeneration when receiving safinamide alone (50 mg/kg/day) or in combination with pramipexole (25 mg/kg/day), with a higher extent of degeneration in the safinamide/pramipexole combination group.

Photoreceptor and ONL changes were identified by electron microscopy in Sprague Dawley rats given 15 or 50 mg/kg/day safinamide, with or without pramipexole, whereas in LE rats, only when in combination with pramipexole did 50 mg/kg/day safinamide cause slight retinal damage with disintegration and disorientation, single degenerating INL and ONL segments and a slight atrophy of the photoreceptor layer (PRC) and ONL. Therefore, under the conditions of this study, albino rats seemed to be more susceptible to safinamide-induced retinal damage when compared to pigmented rats.

In a study designed to evaluate if the retinal degeneration was caused by changes in dopamine turnover in the retina, the levels of dopamine and its metabolic by-products DOPAC and homovanillic acid (HVA) were found not to be affected in the retina of albino (Sprague Dawley) rats after administration of safinamide at 150 mg/kg (Study 1209024).

In studies in pigmented (LE) rats, safinamide (125 and 200 mg/kg/day), and safinamide (125 mg/kg/day) in combination with pramipexole (25 mg/kg/day) modified electroretinography (ERG) responses of the dark-adapted rod-cones after 15 days of treatment. These changes were irreversible after up to 70 days of recovery, and were accompanied by changes in SD-OCT (spectral domain optical coherence tomography) and histology (Study STC 378_10087), where the irreversible reduction of the retinal thickness was confirmed. When these pigmented rats received 125 mg/kg/day safinamide for 1, 2, or 3 days, changes in ERG parameters, lesions of the ONL (found via electron microscopy), and delayed recovery of photoreceptor response (rhodopsin renewal) were observed starting on Day 2 of administration. Complete functional and histological recovery was observed after 14 days without treatment (Study STC 378_10092). These studies confirmed that safinamide-affected retinal function in pigmented rats recovers after 15 days if safinamide was only administered for 2 to 3 days, but histological changes do not recover even after 70 days if safinamide was administered for 2 weeks.

In a time course study using female pigmented (LE) rats receiving 25 or 125 mg/kg/day safinamide, light microscopy examinations revealed that retinal damage started after 4 days of treatment with 125 mg/kg/day safinamide, while the retina of rats treated with the lower dose were unaffected after 4 weeks of treatment (Study T16169). Electron microscopy analysis revealed lesions as early as 24 h after start of treatment. In addition to atrophy of the ONL, retinal changes included the disintegration, disorientation and vacuolar degeneration and atrophy of the photoreceptor layer.

In a comparison study between pigmented (LE) and albino (Sprague Dawley) rats, an oral dose of 125 mg/kg/day for 13 weeks caused a time-dependent increase of severity of the retinal atrophy (minimal at 1 month and marked at 3 months). Although initially the effects seemed more marked in pigmented rats (at 1 to 2 months), the number of nuclei and width of the photoreceptor zone were similar in both rat strains after 13 weeks of administration (Study SOI0056).

In a study investigating the effect of light intensity levels on the retinal changes caused by safinamide, female SD rats received 75 or 150 mg/kg/day safinamide for 4 weeks (Study RE8900). Exposure to a light intensity of 250 to 350 LUX;[7] (normal light exposure) caused an increase in severity and incidence of safinamide-induced retinal degeneration,

[7] Lux is the SI derived unit of illuminance and luminous emittance, measuring luminous flux per unit area.

compared to exposure to a light intensity of 30 to 40 LUX (reduced light exposure). However, safinamide and its metabolites are not expected to be phototoxic, since they did not show absorption in the ultraviolet (UV) light range 290 to 700 nm (Study 1208053).

Binding of safinamide-related radioactivity was observed in the eyes and other pigmented tissues of pigmented (Lister hooded) rats. Significantly higher safinamide concentrations were found in the retinas of pigmented than those of non-pigmented (Wistar) rats (Studies DMPK 17-08 and DMPK 175-07). However, melanin binding does not seem to be related to the development of retinal degeneration/atrophy since this effect was also observed in non-pigmented rats. Since the predominant circulating metabolite NW 1689 was not found in pigmented eyes, its involvement in the development of retinal degeneration can be ruled out.

Since investigative studies could not identify a mechanism underling the development of safinamide-related retinal degeneration, the relevance of this lesion to humans cannot be ruled out.

Liver

In mice, the liver displayed centrilobular hepatocellular hypertrophy and fat vacuolation at ≥ 200 mg/kg and coagulative necrosis at 375/250 mg/kg in females. In rats there was increase in triglycerides and cholesterol, while in monkeys the serum cholesterol tended to be decreased at higher doses. Hepatic effects were limited to increased alkaline phosphatase and alanine aminotransferase in rats (at ≥ 30 mg/kg/day) and monkeys (≥ 50 mg/kg/day), sometimes accompanied by hepatic enlargement. Histologically, increased hepatocellular lipid and centrilobular hypertrophy was seen at ≥ 50 mg/kg/day in rats, and was not seen in monkeys. Although the hepatic changes were not extreme and did not cause death (like the CNS signs), due to safinamide's high permeability and strong lysosomotropic properties, as well as distribution to the liver, accumulation in the liver cannot be ruled out. Caution with the use of safinamide in patients with hepatic impairment has been documented in the draft PI document.

Lungs and adrenal glands

Like the retinal effects, pulmonary phospholipidosis and adrenocortical hyperplasia were limited to rats.

In rats (receiving 180 mg/kg/day for 26 weeks), large areas of pulmonary pallor, incompletely collapsed lungs and bronchi, as well as histologic findings of intra-alveolar macrophages were observed. Foamy alveolar macrophages contained concentric multi-lamellar, myeloid body-like inclusions in the cytoplasm, indicative of lung phospholipidosis. In some instances foamy macrophages were also seen in thymus, liver, uterus, and vagina. Phospholipidosis may be caused by safinamide due its lysosomotropic characteristics (Study DMPK 15-10). Increased adrenal glands size and weight were observed routinely in rats, accompanied by reversible hypertrophy of the zona fascicularis. These findings were not observed in monkeys, and are not expected to be a concern clinically.

Kidneys

Reversible changes in urea and creatinine were observed at doses as low as 30 mg/kg/day in rats and 50 mg/kg/day in monkey. At these dose levels, these changes were not associated with any histopathological change. In monkeys, doses of ≥ 80 mg/kg (which resulted in convulsions, dyspnoea, prostration and death), also caused microscopic renal effects (tubular dilatation, inflammation). Due to the high doses needed to cause these effects, it is not expected that the kidney will be a target organ when safinamide is used clinically.

Genotoxicity

Safinamide was negative for genotoxicity in a gene mutation assay in bacterial cells (Ames test), a mouse lymphoma assay, an unscheduled deoxyribonucleic acid (DNA) synthesis in rat hepatocytes and a micronucleus test in mice.

The circulating metabolites of safinamide (NW-1153, NW-1689 and NW-1689 AG) were not mutagenic in a bacterial assay. NW-1689 AG was not clastogenic in a micronucleus assay.

Carcinogenicity

In standard long-term rodent carcinogenicity studies, safinamide was administered orally (gavage) to mice (0, 50, 100, and 200 mg/kg/day) and rats (0, 25, 50, and 100 mg/kg/day) of both sexes for two years. There was no evidence from either sex for carcinogenic activity by safinamide or metabolites NW-1689 and NW-1153 in rats or mice. Although metabolite NW-1689 AG was not found in either species, it was found not to be genotoxic.

The rat carcinogenicity study used a HD giving an exposure level 3.5 times than that anticipated for humans. Using AUC data from a different study, the mouse carcinogenicity study high dose corresponds to an exposure level 2.8 times that anticipated in humans.

Like the repeat-dose studies, safinamide also induced retinal atrophy, cataracts and lenticular opacities in the rat carcinogenicity studies.

Reproductive toxicity

Reproductive toxicity studies used standard species (rat and rabbit) and appropriate group sizes, timing, durations of treatment and route of administration (oral). Most of the studies were conducted to GLP standards. As shown in the table below, relative exposures for safinamide at the maternal NOAEL ranged from 1 to 7.

Table 3: Relative exposure to safinamide and its metabolites

Study	Dose[a] / period	Day of sample	AUC_{0-24h} (µg·h/mL)			Exposure ratio[b]		
			S	NW-1153	NW-1689	S	NW-1153	NW-1689
Rat Embryo fetal (GD6-GD15), (9382)	50	GD15	41.4	-	-	2.1	-	-
	100	GD15	11.8	-	-	0.6	-	-
	150	GD15	182.5	-	-	9.2	-	-
Rat Embryo fetal, w. levodopa/ carbidopa (GD8-GD17). (SOI0057)	25	GD17	10.1	-	376	0.5	-	13.9
	50	GD17	27.7	-	748	1.4	-	27.6
	100	GD17	72-83 A	-	1590-1770 A	3.6 - 4.2	-	59 - 65
Rat Pre& postnatal, (GD6 to Lactation day 20; F0: 14 d (B)	4	GD 15	0.7	0.25	19.4	0.04	0.1	0.7
	12.5	GD 15	4.4	1.3	89.5	0.2	0.6	3.3
	37.5	GD 15	15.5 C	4.42	187	0.8	2.2	6.9

Study	Dose[a] / period	Day of sample	AUC_{0-24h} (µg·h/mL)			Exposure ratio[b]		
			S	NW-1153	NW-1689	S	NW-1153	NW-1689
(SOI0059)				(C)	(C)			
Rabbit Embryo fetal (GD6-GD18) (19030)	25	GD18	14.7	-	-	0.7	-	-
	50	GD18	64.3	-	-	3.2	-	-
	100	GD18	142	-	-	7.2	-	-
Rabbit Embryo fetal, w. levodopa/carbidopa (GD6-GD19) (SOI0046)	4	GD19	1.4	0.69	12.2	0.1	0.3	0.5
	12	GD19	6.3	2.5	39.1	0.3	1.2	1.4
	40	GD19	40,32 (A)	11.7, 9.38	178, 155 (A)	2.0	5 - 6	6 -7
Human 100 mg/day	6 days, PO, QT/ QTc study	19.8	2.03	27.1	-	-	-	-

Tabulated values refer to total (bound plus unbound) plasma concentrations of analytes; [a] = mg/kg/day by PO (gavage); [b] = animal: human plasma AUC_{0-24h}; A: with and without levodopa/carbidopa; B: AUC_{1-24h}; C: AUC_{0-8h}; bolded: NOAEL (maternal); underlined: NOAEL (offspring).

The reproductive toxicity studies in rats included a combined study of fertility + embryofetal development (treatment from 28/14 days prior to pairing to Gestation Day 6 (GD6), an embryofetal development study (treatment from GD6 to GD15), and a pre- and post-natal development study (treatment from GD6 to lactation day 20 (LD20)). An embryofetal development study with safinamide was conducted in rabbits (treatment from GD6 to GD18), as well as embryofetal development studies in rats and rabbits with safinamide + levodopa/carbidopa. All studies were conducted by oral gavage, which is an appropriate route to model the clinical route. Dose levels were determined by dose range-finding studies and were considered appropriate with clear maternotoxicity at the highest dose level. Toxicokinetic assessment was carried out in pregnant rats and rabbits for safinamide and 2 metabolites. Mechanistic studies were carried out in rats to investigate the nature of pre-postnatal findings and to try to differentiate if exposure was due to in utero transfer or to lactation.

There was no evidence of a treatment-related effect on fertility in rats at a dose of 50 mg/kg/day, however in males, an increase in abnormal sperm morphology (headless sperm, reduced hooks, 'miscellaneous abnormalities') and a decrease in sperm motility were observed at doses of ≥ 100 mg/kg/day. In females, reduced corpora lutea and implantations and increase in pre-implantation loss (resulting in a decrease in live embryos at GD 13), were observed at doses of 150 mg/kg/day. Fertility effects in both male and female rats were observed at more than 3 times the clinical exposure, based on AUC values. There were no histopathology findings in reproductive organs of either sex in repeat-dose toxicity studies in rats and monkeys.

In preliminary studies on embryo-foetal development in pregnant rats, doses of ≥ 200 mg/kg/day were associated with severe maternal toxicity, a higher incidence of intrauterine deaths, reduced foetal weight, small foetuses and cleft palates, while doses of ≥ 300 mg/kg/day were associated with maternal deaths and fetal anasarca. In the pivotal embryo-foetal development study in rats, safinamide induced soft tissue abnormalities including ectopic testes at ≥ 50 mg/kg/day, as well as reductions in foetal weight and urinary system changes (enlarged, kinked ureters) at ≥ 100 mg/kg/day (relative exposure ≥ 0.6 based on AUC).

When safinamide was administered from Day 8 to 17 of gestation at doses of 25, 50 and 100 mg/kg/day alone and in combination with levodopa/carbidopa at 80/20 mg/kg/day, safinamide alone at 100 mg/kg/day and levodopa/carbidopa alone induced an increased incidence of skeletal and soft tissue abnormalities (medially thickened/kinked and irregularly ossified ribs, incompletely ossified metatarsals, rudimentary/absent renal papilla, dilated ureter, displaced testis). Although combination treatment with safinamide and levodopa/carbidopa did not elicit an increase in maternal toxicity, fetal skeletal abnormalities were observed at a higher incidence than when safinamide and levodopa/carbidopa were administered by themselves.

In a preliminary embryofetal study in rabbits, maternal mortality was observed at ≥ 25 mg/kg/day, and lack of pregnancy/total resorptions at 120 mg/kg/day. In the pivotal study, external and visceral findings were non-treatment related at doses up to 100 mg/kg/day administered between GD6 and GD18. There were cases of skeletal variations (in ribs and vertebrae) at the high dose of 100 mg/kg/day, but it was associated with maternal toxicity (including convulsions).

Pregnant rabbits received safinamide alone at 40 mg/kg/day or at 4, 12 and 40 mg/kg/day in combination with levodopa/carbidopa at 80/20 mg/kg/day. No maternal effects were observed even at the highest dose and in combination with levodopa/carbidopa. An increased incidence of minor skeletal abnormalities was observed in foetuses in the safinamide only group. An increased incidence of major cardiovascular abnormalities (ventricular septum defect, single vessel arising from heart) was observed in the group treated with levodopa/carbidopa alone at doses of 80/20 mg/kg/day. An increase of the cardiovascular abnormalities already observed with levodopa/carbidopa alone, plus additional findings (increased foetal deaths and a small number of misshapen heart/atrium/ventricle) were observed in rabbits receiving combination treatment of safinamide and levodopa/carbidopa at all doses. The increased risk of inducing foetal cardiovascular abnormalities when administering safinamide together with levodopa/carbidopa has been observed with other MAO-B inhibitors such as rasagiline.

The length of gestation was dose-dependently increased in two pre- and post-natal studies in rats. In spite of having a longer length of gestation, body weights of offspring at birth were decreased at ≥ 37.5 mg/kg/day. At these doses, incidences of yellow/orange skin and/or skull, hepatic changes (bile duct hyperplasia, cholangitis, hepatocellular hypertrophy and necrosis), as well as pup mortality (mainly during the first week post-partum) were observed. The results of mechanistic studies investigating the aetiology of the morphological findings in rats showed increased postnatal deaths, distended/swollen abdomen, a marked increase in bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) plasma levels associated with degeneration and damage to the hepatobiliary system (animals received 50 mg/kg/day from GD6 to postnatal day (PND) 20). The liver changes showed complete recovery in surviving pups at weaning (Day 21, one day after dosing was stopped), which could mean that surviving pups were less susceptible to the hepatic changes.

Rat pups born to control dams that were fostered, at one day of age, to treated (50 mg/kg/day) dams developed jaundice, although not at the severity or incidence of rat pups from high dose dams that remained with their dam. Pups born to treated dams that

were fostered at one day of age to control dams also developed jaundice, but at lower incidence and severity than litters fostered to treated dams. Results from the cross-fostering study suggested that the toxicity was both prenatal and antenatal. A NOAEL of 12.5 mg/kg/day for the pre and postnatal development of the offspring was established in rats (this dose represents an exposure below that expected clinically).

In summary, developmental toxicity (including teratogenic effects) was observed when safinamide was administered during pregnancy at clinically relevant doses.

Pregnancy classification

The sponsor has proposed Pregnancy Category C[8]. Based on the data presented, this category is not appropriate. There is evidence for treatment-related malformations, but there is no evidence that they are pharmacologically related. The sponsor may have proposed Category C by mistake, since Category C was approved by the FDA (its definition includes '*Animal reproduction studies have shown an adverse effect on the fetus…*'), and the category C in the USA is similar to Category B3;[9] in Australia. Australian Category B3 is applied to a drug for which 'Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans'. A Pregnancy classification of B3 is justified.

Dependence

In vitro studies in recombinant cell systems safinamide showed an affinity to the DA and 5HT transporters (DAT and SERT, respectively) at concentrations of approximately 10 μM, that is, > 17 fold lower than the affinity shown by cocaine, and inhibition of DA and 5HT reuptake with IC_{50}s of approximately 10 μM, that is, >30 times lower potency as compared to cocaine (Study 1205014). An in vivo brain imaging study in baboons confirmed that there is no occupancy of DAT and SERT even at supratherapeutic plasma concentrations (Study TANDD_invivo_2011.013 (MNI-Safinamide-2 REV 01)).

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) (Studies 0901003; MKS45276a_Caccia).

Based on the results of these studies, safinamide is not predicted to have a significant potential for clinical dependence or abuse.

Nonclinical summary and conclusions

Summary

- The nonclinical studies presented were of good quality. The pivotal toxicological studies were performed to GLP standard. The systemic exposures achieved at the NOAEL in the toxicity studies were lower than clinical levels in rodents, and ≥ 7 times the exposure at the MRHD in monkeys. The pharmacokinetic studies confirmed the suitability of the animal species used in the pharmacodynamic and pivotal toxicology studies.

[8] Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
[9] Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

- Degeneration and loss of photoreceptor cells (mostly irreversible) were observed in the retina of both albino and pigmented rats at safinamide plasma exposures lower than that in humans at the maximum recommended human dose, and after as little as 1 to 2 daily doses. The relevance to humans is unknown but cannot be ruled-out.
- The safety pharmacology studies together with the repeat dose toxicity studies indicate there is a potential for mild effects related to the pharmacological activity of safinamide, such as CNS effects, and moderate effects on heart rate and blood pressure at or near the clinical exposure. Electrocardiogram parameters were not affected by treatment.
- There was no evidence of genotoxicity in adequately conducted in vitro and in vivo studies. Carcinogenicity was examined in lifetime studies in mice and rats following oral (gavage) administration. There were no drug- related neoplasms in either species. The NOEL for carcinogenicity was 3 to 3.5 times the clinical exposure based on AUC values.
- Safinamide caused only minor effects on fertility in rats, at doses higher than 50 mg/kg/day (exposures > 3 times that expected clinically). In rabbits, safinamide caused minor skeletal abnormalities at 40 mg/kg/day (twice the expected clinical exposure). Safinamide exacerbated the toxic effects caused by levodopa/carbidopa (cardiovascular abnormalities). In rats, decreased foetal and litter weight and fetal abnormalities (without teratogenicity) were observed even in the absence of maternal toxicity at ≥ 50 mg/kg/day (1 to 2 times the expected clinical exposure). In pre/post-natal studies, exposure to safinamide (around the same as expected clinically) both in utero and through lactation caused hepatobiliary toxicity (reversible in surviving pups at Day 21) and mortality. A Pregnancy Category of B3 is recommended.

Conclusions and recommendations

- Safinamide caused retinal toxicity and cataracts in rats at subclinical relative exposures. The relevance to humans cannot be ruled-out, therefore warning about these possible effects is recommended in the PI.
- The safety pharmacology data suggest that mild depression of the CNS, heart rate and blood pressure are possible with the clinical use of safinamide.
- Safinamide alone and in combination with levodopa and carbidopa produced adverse developmental effects in animals at doses similar to those used in humans. Since the significance of these findings is uncertain in humans, a Pregnancy Category of B3 is recommended.
- The reproductive toxicity studies identified breast milk as a potential source of safinamide exposure, and hepatobiliary damage as a risk for breast-fed infants.
- There are no nonclinical objections to the registration of safinamide for the proposed indication. Amendments to the draft PI were recommended but these are beyond the scope of this AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Clinical rationale

Parkinson's disease is a common neurological disease, with an incidence that increases with age. The cause of Parkinson's disease is unclear, but the primary pathology is degeneration of the SN, a group of dopaminergic neurons located in the brainstem, with subsequent loss of dopaminergic input to the basal ganglia, a collection of deep grey matter in the brain. It is believed that excitotoxicity may play a role in the degeneration of SN cells, or in secondary changes in the basal ganglia, but there are no registered pharmacological agents for Parkinson's disease that have, as their primary mechanism of action, any effect on the degeneration of SN cells or on putative excitotoxic mechanisms. Most treatments are aimed at supporting the failing dopaminergic input to the basal ganglia.

The basal ganglia play an important role in scheduling automatic and semi-autonomic behaviours, and the key features of PD reflect impaired basal ganglia function. Clinicians usually describe Parkinsonism as a triad of tremor, rigidity and bradykinesia (or slowness of movement). Many would consider postural instability, due to impairment of postural righting responses, to be a fourth key feature. In the early stages, patients experiencing slowing of voluntary movements and a reduction in automatic behaviours such as swinging the arms while walking, along with muscle rigidity and, in many cases, a tremor, worse at rest. With advancing disease, slowing of voluntary movement can become severe, and additional neurological deficits may develop, such as dementia and autonomic dysfunction.

Because the primary deficit in Parkinson's disease is dopaminergic input to the basal ganglia, because of reduced functional reserve in degenerating substantia nigra cells, most available pharmacological therapies for Parkinson's disease involve: 1) boosting dopamine production by providing the dopamine precursor, levodopa (L-DOPA); 2) mimicking the effects of endogenous dopamine with dopamine agonists; or 3) prolonging the effective half-life of dopamine. MAO-B inhibitors, such as selegiline and rasagiline fall in the latter category, and work by inhibiting catalysis of endogenous dopamine (including dopamine produced with the assistance of pharmacological doses of levodopa).

Safinamide has been confirmed as a highly selective inhibitor of MAO-B, and it is likely that this accounts for its anti-Parkinsonian efficacy. Safinamide differs from MAO-B inhibitors currently used for PD therapy (selegiline and rasagiline) in its mode of inhibition (non-covalent and reversible for safinamide, as compared with covalent and irreversible for selegiline and rasagiline) and by its additional activity at non-MAO-B targets. It has also been shown to produce state-dependent inhibition of voltage-gated sodium channels and subsequent modulation of stimulated glutamate release. The sponsor has suggested that this may be useful in Parkinson's disease, and some reports in the lay press have generated interest in the potential for safinamide to delay the underlying degeneration of SN cells, by limiting excitotoxicity, but the sponsor has provided no direct evidence that this proposed mechanism contributes to the efficacy of safinamide.

Safinamide was previously assessed as a potential anticonvulsant, because of its sodium-channel blocking properties, but this indication is not currently being pursued. One pharmacodynamic study suggests it may reduce neuronal excitability as measured with transcranial magnetic stimulation.

It remains unclear whether safinamide offers any specific advantages over existing MAO-B inhibitors, but there is a reasonable a priori case that the known pharmacological properties of safinamide would be expected to have utility in Parkinson's disease.

Proposed indication

The proposed indication is:

> *For the treatment of idiopathic Parkinson's Disease (PD) as add-on therapy to levodopa (L-Dopa) alone or in combination with other PD medicinal products.*

The sponsor's study program assessed safinamide in the clinical context:

- as adjunctive therapy to levodopa in mid-to-late Parkinson's disease subjects with motor fluctuations.

The proposed indication does not mention the targeted age group. No paediatric studies were submitted, so the registered indication should be restricted to adult patients with Parkinson's disease. In practice, Parkinson's disease is extremely rare in children.

Guidance

The efficacy and safety studies in the submitted dossier were designed on the basis of regulatory advice and existing guidelines for the conduct of Parkinson's disease studies. In particular, all major efficacy measures were based on the guidance issued by Committee for Medicinal Products for Human Use (CHMP) and FDA. These measures were previously used in the pivotal studies of other anti-Parkinsonian drugs. Guidance from regulatory authorities was not always available for determination of a clinically meaningful response to treatment, so the sponsor applied definitions from the literature;[10,11] in which a meaningful response was defined as a 30% or greater improvement from baseline in Section III of the Unified Parkinson's disease Rating Scale (UPDRS-III). At the time the Phase III program was initiated, no specific guidance was available from any authority regarding the appropriate assessment of dyskinesia, so dyskinesias were assessed by a Dyskinesia Rating Scale (DRS) described in the literature.[12]

Overall, the prospective design of the studies was appropriate and consistent with regulatory guidelines (but the prospective statistical analysis plan was abandoned in some cases, with inappropriate post hoc revision of the analysis approach).[13]

Formulation

Development

Safinamide was originally manufactured in strengths of 50 mg and 100 mg, using a direct compression method (DC). This formulation was used in Studies 016 and 018, and according to the sponsor's Summary of Clinical Pharmacology, it was 'partly used' in Studies 27918 (MOTION) and 27919 (SETTLE). The extent of this partial use was somewhat unclear.

A new tablet of safinamide was then produced using a roller compaction method (RC). This is the formulation intended for marketing (to-be-marketed formulation (TBM)). A dedicated bioequivalence study was conducted to compare these formulations, showing no important differences (Study EMR701165-021).

[10] Schrag A, et al. Minimal Clinically Important Change on the Unified Parkinson's Disease Rating Scale. *Movement Disorders*, 2006; 21: 1200–1207

[11] Goetz CG, Nutt JG, Stebbins GT. The Unified Dyskinesia Rating Scale: Presentation and Clinimetric Profile. *Mov Disord* 2008; 23: 2398-2403

[12] Goetz, CG et al. Utility of an objective dyskinesia rating scale for Parkinson's disease: Inter- and intra-rater reliability assessment. *Movement Disorders*, 1994; 9: 390-394

[13] Sponsor clarification: The post hoc revision referred to was conducted in ESPD studies. These studies were submitted by the sponsor as supporting safety data and comments regarding inappropriate statistical analyses do not relate to the pivotal studies for the indication proposed.

Excipients

The proposed formulation contains the following excipients: microcrystalline cellulose, copovidone, magnesium stearate, colloidal anhydrous silica, hypromellose, macrogol 6000, mica, iron oxide red and titanium dioxide.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- Approximately 20 clinical pharmacology studies, all of which collected some pharmacokinetic (PK) data, one of which was a thorough QT study, and three of which assessed the pressor effect of tyramine when used in combination with safinamide.
- Five clinical studies. Three of these evaluated safinamide as add-on to a single dopamine agonist in early stage Parkinson's disease (ESPD), in patients without motor fluctuations;[14]:
  - Study NW-1015/009/II/2001 (abbreviated to Study 009)
  - Study NW-1015/015/III/2003 (abbreviated to Study 015)
  - Study EMR 27918 (MOTION) (abbreviated to Study 27918)
- Two of the efficacy studies designated as pivotal evaluated safinamide as add-on to L-DOPA (with or without other anti-parkinsonian medications), in late stage Parkinson's disease (LSPD), in patients with motor fluctuations:
  - Study NW-1015/016/III/2006 (abbreviated to Study 016)
  - Study EMR 27919 (SETTLE) (abbreviated to Study 27919)
- Extension studies (Study 018, Study 017 and Study 27938).
- Pooled analyses of the three major excitatory postsynaptic potential (EPSD) studies, and the two major longitudinal study of personality disorders (LSPD) studies.
- Literature references.

Paediatric data

The submission did not include paediatric data. Parkinson's disease is extremely rare in children.

Good clinical practice

The submitted studies appear to have been designed and performed in accordance with Good Clinical Practice (GCP), and the Clinical Study Reports (CSRs) contain statements to that effect.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 4 shows the studies relating to each pharmacokinetic topic.

[14] Sponsor clarification: These data were submitted as additional, supporting safety data for the proposed indication by the sponsor.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK- Single dose	IPAS-PNU-194-99	*
		IPAS-NW/SS-215-99	*
		IPAS-NW/LD-231-00	*
	- Multi-dose	IPAS-PNU-194-99	*
		IPAS-NW/SS-215-99	*
		IPAS-NW/LD-231-00	*
	Mass balance	CRO-02-33	*
	Bioequivalence† - Single dose	EMR701165-021	*
	- Multi-dose	None	
	Food effect	IPAS-NW/FOOD-257-00	*
		EMR701165-022	*
PK in special populations	Target population §- Single dose	Assessed in Pop-PK analysis	
	- Multi-dose		
	Hepatic impairment	28696	*
	Renal impairment	EMR701165_025	*
	Neonates/infants/children/adolescents	None	
	Elderly	IPAS-NW/PAR-254-00	*
Genetic/gender-related PK	Males versus females	Assessed in Pop-PK analysis	
PK interactions	Ketoconazole	28778	*
	L-DOPA	28780	*
	L-DOPA	EMR701165_027	*
	CYP1A2 and CYP3A4 substrates (caffeine, midazolam)	EMR701165_026	*
	Ropinirole	27918, Appendix	

PK topic	Subtopic	Study ID	*
Population PK analyses	Healthy subjects	None	
	Target population	Data collected from Efficacy Studies 015 and 016	

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration, but the ropinirole interaction results could not be located.

Evaluator's conclusions on pharmacokinetics

The PK of safinamide have been adequately characterised in the clinical study program, and the summary provided in the proposed PI is consistent with the submitted studies.

Absorption

Safinamide is rapidly absorbed under fasting conditions, and T_{max} is reached approximately 1.8 to 2.8 h after dosing. Absolute bioavailability is high (95%). A slight delay in T_{max} was observed in the fed state relative to the fasted condition, but there was no significant effect on safinamide $AUC_{0-\infty}$ or peak plasma concentration (C_{max}), so safinamide may be administered with or without food.

Distribution

The volume of distribution (V_{ss}) is approximately 165 L which is 2.5 fold of body volume indicating extensive extravascular distribution of safinamide. Plasma protein binding of safinamide is 88 to 90%.

Clearance

Total clearance is approximately 4.6 L/h.

Metabolism

Safinamide is almost exclusively eliminated via metabolism (approximately 5% of the drug is eliminated unchanged, mainly in urine). Three main metabolic pathways are involved, as described above. None of the metabolites has pharmacological activity.

Safinamide is predominantly metabolised by non-microsomal enzymes (cytosolic amidases/MAOA); CYP3A4 and other CYP isozymes only play only a minor role in its overall biotransformation.

The elimination half-life of safinamide is 20 30 h. Steady-state is reached within one week.

Excretion

Safinamide undergoes almost complete metabolic transformation and the primary route of excretion is through the kidney. After oral administration of ^{14}C-safinamide, most of the radioactivity was excreted in urine (76%) and some in faeces (1.5%).

The terminal elimination half-life of total radioactivity was approximately 80 h.

Hepatic impairment

Safinamide exposure is increased slightly in patients with mild hepatic impairment (30% increase in AUC). Safinamide exposure is increased more substantially in patients with moderate hepatic impairment (approximately 80% increase in AUC).

Renal impairment

Safinamide exposure was similar in patients with moderate or severe renal impairment and patients with normal renal function.

Linearity

The pharmacokinetics of safinamide is linear after single and repeated doses, with no significant time dependency.

Interactions

Safinamide does not appear to significantly induce or inhibit microsomal enzymes at clinically relevant concentrations. Drug-drug interaction studies performed with ketoconazole, L-dopa and CYP1A2 and CYP3A4 substrates (caffeine and midazolam), did not detect any clinically significant interactions. There was no effect on the clearance of safinamide in patients with Parkinson's disease receiving safinamide as add on therapy to chronic levodopa (L-Dopa) and/or DA agonists.

Overall, the PK profile of safinamide appears to be straightforward and do not pose any substantial issues.

Pharmacodynamics

Studies providing pharmacodynamic data

The table below lists the submitted pharmacodynamic studies. The sponsor assessed five pharmacodynamic effects of safinamide, including: inhibition of MAO-B, which is intrinsic to its mode of action; the effects of safinamide on motor neuron excitability, assessed with transcranial magnetic stimulation; the potential for a pressor response to dietary tyramine; the effect of safinamide on the QT interval of the ECG; and potential analgesic effects of safinamide. MAO-B inhibitory effects were generally assessed during studies that also had, as a primary focus, an assessment of safinamide PK.

Table 5: Submitted pharmacodynamic studies

Topic	Studies
MAO inhibition	IPASPNU-194-99 IPASNW/SS-215-99 IPASNW/LD-231-00 IPASNW/PAR-254-00
Effect on Neuronal Excitability	IPASNW/006/I/2000
Tyramine interaction	IPAS-NW 1015/TYR-268-00 CRO-PK-03-101 28558 Efficacy Studies 27918 and 27919

Topic	Studies
	(ambulatory BP)
QT Effect	28559
Analgesic Potential	IPAS-SAFINALGESIC-302-01

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

Safinamide has been shown to be a relatively selective inhibitor of MAO-B at the proposed doses, and this is likely to underlie its efficacy in patients with Parkinson's disease. MAO-B inhibition after single doses is > 90%, and long-lasting, allowing once-daily dosing.

The submitted PD studies do not provide any basis for expecting safinamide to have a very narrow therapeutic window. This should be kept in mind when assessing the clinical efficacy studies in ESPD, where doses of 100 mg/day appeared to have better efficacy, relative to 50 mg/d, but a large study assessing 200 mg/day did not establish significant efficacy at the higher dose. It remains unclear whether the inconsistent results across the dose range of 50 mg/day to 200 mg/day reflect a narrow therapeutic window, or borderline efficacy in some patient groups (particularly ESPD). In LSPD, only doses of 50 mg/day and 100 mg/day were assessed.

The limited available evidence suggests that safinamide has only borderline, equivocal effects on neuronal excitability, unlikely to be of substantial relevance to its efficacy in Parkinson's disease. Although there is some preclinical evidence that safinamide is a sodium channel blocker, there is no evidence in the submitted dossier showing that this is relevant to its efficacy in Parkinson's disease, and no evidence that it has any role in preventing excitotoxicity in Parkinson's disease subjects.

Safinamide has a mild QT shortening effect, producing a shortening of < 10 ms in most subjects and most time-points. This is not expected to be of clinical significance, but the drug should be avoided in subjects with congenital short QT syndrome.

Safinamide has only a weak potential for enhancing the pressor response to dietary tyramine. At the proposed dose, this is less than observed for standard doses of selegiline, which is not associated with any dietary warnings.

Safinamide does not have any known analgesic properties, but the only study assessing this was small and inconclusive.

Dosage selection for the pivotal studies

Dose selection for the major efficacy studies was not explicitly justified by the sponsor, and to some extent the proposed dose of 50 to 100 mg/day has been selected post hoc, after completion of major studies in ESPD. Nonetheless, the range of doses assessed in clinical Parkinson's disease studies (0.5 mg/kg to 1.0 mg/kg for weight-based dosing, and 50 to 200 mg/day for fixed dosing) appears broadly appropriate on the basis of PK/Pharmacodynamic studies of MAO-B inhibition, and in terms of tolerability observed in other PK and Pharmacodynamic studies (which assessed doses well beyond the proposed clinical dose, including doses up to 10 mg/kg).

As discussed in the *Pharmacodynamics* section (see above), MAO-B inhibition in platelets was initially assessed after oral doses of 25-150µg/kg in young subjects. A dose of 150

µg/kg (corresponding to a fixed dose of about 10 mg) resulted in 75% MAO-B inhibition. In another study in elderly subjects, maximal inhibition of platelet MAO-B activity reached 86% at the 300 µg/kg dose and 93% at the 600 µg/kg dose. In a single ascending-dose study almost complete inhibition of platelet MAO-B activity (> 90% on average) was observed for up to 48 h at all doses (2.5, 5.0 and 10.0 mg/kg). Studies in patients with Parkinson's disease with doses ranging from 0.25 mg/kg/day and up to a flat dose of 200 mg also confirmed a long lasting MAO-B inhibition in platelets.

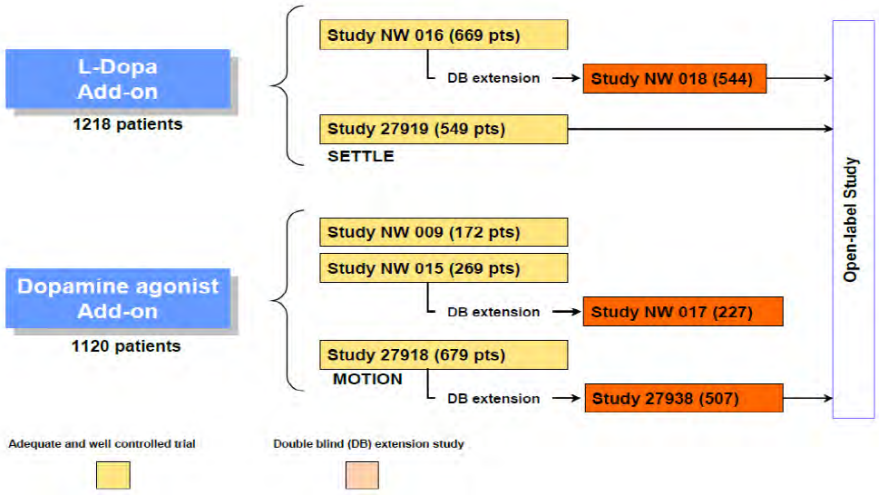
The sponsor therefore assessed doses of 0.5 mg to 1.0 mg/kg in their initial study of ESPD (Study 009). Efficacy appeared to be marginal in the 0.5 mg/kg dose group (mean dose = 34 mg/day) and better in the 1.0 mg/kg/day dose group (mean dose = 76 mg/day). A subsequent study in ESPD assessed fixed doses of 100 mg/day and 200 mg/day (Study 015), but showed no significant efficacy at the primary dose of interest (200 mg/day), so the next major efficacy study assessed doses of 50 mg/day and 100 mg/day (Study 27918). The two major studies of LSPD assessed 50 mg/day and 100 mg/day (Studies 016 and 27919).

Efficacy

Studies providing efficacy data

The main submitted efficacy studies are shown schematically in the figure below.

Figure 3: Schema of efficacy studies



Two of the studies designated as pivotal evaluated safinamide as add-on to levodopa (with or without other anti-parkinsonian medications), in Late Stage PD (LSPD), in patients with motor fluctuations:

- NW-1015/016/III/2006 (Study 016)
- EMR 27919 (SETTLE) (Study 27919)

Three evaluated safinamide as add-on to a single DA agonist in Early Stage PD (ESPD), in patients without motor fluctuations:[15]

- NW-1015/009/II/2001 (Study 009)
- NW-1015/015/III/2003 (Study 015)

[15] These data were submitted as additional, supporting safety data for the proposed indication by the sponsor.

- EMR 27918 (MOTION) (Study 27918)

Evaluator's conclusions on efficacy

The sponsor has submitted two major efficacy studies; both in LSPD, which were consistently positive.

For LSPD, both Phase III studies showed a benefit relative to placebo.

Study 016 was a randomised, placebo-controlled Phase III study that assessed safinamide 50 mg/day and safinamide 100 mg/day in comparison to placebo in the treatment of LSPD, as add-on therapy to levodopa. The study was positive, showing a clinically modest but statistically significant improvement in the primary endpoint, daily 'on' time without troublesome dyskinesia. By Week 24, the increase in 'on' time without troublesome dyskinesia was approximately 55% higher in the safinamide 50 mg/day and safinamide 100 mg/day groups, compared to placebo. As reported in the sponsor's Summary of Clinical Efficacy (SCE), the mean (standard deviation (SD)) increase in the placebo group was 0.97 (2.375) h; in the 50 mg/day group, it was 1.37 (2.745) h; and in the 100 mg/day group, it was 1.36 (2.625 h). The mixed model repeated measures (MMRM) means differences from placebo were 0.51 h for the 50 mg/day dose group, and 0.55 h for the 100 mg/day dose group. That is, about 30-35 minutes of 'on' time was gained with active treatment, about one twentieth of the patients' total 'on' time (approximately 10 h per day).

Secondary endpoints were generally consistent with the primary endpoint, with formal superiority over placebo demonstrated for decrease in 'off' time, UPDRS-III and Clinical Global Impressions Change (CGI-C).

Study 27929 was a randomised, placebo-controlled study that assessed safinamide as add-on therapy to levodopa in subjects with LSPD. It assessed an adjustable dose of safinamide (within the range 50-100 mg/day) in comparison to placebo. The primary endpoint was the change in total daily 'on' time without troublesome dyskinesia. This improved in both treatment groups, but the improvement was significantly greater in the active treatment group ($p < 0.001$ by analysis of co-variance (ANCOVA)). From a baseline value of about 9.5 h (mean 9.3 in safinamide group, 9.06 in the placebo group), the safinamide group had a mean (SD) change in daily on time of 1.42 h (2.80), while the placebo group had a mean (SD) change of 0.57 h (2.47). The LS mean (SE) difference between the groups was 0.96 h (0.21), indicating an attributable increase in daily on time with safinamide of about one hour. A number of secondary analyses and secondary endpoints were consistent with these positive findings.

In conclusion, the results from LSPD studies showed an improvement in 'on' time of about 30 min to one hour, when safinamide was added to stable doses of levodopa.

Safety

Studies providing safety data

No pivotal studies were primarily focussed on safety.

The sponsor's Summary of Clinical Safety (SCS) was based on 37 studies, consisting of 20 Phase I studies, 9 Phase II studies, and 8 Phase III studies. The sponsor reports that, at the time of the submission, no clinical trial was ongoing and that all safinamide data collected to date were included in their analysis of safety.

Pivotal efficacy studies

In the major efficacy studies, the following safety data were collected:

- Demographic and Baseline Characteristics (Baseline)
- Medical History (Baseline)
- Subject Disposition
- Treatment Exposure
- Treatment-emergent adverse events (TEAEs)
- Deaths
- Serious AEs (SAEs)
- AEs leading to treatment dose reduction
- AEs leading to treatment discontinuation
- Laboratory evaluations (chemistry, haematology, and urinalysis)
- Vital signs (including orthostatic blood pressure and pulse)
- Electrocardiogram (ECG) data
- Physical/neurological examinations
- Dermatology examinations
- Ophthalmological examinations: visual acuity, colour vision, funduscopy (with photographs), perimetry, standard eye examination (including slit lamp), ocular coherence tomography (OCT) in selected studies MOTION (Study 27918), MOTION extension (Study 27938), SETTLE (Study 27919), and Study 024 (Cognition); electroretinography (ERG; in a subset of patients in MOTION)
- Epworth Sleepiness Scale (ESS): In Studies 016 and 018, MOTION and SETTLE
- Non-Motor Aspects of Experiences of Daily Living scale (equivalent ESS) in Study 024
- Questionnaire for Impulsive-Compulsive Disorders in PD (QUIP) in the MOTION and SETTLE studies
- Dyskinesia Rating Scale (DRS): Studies 016 and SETTLE, every 3 months and 018 every 6 months.

Patient exposure

Exposure to safinamide in the study program is summarised in the table below, with subgroups based on the clinical context (ESPD or LSPD).

Table 6: Exposure to safinamide, placebo or comparator

Investigational Arm	Safinamide	Placebo [A]	Overall number of subjects [B]
PD patients in placebo-controlled studies and OLE Phase (pooled data)			
Early stage PD	**795**	**422**	**1217**
Mid-Late stage PD on L-DOPA	**721**	**497**	**1218**
PD patients that took safinamide for the first time in the OLE extension study	400 (B)		
TOTAL	**1916**	**919**	**2435**
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	*2013*	*947*	*2539*
Other studies in non PD subjects			
Therapeutic studies	56	2	58
Non therapeutic studies	399	210	572
TOTAL	**455**	**212**	**630**
Overall total	*2468*	*1159*	*3169*

[A] placebo and/or active comparator
[B] 400 patients in the OLE phase (previously on placebo) and 58 enrolled in crossover study are counted only once in the overall safinamide program.

The sponsor also pooled safety data into 3 groups:

- Group 1: patients with Parkinson's disease in completed controlled therapeutic trials, presented separately for ESPD and LSPD.
- Group 2: patients with Parkinson's disease in open-label trials.
- Other: patients in non-Parkinson's disease trials and healthy volunteers (HV).

Exposure in the first two groups (patients with Parkinson's disease in controlled and in open-label studies) is summarised in the table below, by duration of exposure.

Table 7: Key exposure parameters by pooled dataset for group 1 and group 2

	Group 1 ESPD		Group 1 LSPD		Group 2 (N=1025)
	Safinamide (N=795)	Placebo[a] (N=422)	Safinamide (N=721)	Placebo (N=497)	
Mean (SD) treatment duration, years	1.1 (0.69)	1.0 (0.69)	1.1 (0.77)	0.9 (0.73)	2.1 (1.38)
Median treatment duration (yrs)	1.2	0.8	0.6	0.5	1.9
Mean (SD) treatment duration, weeks	55.7 (36.06)	49.8 (35.99)	59.1 (40.24)	48.3 (37.95)	108.0 (72.24)
Median treatment duration, weeks	64.0	39.3	30.4	25.1	98.1
Subjects with exposure, n (%)					
<4 weeks	19 (2.4)	9 (2.1)	24 (3.3)	17 (3.4)	12 (1.2)
≥4 weeks to <12 weeks	60 (7.5)	48 (11.4)	23 (3.2)	19 (3.8)	34 (3.3)
≥12 weeks to <24 weeks	154 (19.4)	89 (21.1)	65 (9.0)	57 (11.5)	70 (6.8)
≥24 weeks to <52 weeks	134 (16.9)	83 (19.7)	273 (37.9)	237 (47.7)	165 (16.1)
≥ 52 weeks to < 2 years	366 (46.0)	170 (40.3)	219 (30.4)	104 (20.9)	262 (25.6)
≥ 2 years to < 3 years	62 (7.8)	23 (5.5)	117 (16.2)	63 (12.7)	260 (25.4)
≥3 years					222 (21.7)

*"All" Placebo category from Group 1 ESPD placebo population

Table 8: Demographics and baseline characteristics for group 1 patients with ESPD

	Safinamide (mg/day)				Placebo		
	50 (N=282)	100 (N=424)	150-200 (N=89)	All (N=795)	Pure (N=343)	Mixed (N=79)	All (N=422)
Age (years)							
N	281	424	89	794	343	79	422
Mean	60.5	60.3	58.5	60.2	61.9	56.8	60.9
S.D.	9.95	10.23	11.68	10.31	9.94	10.46	10.22
Median	62.0	61.0	59.0	61.0	63.0	58.0	62.0
Min, Max	34.0, 80.0	30.0, 80.0	31.0, 82.0	30.0, 82.0	33.0, 79.0	36.0, 76.0	33.0, 79.0
Age Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
< 55	72 (25.5)	115 (27.1)	31 (34.8)	218 (27.4)	81 (23.6)	31 (39.2)	112 (26.5)
55-75	200 (70.9)	280 (66.0)	51 (57.3)	531 (66.8)	241 (70.3)	47 (59.5)	288 (68.2)
>= 75	9 (3.2)	29 (6.8)	7 (7.9)	45 (5.7)	21 (6.1)	1 (1.3)	22 (5.2)
Gender	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Male	179 (63.5)	294 (69.3)	54 (60.7)	527 (66.3)	209 (60.9)	48 (60.8)	257 (60.9)
Female	103 (36.5)	130 (30.7)	35 (39.3)	268 (33.7)	134 (39.1)	31 (39.2)	165 (39.1)
Race	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Caucasian	235 (83.3)	328 (77.4)	52 (58.4)	615 (77.4)	279 (81.3)	47 (59.5)	326 (77.3)
Non-Caucasian	47 (16.7)	96 (22.6)	37 (41.6)	180 (22.6)	64 (18.7)	32 (40.5)	96 (22.7)
Ethnicity	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hispanic/Latin American	70 (24.8)	125 (29.5)	33 (37.1)	228 (28.7)	98 (28.6)	33 (41.8)	131 (31.0)
[Non-]Hispanic/Latin American	212 (75.2)	299 (70.5)	56 (62.9)	567 (71.3)	245 (71.4)	46 (58.2)	291 (69.0)
Weight (kg)							
N	281	423	89	793	342	79	421
Mean	74.5	75.5	68.0	74.3	76.2	69.5	74.9
S.D.	15.02	15.15	12.46	14.98	15.34	14.37	15.37
Median	74.3	75.3	67.0	74.1	75.0	69.0	73.6
Min, Max	38.8, 120.2	34.0, 133.5	42.0, 100.3	34.0, 133.5	36.0, 131.0	35.0, 120.0	35.0, 131.0
Weight Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
< Median of Early Stage PD Subjects	138 (48.9)	189 (44.6)	60 (67.4)	387 (48.7)	158 (46.1)	54 (68.4)	212 (50.2)
>= Median of Early Stage PD Subjects	144 (51.1)	235 (55.4)	29 (32.6)	408 (51.3)	185 (53.9)	25 (31.6)	210 (49.8)
BMI (kg/m^2)							
N	281	422	89	792	342	79	421
Mean	26.4	26.7	25.2	26.4	27.2	25.5	26.9
S.D.	4.32	4.28	4.34	4.32	4.54	4.26	4.53
Median	26.2	26.4	24.7	26.0	27.0	25.4	26.5
Min, Max	16.3, 42.6	15.7, 44.1	16.8, 40.8	15.7, 44.1	16.0, 42.6	16.2, 38.1	16.0, 42.6
BMI Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
< Median of Early Stage PD Subjects	143 (50.7)	206 (48.6)	60 (67.4)	409 (51.4)	150 (43.7)	51 (64.6)	201 (47.6)
>= Median of Early Stage PD Subjects	139 (49.3)	218 (51.4)	29 (32.6)	386 (48.6)	193 (56.3)	28 (35.4)	221 (52.4)
Geographic Region	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
NA	31 (11.0)	48 (11.3)	0 (0.0)	79 (9.9)	46 (13.4)	0 (0.0)	46 (10.9)
Non-NA	251 (89.0)	376 (88.7)	89 (100.0)	716 (90.1)	297 (86.6)	79 (100.0)	376 (89.1)
Dopamine Agonist	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
WHODRUG ATC Code N04BC	255 (90.4)	350 (82.5)	87 (97.8)	692 (87.0)	265 (77.3)	79 (100.0)	344 (81.5)
no ATC Code N04BC	27 (9.6)	74 (17.5)	2 (2.2)	103 (13.0)	78 (22.7)	0 (0.0)	78 (18.5)
Dopa and dopa derivatives	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
WHODRUG ATC Code N04BA	26 (9.2)	42 (9.9)	12 (13.5)	80 (10.1)	33 (9.6)	20 (25.3)	53 (12.6)
no ATC Code N04BA	256 (90.8)	382 (90.1)	77 (86.5)	715 (89.9)	310 (90.4)	59 (74.7)	369 (87.4)
Other dopaminergic agonists	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
WHODRUG ATC Code N04BX	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
no ATC Code N04BX	282 (100.0)	424 (100.0)	89 (100.0)	795 (100.0)	343 (100.0)	79 (100.0)	422 (100.0)
Disease Duration (years)							
N	282	424	89	795	343	79	422
Mean	2.1	2.7	2.3	2.5	2.5	2.3	2.5
S.D.	1.45	2.53	1.32	2.11	2.60	1.27	2.41
Median	1.8	2.2	2.2	2.1	1.7	2.1	1.9
Min, Max	0.0, 5.1	0.0, 14.5	0.1, 5.5	0.0, 14.5	0.1, 20.8	0.1, 5.4	0.1, 20.8
Disease Duration Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
< Mean of Early Stage PD Subjects	156 (55.3)	199 (46.9)	36 (40.4)	391 (49.2)	185 (53.9)	36 (45.6)	221 (52.4)
>= Mean of Early Stage PD Subjects	126 (44.7)	225 (53.1)	53 (59.6)	404 (50.8)	158 (46.1)	43 (54.4)	201 (47.6)

Table 9: Demographics and baseline characteristics for group 1 patients with LSPD

	Safinamide (mg/day)			Placebo[1]
	50 (N=243)	100 (N=478)	All (N=721)	Randomized (N=497)
Age (years)				
N	243	478	721	497
Mean	60.5	60.8	60.7	60.9
S.D.	9.60	9.12	9.28	9.25
Median	61.0	61.0	61.0	61.0
Min, Max	35.0, 78.0	35.0, 80.0	35.0, 80.0	30.0, 79.0
Age Category	n (%)	n (%)	n (%)	n (%)
< 55	62 (25.5)	115 (24.1)	177 (24.5)	116 (23.3)
55-75	172 (70.8)	345 (72.2)	517 (71.7)	361 (72.6)
>= 75	9 (3.7)	18 (3.8)	27 (3.7)	20 (4.0)
Gender	n (%)	n (%)	n (%)	n (%)
Male	170 (70.0)	321 (67.2)	491 (68.1)	323 (65.0)
Female	73 (30.0)	157 (32.8)	230 (31.9)	174 (35.0)
Race	n (%)	n (%)	n (%)	n (%)
Caucasian	50 (20.6)	221 (46.2)	271 (37.6)	230 (46.3)
Non-Caucasian	193 (79.4)	257 (53.8)	450 (62.4)	267 (53.7)
Ethnicity	n (%)	n (%)	n (%)	n (%)
Hispanic/Latin American	2 (0.8)	10 (2.1)	12 (1.7)	9 (1.8)
[Non-]Hispanic/Latin American	241 (99.2)	468 (97.9)	709 (98.3)	488 (98.2)
Weight (kg)				
N	243	476	719	496
Mean	63.1	68.5	66.7	67.9
S.D.	12.48	16.03	15.14	15.13
Median	61.0	67.0	65.0	66.0
Min, Max	38.5, 97.6	34.0, 125.0	34.0, 125.0	34.0, 124.5
Weight Category	n (%)	n (%)	n (%)	n (%)
< Median of Late Stage PD Subjects	142 (58.4)	215 (45.0)	357 (49.5)	231 (46.5)
>= Median of Late Stage PD Subjects	101 (41.6)	263 (55.0)	364 (50.5)	265 (53.5)
BMI (kg/m^2)				
N	243	475	718	496
Mean	23.9	24.8	24.5	24.8
S.D.	4.14	4.62	4.49	4.22
Median	23.6	24.5	24.1	24.4
Min, Max	15.0, 38.7	14.5, 43.0	14.5, 43.0	15.1, 43.1
BMI Category	n (%)	n (%)	n (%)	n (%)
< Median of Late Stage PD Subjects	141 (58.0)	233 (48.7)	374 (51.9)	237 (47.7)
>= Median of Late Stage PD Subjects	102 (42.0)	245 (51.3)	347 (48.1)	260 (52.3)
Geographic Region	n (%)	n (%)	n (%)	n (%)
NA	3 (1.2)	48 (10.0)	51 (7.1)	51 (10.3)
Non-NA	240 (98.8)	430 (90.0)	670 (92.9)	446 (89.7)
Dopamine Agonist	n (%)	n (%)	n (%)	n (%)
WHODRUG ATC Code N04BC	158 (65.0)	331 (69.2)	489 (67.8)	345 (69.6)
no ATC Code N04BC	85 (35.0)	147 (30.8)	232 (32.2)	151 (30.4)
Dopa and dopa derivatives	n (%)	n (%)	n (%)	n (%)
WHODRUG ATC Code N04BA	243 (100.0)	476 (99.6)	719 (99.7)	496 (99.8)
no ATC Code N04BA	0 (0.0)	2 (0.4)	2 (0.3)	1 (0.2)
Other dopaminergic agonists	n (%)	n (%)	n (%)	n (%)
WHODRUG ATC Code N04BX	66 (27.2)	125 (26.2)	191 (26.5)	109 (21.9)
no ATC Code N04BX	177 (72.8)	353 (73.8)	530 (73.5)	388 (78.1)
Disease Duration (years)				
N	243	478	721	497
Mean	8.0	8.6	8.4	8.7
S.D.	4.00	4.07	4.05	4.39
Median	6.6	7.5	7.1	7.3
Min, Max	-0.2, 25.3	0.9, 28.4	-0.2, 28.4	0.2, 30.6
Disease Duration Category	n (%)	n (%)	n (%)	n (%)
< Mean of Late Stage PD Subjects	147 (60.5)	221 (46.2)	368 (51.0)	241 (48.5)
>= Mean of Late Stage PD Subjects	96 (39.5)	257 (53.8)	353 (49.0)	256 (51.5)

Abbreviations: ATC = Anatomical Therapeutic Chemical; BMI = body mass index; Max = maximum; Min = minimum; NA = North America; PD = Parkinson's disease; SD = standard deviation.

a. Placebo randomized includes 8 subjects randomized to the placebo group who received at least 1 dose of safinamide at any visit, either due to packaging or treatment administration errors. The number of safinamide doses were few in each case and AEs reported during safinamide dosing were reviewed to support the decision to report these as placebo subjects.

Safety issues with the potential for major regulatory impact

Liver toxicity

In the placebo-controlled studies, AEs related to liver toxicity were reported only rarely, with a similar incidence in the safinamide and placebo groups (ESPD: safinamide 0.1%, placebo 0.5%; LSPD: safinamide 0.3%, placebo 0.2%). Only one patient, who was a placebo recipient, met the criteria for Hy's Law.

For the Group 1 subjects with ESPD, treatment-emergent hepatic AEs were as follows: in the safinamide 100 mg/day group, one subject had hepatic steatosis and in the pure placebo group, hepatic steatosis and 'liver disorder' were reported for 1 subject each. No hepatic AEs were reported for any subjects in the safinamide 50 mg/d, safinamide 150 to 200 mg/day, or mixed placebo groups.

For Group 1 subjects with LSPD, treatment-emergent hepatic AEs were as follows: in the safinamide 50 mg/day group, one subject had hepatic steatosis; in the safinamide 100 mg/day group, 'liver disorder' was reported for one subject; and in the placebo group, 'liver disorder' was reported for one subject.

In the open label study, two patients (0.2%) hepatic AEs (one with ascites and one with hepatic encephalopathy) but it is difficult to draw any conclusions from this in the absence of a control group.

Overall, there does not appear to be any evidence of a significant risk of hepatotoxicity with safinamide.

Haematological toxicity

There is no evidence of significant haematological toxicity with safinamide.

Serious skin reactions

There is no evidence of significant dermatological toxicity with safinamide. Shifts in dermatological findings on physical examination were not more common in safinamide recipients, and there was no consistent pattern in the incidence of TEAEs in the dermatological category.

Cardiovascular safety

The submitted safety data did not suggest that safinamide produces substantial cardiological problems. Cardiac AEs and AEs related to the ECG were not particularly more common with safinamide. Safinamide has been shown to produce mild shortening of the QT interval of the ECG, but this is not known to be of clinical significance. Subjects with congenital short QT syndrome should avoid the drug.

Postmarketing data

The proposed PI mentions a single post-marketing adverse event:

'A post-marketing report describes a patient who developed a hypersensitivity reaction consisting of swelling of the tongue and gingiva, dyspnoea and skin rash. The symptoms resolved shortly after Xadago was discontinued, but reappeared following rechallenge a month later.'

Evaluator's conclusions on safety

The safety of safinamide was broadly acceptable, as indicated in an integrated analysis of 37 studies and over 2000 patients in therapeutic trials (> 500 were treated for 2 years, and > 150 for 4 years or more).

Safinamide at doses up to 200 mg/day has a range of side effects that are expected in any agent that increases dopaminergic effects in the brain, and which are common among all effective PD treatments.

The overall incidence of patients experiencing TEAEs in the combined safinamide (76.1%) and placebo (75.8%) groups was similar, with no difference in the proportion of patients experiencing severe TEAEs. The incidence of SAEs was also similar between safinamide and placebo in both ESPD (6.9% versus 5.0%) and LSPD (12.9% versus 11.5%) datasets. Mortality rates for safinamide and placebo were similar with safinamide and placebo (safinamide 1.5 versus placebo 2.5 deaths/100 person-years).

In patients with LSPD, dyskinesia, Parkinson's disease (worsening), and falls were the 3 most frequently-reported TEAEs in safinamide treated subjects that also had at ≥ 2% higher incidence than placebo. The difference was most marked for dyskinesia: in LS patients with Parkinson's disease, dyskinesia was reported 24.3% of safinamide recipients, compared to 12.9% of the placebo group, but it was rated as severe in only 1.9% of safinamide and 1.8% of placebo patients. A total of 8 patients on safinamide (1.1%) and one patient on placebo (0.2%) discontinued treatment due to dyskinesia.

More serious idiosyncratic reactions appeared to be rare. The incidence of adverse events of hepatotoxicity, cardiovascular events, and hypertensive crisis was low and similar in the safinamide and placebo groups. Only one subject experienced a suspected serotonin syndrome.

A monitoring program was conducted in over 2000 patients in placebo controlled trials, evaluating the ocular safety of safinamide, including visual acuity, colour vision, visual field, fundus examination, optical coherence tomography (in a selected subset). This program did not detect any significant differences in the incidence of ocular abnormalities between safinamide and placebo recipients.

In summary, apart from the expected tolerability issues common to most Parkinson's disease therapies, safinamide is not associated with any major safety concerns.

First round benefit-risk assessment

First round assessment of benefits

The benefits of safinamide in the treatment of mid-to-late Parkinson's disease have been confirmed in two Phase III studies, assessing fixed doses of 50 mg/day or 100 mg/day, or flexible dosing in the range 50 to 100 mg/day. In both studies, an improvement in 'on' time without troublesome dyskinesia was observed, amounting to about 30 to 60 minutes. Many secondary endpoints also showed an improvement on active treatment, including a small improvement in UPDRS-III. Responses to 100 mg/day were generally superior to 50 mg/day.

First round assessment of risks

The risks of safinamide in the proposed usage are:

- An increased risk of dyskinesia in subjects on safinamide,
- The risk that rare idiosyncratic safety issues might arise with more widespread exposure,
- The risk that subjects prescribed safinamide will be unable to use MAO-B inhibitors with a proven safety and efficacy record while they are taking safinamide.

First round assessment of benefit-risk balance

The proposed indication is

> *For the treatment of idiopathic Parkinson's disease (PD) as add-on therapy to levodopa (L-DOPA) alone or in combination with other PD medicinal products.*

The benefit-risk balance of safinamide given the proposed usage is unfavourable because the proposed indication does not distinguish between a clinical context in which efficacy is proven (add-on therapy to levodopa in LSPD) and a clinical context in which efficacy remains uncertain (add-on therapy to a single dopamine agonist in ESPD).

The benefit-risk balance of safinamide would become favourable if the sponsor proposed an indication in line with that already approved in the EU:

> *For the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-DOPA) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients.*

First round recommendation regarding authorisation

The current proposal to register safinamide should be rejected.

The sponsor should propose an alternative wording for the indication.

Second round evaluation of clinical data submitted in response to questions

Clinical questions

Question 1

The study program assessed safinamide in two clinical contexts:

- adjunctive therapy to a dopamine agonist in early Parkinson's disease; and
- adjunctive therapy to levodopa in mid-to-late Parkinson's disease in subjects with motor fluctuations.

The proposed indication does not directly correspond to either of these clinical settings. It makes no mention of the stage of disease or the presence of motor fluctuations, implying that safinamide is indicated in both early and mid-to-late PD but it does not propose using safinamide as add-on therapy to a dopamine agonist, which is the only way the drug was assessed in early patients with Parkinson's disease in the clinical study program.

Please clarify whether the drug is proposed for use in both of the clinical settings assessed in the study program, or just the mid-to-late Parkinson's disease subjects. If registration is sought for both clinical settings, please reword the indication to include adjunctive therapy to a dopamine agonist and provide justification for use in this clinical context, because the efficacy data in this clinical setting were disappointing. Conversely, if registration is sought for subjects with mid-to-late disease and motor fluctuations, please reword the indication to make this explicit. Finally if it is proposed that the drug be used as add-on therapy to levodopa in subjects with early Parkinson's disease and no motor fluctuations, please justify this proposed usage, given that no studies assessed this clinical setting.

Sponsor response

The sponsor begins their response to this question by stating (emphasis added):

The clinical development program for Xadago as an idiopathic Parkinson's disease (PD) treatment investigated the safety and efficacy of safinamide as add-on therapy to:

- *Dopamine (DA) agonist monotherapy (Studies 009, 015 and 27918) and;*
- *Levodopa (L-DOPA) alone or in combination with other PD medications (Studies NW-016, NW-018 and 27919 (SETTLE))*

As add-on to DA agonist monotherapy, safinamide was found to be safe and well tolerated. However as noted by the clinical evaluator, efficacy results were inconclusive. *Therefore, in the Australian application, registration is only sought for safinamide as add-on therapy to L-DOPA alone, or in combination with other PD medicinal products.* ***Data generated in DA agonist monotherapy studies 009, 015 and 27918 were included in the data package as additional, supporting data*** *for the proposed use of safinamide as L-DOPA add-on-therapy.* ***While this was noted in the Cover Letter*** *of the initial application, Seqirus apologises if this was unclear and the inclusion of these data has caused confusion during the evaluation or uncertainty in relation to the scope of the application.*

The proposed Australian indication for safinamide is: 'For the treatment of idiopathic Parkinson's disease (PD) as add-on therapy to levodopa (L-DOPA) alone or in combination with other PD medicinal products.'

The remainder of the sponsor's response focuses on objections to the expression 'adult patients' because they suspect efficacy in children is similar to that demonstrated in adults, to the mention of 'stable doses', because they claim that this was only important within a trial setting, to the phrase 'mid-to-late stage' on the basis that it is not a rigid, unambiguous identifier, and also on the term 'fluctuating', given that there may be difficulty determining whether fluctuations are present. Each of these objections is considered below.

Evaluator comment on indication

While it may be the case that the sponsor's cover letter clarified their intended target population, this Clinical question expressed concerns that the *proposed indication in the PI* failed to indicate a clear target population that was justified on the basis of the submitted evidence.

Note that the wording for the proposed indication is ambiguous. With no more than punctuation and spacing changes, it can be parsed in three different ways:

1. *'For the treatment of idiopathic Parkinson's disease (PD):*
   - *as add-on therapy to levodopa (L-DOPA);*
   - *alone; or*
   - *in combination with other PD medicinal products.'*
2. *'For the treatment of idiopathic Parkinson's disease (PD):*
   - as add-on therapy to levodopa (L-DOPA) alone; or
   - *in combination with* other PD medicinal *products.'*
3. *'For the treatment of idiopathic Parkinson's disease (PD) as add-on therapy to levodopa (L-DOPA):*
   - *alone; or*
   - *in combination with other PD medicinal products.'*

The first parsing implies that safinamide can be used in three different ways: 1) as an add-on to levodopa; 2) as monotherapy, or 3) as an add-on to other Parkinson's disease drugs,

such as dopamine agonists. The second parsing implies that safinamide can only be used as add-on therapy, but the regimen to which it is added can be 1) levodopa alone or 2) any other combination of Parkinson's disease drugs, including those without levodopa. The sponsor claims that the third parsing is intended, with safinamide to be used as add-on therapy to any regimen involving levodopa (with additional verbiage that potentially adds confusion, by pointing out that the levodopa containing regimen may also contain other agents, though the presence or absence of those other agents has no effect). There are many other ways of describing the intended indication that would not be so susceptible to changes in interpretation; for instance: *'For the treatment of idiopathic Parkinson's disease (PD) as add-on therapy to regimens that include levodopa (L-DOPA).'*

Apart from the ambiguity of the proposed indication, the other major problem is that *it is far more inclusive than the evidence justifies.* Clear evidence of benefit was only obtained in subjects with motor fluctuations, and largely consisted in improvements in 'on' time. Studies in non-fluctuating patients assessed safinamide as add-on therapy to dopamine agonists, and these studies produced no convincing evidence of efficacy. The sponsor's study program was not designed to tease out whether it was the presence of fluctuations that was important in producing a response to safinamide, or whether it was co-treatment with levodopa that was important, because these variables were not assessed independently: the studies that recruited fluctuating patients also required that the subjects were on levodopa. Patients not on levodopa and without fluctuations did not have a convincing efficacy response, as conceded by the sponsor, but the study program did not assess other combinations, such as patients not on levodopa with fluctuations, and patients on levodopa but without fluctuations. This means that the only population for whom there is good evidence of efficacy consists of patients who both: 1) had motor fluctuations; and 2) were on levodopa. The indication needs to reflect this (and this has also been the opinion of every regulatory authority that has assessed this issue, as discussed in Question 2).

Table 10: Summary of the evidence for efficacy of safinamide

	Dopamine agonist add-on	Levodopa add-on
No fluctuations	Negative/weak studies	No studies
Fluctuations	No studies	Positive studies

The clinical evaluator originally proposed that Australia adopt an indication similar to that approved in Europe: *'For the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-DOPA) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients.'*

Although this indication includes reference to fluctuations, which is appropriate, it is nonetheless capable of being parsed in different ways, including:

> *For the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-DOPA):*
>
> - *alone;*
> - *or in combination with other PD medicinal products*
>
> *in mid-to late-stage fluctuating patients.'*
>
> *For the treatment of adult patients with idiopathic Parkinson's disease (PD):*
>
> - *as add-on therapy to a stable dose of Levodopa (L-DOPA) alone; or*

- *in combination with other PD medicinal products in mid-to late-stage fluctuating patients.'*

For the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy:

- *to a stable dose of Levodopa (L-DOPA) alone; or*
- *in combination with other PD medicinal products,*

in mid-to late-stage fluctuating patients.'

A more appropriate indication would be as follows:

> *'For the treatment of adult patients with mid-to late-stage, fluctuating idiopathic Parkinson's disease (PD) as add-on therapy to a regimen that includes a stable dose of levodopa (L-DOPA, alone, or in combination with other PD medications).'*

The following would also be acceptable:

> *'For the treatment of adult patients with mid-to late-stage, fluctuating idiopathic Parkinson's disease (PD) as add-on therapy to a regimen that includes a stable dose of levodopa (L-DOPA).'*

Evaluator comment regarding adult patients:

The clinical evaluator acknowledges that Parkinson's disease is rare in children and it is unlikely that large, adequately powered studies showing efficacy of all the various potential PD treatments will ever be conducted in a paediatric setting. This means that, for a clinician anticipating treatment of PD in children, it is generally not possible to prescribe on the basis of an adequate evidence base, and this is likely to be an ongoing problem. In choosing a treatment, such a clinician will inevitably draw on the published experience in adults, and on the studies that lead to registration in adults, to inform their choice of agent in children. The paediatric physician in that setting is, to some extent, forced to go out on a limb, making decisions with inadequate evidence. It would be perfectly reasonable for a physician in that position to conclude that on balance the likely benefits of safinamide in children are likely to outweigh the risks. The issue is whether it is more appropriate for the physician in that setting to be forced to prescribe off-label (which highlights the poor evidence base to the prescriber and to the patient's family, alerting both to the need for vigilance in assessing safety and efficacy), or for the approved indication to be extended beyond the populations actually studied (which means that the regulatory authority then assumes the bulk of the responsibility for the prescriber going out on an evidentiary limb, and possibly communicates to the clinician the false notion that the submitted evidence supports use in children, when in fact this is merely an untested assumption).

The clinical evaluator believes that making an individual decision to prescribe off-label to a child with Parkinson's disease may be appropriate, but if the indication were officially extended to include children, this would imply an official, regulatory conclusion that the evidence in this patient group was adequate, when this is clearly not the case.

The sponsor points out that the indication for Azilect (rasagiline mesilate) does not mention an age group, and proposes that the indication for safinamide should similarly ignore age, for consistency. The clinical evaluator is of the opinion that the PI for Azilect should only endorse treatment in patient groups for whom there is adequate evidence, and that it is not appropriate to broaden the indications for one agent beyond what the evidence supports merely because this might have been done for a different agent.

The sponsor also notes that *'information on the status of clinical development in the paediatric population is clearly reflected in Section 4.4 Special Warning and Precautions for Use of the proposed PI under the Paediatric use section, which states: The safety and efficacy of safinamide in children and adolescents* under 18 years of age has not been established.'

Although this warning is appropriate, the indication itself is the main part of the PI that clinicians consult to identify the target population for a drug, and the warning in Section 4.4 [in the PI] would carry much more weight if the indication also reflected the lack of evidence supporting use in children.

Evaluator comment regarding Stable Doses

The sponsor writes (emphasis added):

> *'In the clinical investigation of any new PD medicinal product, it is therefore important to minimise/restrict changes to any existing concomitant PD medications to ensure that any observed clinical benefit can be attributed to the intervention being tested. This is consistent with the recommendation of the TGA-adopted EU Guideline on Clinical Investigation of Medicinal Products in the Treatment of Parkinson's disease, which says that 'In all conditions concomitant L-DOPA+ and other relevant medication should be kept constant during the trial'. A logical extension is that medication should be stable in the period immediately before study start, again to ensure that any changes observed during the trial can confidently be attributed to the test treatment. Consistent with this clinical design principle, in both NW-016 and SETTLE, patients were required to be on a stable dose of L-DOPA for at least 4 weeks to be eligible for trial enrolment. Similarly, in the Azilect pivotal trials for rasagiline as an adjunct to L-DOPA (PRESTO1 and LARGO2), patients were required to be on a stable dose of L-DOPA for at least 14 days prior to study start.*
>
> ***Although it is appropriate within a clinical trial environment to require patients to be on a stable dose of L-DOPA prior to investigation of the safety and efficacy of safinamide or rasagiline, it is not appropriate or necessary for trial inclusion criteria to be specified within the registered therapeutic indication of a product.*** *Consistent with this, the Australian indication for rasagiline does not specify that stable concomitant levodopa/decarboxylase inhibitor therapy is required for initiation of adjunctive rasagiline treatment.'*

The sponsor is correct in noting that not all study criteria need to be reproduced in clinical use and that some entry criteria used in a study are primarily adopted to make interpretation of the results more straightforward. *On this particular issue, though, there is a good clinical reason to ensure levodopa doses are stable: creating a situation in which it is possible to determine, on an individual patient basis, whether subsequent changes in motor signs and symptoms, or potential dopaminergic and other side effects, are attributable to the introduction of safinamide or to changes in levodopa dose.*

The response to levodopa has both short-term and long-term effects and it may take a month for the full effects of a levodopa dose change to be apparent in an individual patient. A clinician that introduced safinamide soon after a dose change in levodopa could mistakenly infer that an observed benefit or harm was attributable to one drug when in fact it was the other drug that had produced the dominant effect. Most neurologists already know this, and would usually avoid changing two major aspects of a Parkinson's disease drug regimen at the same time but the drug is not proposed for prescription only by neurologists or by other prescribers with expertise in Parkinson's disease; it could be prescribed by general practitioners unfamiliar with the desirability of a stable baseline levodopa dose. It is appropriate for the PI to reflect the desirability of stable baseline levodopa dosing. (In individual situations where a stable dose was not possible, then clinicians would be free to make their own choice about the appropriateness of introducing safinamide, but such situations are likely to be rare, and the sponsor has advanced no argument that this is a problem in practice.)

Evaluator comment regarding mid-to-late stage disease

The sponsor writes: *'Due to the complexity in PD pathophysiology and marked variability and heterogeneity in signs, symptoms and disease progression, the phrase 'mid to late stage', from a clinical perspective, is subjective and arbitrary. [...] Inclusion of the non-specific phrase 'mid-to late-stage' in the indication may, therefore, lead to inconsistent and/or inappropriate prescribing practices.'*

The clinical evaluator acknowledges that some degree of subjectivity is involved in classifying subjects as having early-stage, mid-stage or late-stage Parkinson's disease. It should be noted, though, that there is also subjectivity in making the diagnosis of Parkinson's disease in the first place, given that there is no definitive diagnostic test, and also in deciding that first-line agents are not working adequately. The distinction between early-stage disease and mid-stage disease is arbitrary, but just because a category has an unclear or arbitrary border does not mean that the entire category lacks utility. Also, the sponsor's study program was itself divided into ESPD and LSPD studies, and the terms 'early' and 'mid-to-late' were used throughout the provided summaries. As shown in the sponsor's response to Question 2, below, the indications originally sought in the EU, Switzerland and USA used the terms 'early' and 'mid-to-late'. The sponsor's dissatisfaction with these descriptors therefore appears to have arisen only after regulatory authorities rejected the sponsor's initial attempt to have broader indications approved.

The flexibility in the term used in the EU indication, 'mid-to-late stage disease', allows clinicians to apply some degree of common sense in deciding whom to treat. Extending the indications to include subjects with early disease would circumvent the need to make an arbitrary decision, but only by arbitrarily deciding that the treatment of early-phase subjects was appropriate. Despite the imprecision of the terms, any clinician capable of prescribing safinamide appropriately should be able to make a reasonable judgement about whether or not the patient could be considered to have mid-to-late disease. The definition could be made more precise, by specifying disease severity according to one of the scales developed for this purpose, but this would make the PI difficult to interpret for clinicians unfamiliar with the scale employed. The main point is that subjects with minimal Parkinsonism who have only recently been diagnosed and who have no motor fluctuations are not known to be responsive to safinamide, and use of safinamide in such patients should not be approved. The EU indication conveys this important message quite well. If such early-stage patients were on a low dose of levodopa, but had no other features in common with the study cohorts of the pivotal positive studies, then the sponsor's proposed wording would make them eligible for treatment, when this is not appropriate.

On balance, though, this issue is less important than the next one, which relates to the presence of motor fluctuations; to a large extent, if the target group were restricted to patients with motor fluctuations, then early-stage patients would be excluded anyway, and in that case the clinical evaluator agrees that the additional term 'mid-to-late stage' would not strictly be necessary.

Evaluator comment regarding motor fluctuations

As noted in the sponsor's response to Question 2 considered below, all major regulatory authorities have restricted approval of safinamide to patients with motor fluctuations. Despite this, the sponsor has proposed that, in Australia, safinamide should also be approved in non-fluctuating patients as long as their current regimen includes any levodopa (even at a low dose, in recently diagnosed subjects, and even if the dose has not had time to be properly assessed). There is no evidence that it is the concurrent use of levodopa that was important in producing the safinamide response in the pivotal LSPD studies, and it appears likely that the defining characteristic of the population targeted in the positive pivotal studies was that the patients had fluctuations; *indeed, the primary endpoint, 'on' time, is only meaningful in fluctuating patients.*

The sponsor writes (emphasis added):

> *'The important point here is that if a patient's symptoms are being adequately managed by his or her current treatment program, there is little reason to add an additional medicine. Seqirus is seeking an indication to use Xadago as add on therapy to L-DOPA alone or in combination with other PD medications.* ***The main reason that a clinician would initiate therapy with Xadago is because patients are fluctuating on their current treatment program, otherwise there would be no reason to add safinamide.*** *Thus, including the word 'fluctuating' in the indication would be considered unnecessary and not add any beneficial information.'*

This logic is rather odd. First, the sponsor explicitly concedes that safinamide is only likely to produce benefit in fluctuating patients, implying that: 1) they believe 'fluctuating patients' is a meaningful clinical group that can be identified; and 2) the drug is not indicated outside this group; they then appear to assert that these conclusions are so obvious that a clinician would not even consider the drug in a non-fluctuating patient, so it is not necessary to mention it in the indication.

It is simply not true that fluctuations are the only conceivable indication for adjunctive therapy in Parkinson's disease; half the sponsor's study program was performed in non-fluctuating patients, in whom it was obviously hoped an overall improvement in motor scores might be achieved, and the sponsor tried, unsuccessfully, to have the drug registered for non-fluctuating patients in the EU, Switzerland and USA. Clinicians could prescribe safinamide with the same hope that led the sponsor to initiate the negative ESPD studies. Also, even if it is obvious to the sponsor that '*there would be no reason to add safinamide*' in the absence of fluctuations, it is far from clear how a clinician would know this if the word 'fluctuating' had been left out of the indication, unless the clinicians took the time to evaluate all of the relevant studies. Finally, for clinicians who already agree with the sponsor that there would be no reason to add safinamide in the absence of motor fluctuations, there is no conceivable problem that could arise from having this point made explicit in the PI; it would only confirm that the clinician's intended use was appropriate.

Far from proving that the word 'fluctuating' should be left out of the indication, this part of the sponsor's response makes it even clearer that the indication should contain the word.

Conclusion

The sponsor has conceded that half of their study program, conducted in ES patients with Parkinson's disease, produced only weak supportive evidence, but they have nonetheless argued that their proposed wording, which is ambiguous and overly inclusive, should be maintained. Most of their arguments appear to be directed at keeping the most inclusive indication possible, and only mentioning levodopa usage as a necessary precursor to safinamide treatment, rather than any of the other features that defined the LSPD study subjects. Even if the ambiguities were corrected, their proposed indication would imply that early-stage, non-fluctuating patients would benefit from safinamide. From the submitted evidence and by their own admission, it seems likely that the presence of motor fluctuations is the main factor that determines whether patients are likely to respond to safinamide. Common sense also dictates that, where possible, safinamide should be introduced on a background of stable levodopa dosing. Prudence suggests that regulatory authorities are not currently in a position to endorse usage in children.

In combination, these issues suggest that the following wording would be appropriate:

> *'For the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a regimen that includes a stable dose of levodopa (L-DOPA, alone, or in combination with other PD medications) in mid-to late-stage fluctuating patients.'*

Question 2

The summary of the overseas regulatory status for safinamide implies that the indications accepted in the EU, USA and Switzerland are narrower than those sought in Australia, because the proposed Australian indication makes no mention of disease stage or fluctuations.

Please clarify whether submissions in the EU, USA and Switzerland initially requested broader indications than those in the table, and whether these were rejected or modified by regulatory authorities. If broader indications were rejected by any regulatory authority, please provide the details, including the reasons for rejection. Conversely, if the overseas submissions only applied for the narrow indications listed in the table (mid-to-late disease, or Parkinson's disease *with fluctuations), please explain why broader indications are sought in Australia.*

Sponsor response

The sponsor writes (parentheses added for disambiguation):

> *Xadago regulatory submissions to the European Union (EU), Switzerland and USA initially sought registration of safinamide as add-on therapy to dopamine (DA) agonist monotherapy and levodopa (L-DOPA, alone or in combination with other PD medications). For each country/region, the wording of the initial proposed and final approved indication is presented in Table 2 [Table 11]. Due to limitations of the clinical data currently available to support safinamide as add-on therapy to DA monotherapy, which have similarly been noted by the TGA Clinical Evaluator, this indication was not approved in the EU, Switzerland or USA. For this reason, in the Australian submission TGA approval is only sought for safinamide as an add-on to L-DOPA (alone or in combination with other PD medications).*

Table 11: Requested and approved indications in EU, USA and Switzerland

Country/ Region	Indication Requested:	Indication Approved:
European Union	For the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to: A single Dopamine Agonist (DA-agonist) at a stable dose in early stage non-fluctuating patients, and A stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products in mid- to late-stage fluctuating patients.	For the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients.
United States of America		As adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes
Switzerland		For the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients.

Evaluator comments

Most aspects of the approved EU indication have been discussed above, in the context of the previous clinical question. The indication approved in Switzerland is identical to the EU indication. These indications are broadly appropriate, though they are capable of being misinterpreted, as discussed above.

The USA indication is simpler, and focuses on the presence of fluctuations as the defining characteristic of patients likely to respond to safinamide. Although there is no explicit mention in the USA of mid-to-late stage disease, the USA indication is potentially the most restrictive of all.

Many neurologists would consider motor fluctuations to be present in patients who describe end-of-dose slowing; such patients may fluctuate from a fully 'on' state to a partially 'on' state that is clearly better than the untreated state, but not as quick and agile as their best motor state. The USA indication could be read in such a way that such patients, fluctuating between 'fully on' and 'partially on', were not eligible because they were never completely 'off'.

The major study in late-stage/fluctuating patients primarily used the following inclusion criteria:

'Adult subjects of either gender, aged 30 to 80 years, were eligible if they had a diagnosis of idiopathic PD of more than 5 years duration (or more than 3 years if approved by a central committee), and had motor fluctuations with an H&Y stage of I-IV during their 'off' phase, and > 1.5 h 'off' time during the day.' This means that all patients in the major positive Phase III study had at least some 'off' time, and patients who merely showed a fluctuating quality to their 'on' time were not eligible. It could be argued, then, that the USA indication more accurately reflects the evidence. The clinical evaluator does not favour the USA wording, though, because the difficulties in defining the 'off' state exceed those in defining 'fluctuating' patients.

Question 3

A PK analysis of ropinirole concentration data from Study 27918 (the main dopamine agonist add-on study) was mentioned in the Summary of Clinical Pharmacology. (*Newron analysis on the effect of safinamide treatment on ropinirole concentrations; Quintiles Analytical Study No Q-29056.*) The Summary of clinical pharmacology reported these results as follows:

> *Plasma concentrations of Ropinirole measured at baseline (prior to the first administration of IMP, visit 2.00), 5 h post-dose (visit 2.50), and at one LOBS visit, showed no significant differences across visits in the three treatment groups (placebo, safinamide 100 mg/day, and safinamide 50 mg/day) indicating that safinamide does not interfere with ropinirole metabolism.*

The actual data comparing ropinirole concentration across groups or across visits was difficult to find. The provided hyperlinks led to files that reported the analytical techniques used to measure the drug concentrations, rather than the between-visit or between-group differences.

Please direct the evaluator to the data, or provide a table displaying this data with descriptive statistics, along with a comparative statistical analysis, such as 95% confidence intervals for estimates of the changes in ropinirole concentrations from the pre-safinamide baseline to visits while on safinamide, and differences across groups (safinamide 100 mg/day, safinamide 50 mg/day, or placebo).

Sponsor response

The sponsor writes:

> *'Information requested by the clinical evaluator are reported in the Analytical report Q-29056 - Determination of Ropinirole in Human Plasma Samples from Clinical Study No. 22 (MOTION, 27918), submitted in Appendix 16.5.1 to study 27918 Clinical Study Report. This report is included in the file '27918-pharmacokinetics-reports.pdf' (pages 2 to 171). The plasma concentration data is presented in data table 1, 2 and 3, Section 14 of Analytical report Q-29056.'*

Evaluator comment

The table extracts of the file indicated consists of individual patient data, and as a result they are completely unsuitable for evaluation. The tables run over approximately 15 to 30 pages each, and would require extensive time spent on data entry and subsequent analysis

to be in any format suitable for Clinical Evaluation. Indeed, these tables were found by the clinical evaluator during preparation of the First round clinical evaluation report, but were dismissed as obviously unsuitable, and that is what prompted this Clinical Question.

The sponsor has not answered the question; they not provided a table 'comparing ropinirole concentration across groups or across visits', and they have not provided 'descriptive statistics, along with a comparative statistical analysis, such as 95% confidence intervals for estimates of the changes in ropinirole concentrations from the pre-safinamide baseline to visits while on safinamide, and differences across groups' as requested in the Clinical Question.

Of note, in their summary of the clinical evaluator's question, the sponsor omitted:

- the actual request for the summary information (as underlined above); and
- the tables that they cited in their response (as partially reproduced below).

These omissions have the effect of making it appear, on a superficial reading of their response, that they have provided an adequate answer to the Clinical Question, when this is not the case.

Conclusion

The sponsor's original submission makes the following claim: '*Plasma concentrations of Ropinirole measured at baseline (prior to the first administration of IMP, visit 2.00), 5 h post-dose (visit 2.50), and at one LOBS visit, showed no significant differences across visits in the three treatment groups.'*

The submission appears not to have provided any suitable presentation of the analysis that led to this claim, including the statistical results of such an analysis, or even a broad summary of the comparison using descriptive statistics. On having this omission pointed out to them, the sponsor has not provided the requested information, but merely directed the clinical evaluator to raw data that is clearly unsuitable for evaluation.

Question 4

In Study 009, two different subgroup analyses of the primary endpoint were performed that divided patients according to prior treatment status: one based on a three-group categorisation of patients' prior treatment history (de novo subjects, subjects on a stable dose of a single DA agonist, and subjects previously treated with other PD treatments), and one based on a two-group categorisation (safinamide as de novo monotherapy or as add-on to a single DA agonist). At the time of randomisation, subjects were stratified using a three-category approach, but the Clinical Overview and other submitted summaries emphasise a subgroup analysis based on only two categories. Because of the various amendments, it was not clear to the evaluator:

- whether the second, two-group approach had been chosen post hoc;
- when it was decided to use the different subgroup categorisations as part of the logistic regression analysis; and
- whether these choices changed the overall nominal significance of the study.

Please clarify these issues, stating when the two-group categorisation was first chosen as a major analysis approach, and noting which changes to the analysis were performed after unblinding of the data.

Sponsor response

The sponsor writes:

> *'Zambon confirms that the two-group approach was chosen post hoc and specified in a Report Amendment (Date of Amendment #1 to the Report 29 June 2004).*

> *The different subgroup categorisations (ie using two categories in addition to the planned analysis with three categories) were decided after the unblinding of the data.'*

Evaluator comment

Because the two-group approach was chosen post hoc, after the data were unblinded, the p values associated with the two-group approach lack statistical validity.

The sponsor also writes: *'The decision to make further subgroup analyses by using a two-category approach did not change the parameters used in the logistic regression model for primary endpoint analysis as defined in the study protocol (that is, the covariate 'Patient's treatment history' defined using the three-category approach).'*

This means that, despite the shift in emphasis in reporting the results, the actual primary endpoint of the study was still based on the three-category approach (and it was negative, though this was difficult to appreciate from reading the sponsor's description). This endpoint should, therefore, have been given prominence in the sponsor's presentation of this study. Instead, the p value associated with the three-category approach was not highlighted (and was probably not even mentioned in any of the main summary documents; see below). Furthermore, all follow-up analyses in the hierarchy of endpoints should also be considered negative.

Question 5

In Study 009, it was unclear whether the primary prospective efficacy analysis achieved a significant p value. The prospective statistical analysis plan stated: *'To test the statistical null hypothesis, the response rates of the three treatment groups will be compared using a logistic regression with an α of 0.05 and taking into account UPDRS section III score at baseline (Visit 2) and the country. In case of a statistically significant result, additional pairwise comparisons between treatment groups using logistic regressions with an α of 0.05 and taking into account UPDRS section III score at baseline (Visit 2) and the country will be performed.'*

The quoted section makes it clear that the logistic regression of all three treatment groups was the primary method of analysis, and pairwise comparisons were only to be attempted if the primary method achieved a significant result.

Please report the results of the initial primary prospective logistic regression analysis for Study 009, along with a statement of whether the study was formally negative or positive according to its prospectively identified analysis techniques.

Sponsor response

The sponsor writes:

> *The 'primary prospective efficacy analysis' consisting of the global test of the three treatment groups obtained through the pre-specified logistic regression analysis achieved a p value of 0.0504 (see Table [below]). The result was deemed sufficient to further investigate Safinamide in the phase III studies.'*

Table 12: Primary results for Study 009

LR Statistics For Type 3 Analysis			
Source	**DF**	**Chi-Square**	**Pr > ChiSq**
Treatment	2	5.98	**0.0504**
Basal UPDRS III	1	0.57	0.4511
Country	4	13.57	0.0088
Patient's treatment history	2	2.90	0.2343

Computations performed using SAS version 9.4

Evaluator comment

The sponsor's response indicates that the actual p-value for this study was 0.0504, and that it was therefore a negative study according to its own prospective analysis plan. Unfortunately, the fact that it was negative was not highlighted in the sponsor's submission, and the primary results were suppressed. A digital search of the sponsor's Clinical Overview and Summary of Clinical Efficacy for the digit sequence '0504' finds no mentions of this result. A digital search of the main report for Study 009 also produced no hits. The synopsis for Study 009 was not digitally searchable, because it was based on a scanned image, but it did not appear to mention this result either.

The clinical evaluator finds it concerning that the sponsor's Clinical Overview and other summaries of Study 009 did not clearly describe this as a negative study. In fact, the Clinical Overview, under 'Summary of Benefits', strongly implies that it was a positive study, because *only significant p values are mentioned*, as follows (emphasis added):

> *'Overall, the results from the 3 placebo-controlled studies in early-stage patients on a DA agonist (Studies009, 015 and MOTION) provide a consistent pattern of benefit for motor symptoms (UPDRS III).*
>
> ***Differences in mean changes from baseline, compared to placebo, on the UPDRS III were statistically significant for the safinamide 0.5 mg/kg/day dose (mean dose = 34 mg/day) and the 1.0 mg/kg/day dose (mean dose = 76 mg/day) in the DA agonist sub-population in Study 009 (p=0.045 and p=0.006, respectively;*** *ANCOVA [LOCF]), for the 50-100 mg/day dose range (mean dose >90 mg/day; p=0.0419; MMRM - ITT population) in Study 015, and for the 100 mg/day dose in MOTION (p=0.0396; ANCOVA [LOCF], DA agonist monotherapy population).'*
>
> LOCF= Last Observation Carried Forward

This omission raises substantial concerns about the degree to which the overall submission represented a fair and accurate portrayal of the evidence, but it does not directly impact on the decision to register the drug for a suitably defined target population, given that the sponsor now concedes that safinamide is not indicated in patients without fluctuations, and that efficacy as an add-on to a dopamine agonist has not been demonstrated.

Question 6

Adding to the lack of clarity for the results Study 009, changes in the UPDRS and Hamilton Depression Scale (HAMD) scores were first checked for normality with the Shapiro-Wilk test, and, according to the sponsor, the initial assessment of the raw data led to the conclusion that the data were not normally distributed. This led to use of a Kruskal-Wallis non-parametric analysis of variance (ANOVA) procedure in the initial analysis of these two endpoints.

Later, it was determined that the normality assumption was not actually violated, and the data were re-analysed with a parametric ANCOVA model, in accordance with the

prospective analysis plan. It remains unclear whether the decision to change model was made in response to a lack of statistical significance with the original analyses, and whether the change in model should be considered to have been *mandatory*, because the first analysis was unambiguously flawed, or *optional* (in which case it was *post hoc* and lacks validity, raising concern about multiplicity of statistical approaches).

Please provide a more detailed account of the decision process by which the original rejection of normality by the Shapiro-Wilk test was overturned, and state whether this decision changed the significance of the primary endpoint. Was the initial rejection of normality (which was later overturned): 1) an unequivocal statistical error; 2) a defensible but suboptimal approach; 3) a perfectly valid application of the prospective statistical analysis plan; or 4) something else? Which endpoints had their nominal significance changed from negative to positive by the change in model? [The 'primary' was an editing mistake].

Sponsor response

The sponsor's response implies that the original rejection of normality was an unequivocal statistical error, though unfortunately they did not state this explicitly as hoped (despite the fact that the Clinical question was phrased as a multiple choice question). As noted above, the primary endpoint for this study was negative, and the sponsor reports that it was not affected by changes in the ANOVA/ANCOVA approach: '*the decision has no impact on the logistic regression model used for the primary endpoint analysis, since the parameters (dependent and independent variables) of the model remain the same as defined in the study protocol.'*

The sponsor also provides a list of endpoints that had their nominal significance changed by post hoc changes in analysis techniques. These included CGI scores, changes in UPDRS section III score, and the logistic regression model for the responder rates, all of which benefited from post hoc changes in the analytical approach.

Evaluator comment

The sponsor's response to a previous Clinical question suggests that the primary endpoint for this study was negative, and many endpoints described as positive in the various study summaries benefited from post hoc reanalysis that increased their apparent nominal significance. Because 1) the primary endpoint was negative, 2) most of the quoted analyses were post hoc, and 3) the study had a very high number of 'degrees of investigator freedom', the results of this study cannot be considered to provide robust support for the sponsor's initial claims of efficacy in the ESPD/non-fluctuating cohort (claims made, for instance, in the original EU submission). This is less important for the Australian submission, where the proposed use of safinamide as add-on therapy to dopamine is not currently being pursued, but it remains important given the apparent reluctance of the sponsor to mention fluctuations or disease stage in their proposed indication.

Question 7

For Study 015, the Clinical Overview and Summary of Clinical Efficacy propose that the negative result in the High dose group was partly due to a high dropout rate at this dose (completion rates were 79% for the High dose group, compared to 90% for the Low Dose and Placebo groups).

Do the data from Study 015 provide any support for the hypothesis that efficacy results were biased against the High dose group because of excess withdrawals?

Sponsor response

The sponsor writes:

> *As reported in the Clinical Study Report for Study 015, there was a higher dropout rate (21%) in the High dose group compared with the Low Dose and Placebo groups*

(10% for both these groups). Even though the data showed for the observed cases there is a slightly larger difference between the High dose group versus Placebo in the change in UPDRS part III score, compared to that for the ITT analysis (LOCF) ([see Table…]), the result is not sufficient to support the hypothesis that the efficacy results were biased against the High dose group due to excess withdrawals.

Evaluator comment

The sponsor's Clinical Overview and Summary of Clinical Efficacy strongly imply that unequal withdrawal rates were a major reason behind the failure of Study 015 to achieve a positive result. In this response, the sponsor acknowledges that this post hoc hypothesis is not supported by the evidence. Thus, the negative results of Study 015 should be considered as evidence of poor efficacy in this setting, rather than as resulting from a bias introduced by a high withdrawal rate in the High dose group. This means that analyses that excluded the High dose group cannot be considered fair or robust. Such analyses include the sponsor's pooled analysis of the negative ESPD studies.

Question 8

In Study 27918, what were the results for the primary efficacy variable in the PP population?

Sponsor response

The sponsor provided a link to the table reproduced below (which was also contained in the original submission). The tables show that, in Study 27918, the results in the PP Population were not significant.

Table 13: UPDRS Section III score and change from baseline by time point and treatment group on treatment (ANCOVA) Per Protocol Population

		Safinamide 50 mg/day (n=193)		Safinamide 100 mg/day (n=199)		Placebo (n=189)	
Timepoint	Statistics	Value	Change	Value	Change	Value	Change
Baseline	n (missing)	193 (0)		199 (0)		189 (0)	
	Mean ±SD	20.87 ±9.04		18.86 ±8.47		20.05 ±8.99	
	Median	20.00		17.00		19.00	
	Min; Max	5.0; 52.0		2.0; 47.0		1.0; 61.0	
Week 2	n (missing)	193 (0)	193 (0)	198 (1)	198 (1)	189 (0)	189 (0)
	Mean ±SD	18.27 ±8.26	-2.60 ±4.73	16.65 ±8.16	-2.20 ±4.17	18.71 ±8.74	-1.34 ±4.10
	Median	17.00	-2.00	15.00	-2.00	18.00	-1.00
	Min; Max	3.0; 49.0	-29.0; 9.0	3.0; 43.0	-18.0; 17.0	1.0; 53.0	-12.0; 15.0
Week 4	n (missing)	193 (0)	193 (0)	199 (0)	199 (0)	189 (0)	189 (0)
	Mean ±SD	17.33 ±8.30	-3.54 ±4.98	16.32 ±8.25	-2.54 ±4.59	17.65 ±8.44	-2.41 ±4.27
	Median	16.00	-3.00	15.00	-2.00	17.00	-2.00
	Min; Max	0.0; 51.0	-23.0; 6.0	1.0; 43.0	-17.0; 16.0	1.0; 52.0	-14.0; 12.0
Week 8	n (missing)	190 (3)	190 (3)	198 (1)	198 (1)	189 (0)	189 (0)
	Mean ±SD	17.24 ±8.08	-3.65 ±5.68	15.79 ±7.90	-3.10 ±5.11	17.65 ±9.08	-2.41 ±4.78
	Median	16.00	-3.00	14.00	-3.00	18.00	-3.00
	Min; Max	2.0; 47.0	-25.0; 10.0	1.0; 44.0	-21.0; 15.0	1.0; 57.0	-14.0; 16.0
Week 12	n (missing)	193 (0)	193 (0)	197 (2)	197 (2)	188 (1)	188 (1)
	Mean ±SD	17.23 ±8.85	-3.64 ±6.52	16.19 ±8.19	-2.62 ±5.29	17.73 ±9.11	-2.31 ±4.95
	Median	16.00	-3.00	15.00	-2.00	17.00	-2.00
	Min; Max	2.0; 44.0	-28.0; 20.0	1.0; 47.0	-17.0; 22.0	1.0; 58.0	-19.0; 21.0
Week 18	n (missing)	192 (1)	192 (1)	198 (1)	198 (1)	187 (2)	187 (2)
	Mean ±SD	17.56 ±9.51	-3.35 ±7.12	16.08 ±8.37	-2.70 ±5.03	18.16 ±9.28	-1.84 ±5.27
	Median	16.00	-3.00	15.00	-2.00	18.00	-1.00
	Min; Max	3.0; 55.0	-37.0; 25.0	1.0; 44.0	-20.0; 10.0	1.0; 60.0	-21.0; 20.0
Week 24	n (missing)	191 (2)	191 (2)	197 (2)	197 (2)	189 (0)	189 (0)
	Mean ±SD	18.20 ±9.76	-2.57 ±7.19	16.60 ±8.85	-2.21 ±5.44	18.56 ±9.53	-1.49 ±6.03
	Median	16.00	-2.00	16.00	-2.00	19.00	-2.00
	Min; Max	2.0; 57.0	-32.0; 35.0	0.0; 50.0	-17.0; 13.0	1.0; 55.0	-18.0; 19.0
	LS Mean (SE)		-2.22 (0.44)		-2.29 (0.44)		-1.30 (0.45)

Table 14: UPDRS Section III score and change from baseline by time point and treatment group on treatment (ANCOVA) Per Protocol Population

		Safinamide 50 mg/day (n=193)		Safinamide 100 mg/day (n=199)		Placebo (n=189)	
Timepoint	Statistics	Value	Change	Value	Change	Value	Change
	LS Diff vs Placebo (SE)		-0.91 (0.61)		-0.99 (0.61)		
	95% CI of LS Diff		(-2.12, 0.29)		(-2.18, 0.21)		
	p-value vs Placebo		0.137		0.105		

T:\BIOMET08\SAFINAMIDE\27918\FINAL\TABLES\PGM\EF01_G.SAS 02MAY2012
Parametric ANCOVA model is based on the change from baseline to endpoint with fixed effects for treatment, region and baseline value as a covariate.
All p-values, LS means, and confidence intervals are calculated from the ANCOVA model.

Evaluator comment

The negative results in the PP Population are consistent with the negative outcome observed in the ITT Population.

Second round benefit-risk assessment

The sponsor has not submitted any new data or argument that substantially modifies the original assessment of the potential benefits and risks of safinamide. The sponsor has clarified their position on the benefits that were originally claimed in non-fluctuating patients, conceding that:

- Study 009 was negative;
- The overall program assessing safinamide as add-on therapy to a dopamine agonist in the non-fluctuating, ESPD population did not produce robust evidence of efficacy, as acknowledged by the sponsor and overseas regulatory authorities; and
- The drug should not be considered in patients without fluctuations (The sponsor states: *'The main reason that a clinician would initiate therapy with Xadago is because patients are fluctuating on their current treatment program, otherwise there would be no reason to add safinamide.'*)

The main benefit of safinamide, then, is observed in fluctuating patients, where it would be expected to improve 'on' time without troublesome dyskinesia by about 30 minutes per day.

The risks of safinamide are those discussed in the first round clinical evaluation.

Second round recommendation regarding authorisation

Safinamide should not be approved for the indication proposed by the sponsor, because the proposed indication does not accurately identify the group in whom benefit has been demonstrated.

The benefit-risk balance of safinamide would become favourable if the sponsor proposed the following indication:

> *For the treatment of adult patients with mid-to-late stage, fluctuating idiopathic Parkinson's disease (PD) as add-on therapy to a regimen that includes a stable dose of levodopa (L-DOPA, alone, or in combination with other PD medications).*

It could be acceptable to omit the phrase 'mid-to-late stage' from the indication, provided that the terms 'adult', 'stable dose', and (most importantly) 'fluctuating' remain in the indication. On the other hand, the inclusion of the phrase 'mid-to-late' is likely to create a clearer picture of the appropriate target population, while still leaving sufficient flexibility for clinicians to determine whether safinamide is likely to be appropriate in individual cases.

Prior to registration, the sponsor should edit the PI as suggested and provide an adequate answer to Clinical question 3 (see above).

VI. Pharmacovigilance findings

Risk management plan (RMP)

Summary of RMP evaluation[16]

The sponsor has submitted EU-RMP version 5 (dated 16 February 2018; data lock point (DLP) 24 August 2016) and Australian Specific Annex (ASA) version 1 (dated July 2017) updated to version 2.0 (dated 26 March 2018) in support of this application.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below:

Table 15: Summary of ongoing safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important identified risks	Adverse event of Dyskinesia in mid/late patients with Parkinson's disease on concomitant use of L-DOPA, alone or in combination with other dopaminergic medication.	ü	–	ü	–
	Teratogenicity	ü	–	ü	–
Important potential risks	Risk of retinal degeneration in patients with Parkinson's disease treated with safinamide	ü[a]	–	ü	–
	Severe hepatic impairment	ü	–	ü	–
	Risk of Impulse Control Disorder	ü	–	ü	–
	Concomitant use of MAOIs, serotonergic drugs and	ü	–	ü	–

[16] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
	pethidine				
Missing information	Treatment with safinamide in patients with presence and/or history of retinal disease	ü[a]	–	ü	–
	Use of safinamide in patients aged<30 years and >75 years	–	ü[b]	–	–
	Effects of Overdose	ü	–	ü	–
	Patients with severe, disabling peak-dose or biphasic dyskinesia, or with unpredictable or widely swinging fluctuations	ü	–	–	–
	Patients who have undergone stereotactic surgery as a treatment for Parkinson's disease	ü	–	–	–
	Use in patients with psychiatric illness, specifically psychosis, bipolar disorder, or severe depression	–	ü[b]	–	–
	Long term use >3 years	ü	–	–	–
	Whether specific inhibitors of the amidases involved in the metabolism of safinamide to NW-1153, may increase the exposure of safinamide	–	ü[c]	ü	–

[a] Includes targeted questionnaire. [b] Drug utilisation study. [c] In vitro study (complete)

The summary of safety concerns is adequate in relation to the indication treated.

A post-commercialisation observational safety /drug utilisation study is proposed to investigate the safety of safinamide in groups likely to be exposed to safinamide that were not well studied during the clinical trials and is appropriate. This is acceptable in relation to the nature of the safety concerns.

No additional risk minimisation activities are proposed, which is acceptable in relation to the nature of the safety concerns.

New and outstanding recommendations after the second round evaluation

Recommendations were made by the RMP evaluator in the first round evaluation. The sponsor responses are considered acceptable with the following to be noted:

- the sponsor should provide an updated ASA (when available) which includes corresponding changes to the wording for the issues the sponsor has clarified in its response. This should not delay registration.
- the sponsor should provide an updated EU-RMP (when available) which includes changes to the wording for the issues the sponsor has clarified in its response. This should not delay registration.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *Implement EU-RMP (version 05; date 16/02/2017; DLP 24/08/2016) with Australian Specific Annex (version 2.0, date March 2018), included in submission number PM-2017-01877-1-1, and any future updates as a condition of registration.*

The following wording is recommended for the PSUR requirement:

> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.*

As Xadago is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration.

The following wording is recommended for the condition of registration:

> *Safinamide mesilate (Xadago) is to be included in the Black Triangle Scheme. The PI and CMI for [Xadago] must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.*

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Guidance used

Overall, the prospective design of the studies was appropriate and consistent with regulatory guidelines. The clinical evaluator noted that the prospective statistical analysis

plan was abandoned in some cases, with inappropriate post hoc revision of the analysis approach which was clarified during the sponsor's responses to Clinical question[17]

The efficacy and safety studies in the submitted dossier were designed on the basis of regulatory advice and existing guidelines for the conduct of Parkinson's disease studies. All major efficacy measures were based on the guidance issued by CHMP and FDA. Guidance from regulatory authorities was not always available for determination of a clinically meaningful response to treatment, so the sponsor applied definitions from the literature;[10,11] in which a meaningful response was defined as a 30% or greater improvement from baseline in Section III of the UPDRS-III. At the time the Phase III program was initiated, no specific guidance was available from any authority regarding the appropriate assessment of dyskinesia, so dyskinesias were assessed by a Dyskinesia Rating Scale (DRS) described in the literature.[12]

Quality

The registration of the proposed product is recommended from a pharmaceutical chemistry and biopharmaceutical perspective, provided that the particle size limits are amended as requested below and the revised drug substance provided for review.

- The particle size limit in the drug substance specification applied by the finished product manufacturer [information redacted] should be tightened in line with batch data (including the clinical and biobatches) to [information redacted]. Please note the particle size limit should be expressed as NLT xxx for D10, include a range for D50, and NMT xxx for D90.

The revised drug substance specification applied by the finished product manufacturer [information redacted] should be provided for review.

Nonclinical

There are no nonclinical objections to the registration of safinamide for the proposed indication.

Safinamide caused retinal toxicity and cataracts in rats at subclinical relative exposures. The relevance to humans cannot be ruled out; therefore warning about these possible effects is recommended in the PI document.

The safety pharmacology data suggest that mild depression of the CNS, heart rate and blood pressure are possible with the clinical use of safinamide.

Safinamide alone and in combination with levodopa and carbidopa produced adverse developmental effects in animals at doses similar to those used in humans. Since the significance of these findings is uncertain in humans, a Pregnancy Category of B3;[9] is recommended.

The reproductive toxicity studies identified breast milk as a potential source of safinamide exposure, and hepatobiliary damage as a risk for breast-fed infants.

Clinical

The clinical evaluator has recommended approval of safinamide for indication of adult patients with Parkinson's disease provided indication wording is as below.

[17] Sponsor clarification: The post hoc revision referred to was conducted in ESPD studies. These studies were submitted by the sponsor as supporting safety data and comments regarding inappropriate statistical analyses do not relate to the pivotal studies for the indication proposed.

For the treatment of adult patients with mid-to-late stage, fluctuating idiopathic Parkinson's disease (PD) as add-on therapy to a regimen that includes a stable dose of levodopa (L-DOPA, alone, or in combination with other PD medications).

In the sponsor's response and subsequent reviews, the sponsor has accepted the most of the changes to the indication apart from 'stable' and 'mid-late stage'. There is also new addition of specific '2 weeks' interval in dosing section when patient can be escalated from 50 mg/day to 100mg/day depending on tolerability and clinical need. This addition has been questioned by clinical evaluator.

Pharmacokinetics

Overall PK of safinamide appears to be linear and well characterised in the clinical program without posing any substantial issues. Safinamide can be administered with or without food. Absolute bioavailability is high (95%) with extensive extravascular distribution and plasma protein binding of around 88 to 90%. Safinamide is almost exclusively eliminated via metabolism (approximately 5% of the drug is eliminated unchanged, mainly in urine) and the primary route of excretion is through the kidney. None of the metabolites has pharmacological activity. Safinamide is predominantly metabolised by non-microsomal enzymes (cytosolic amidases/MAOA); CYP3A4 and other CYP isozymes only play only a minor role in its overall biotransformation. The elimination half-life of safinamide is 20 to 30 h and steady-state is reached within one week.

Safinamide exposure is increased slightly in patients with mild hepatic impairment (30% increase in AUC). Safinamide exposure is increased more substantially in patients with moderate hepatic impairment (approximately 80% increase in AUC). Safinamide exposure was similar in patients with moderate or severe renal impairment and patients with normal renal function.

Safinamide does not appear to significantly induce or inhibit microsomal enzymes at clinically relevant concentrations. Drug-drug interaction studies performed with ketoconazole, L-dopa and CYP1A2 and CYP3A4 substrates (caffeine and midazolam), did not detect any clinically significant interactions. There was no effect on the clearance of safinamide in patients with Parkinson's disease receiving safinamide as add on therapy to chronic levodopa (L-Dopa) and/or DA agonists.

Pharmacodynamics

Safinamide has been shown to be a relatively selective inhibitor of MAO-B at the proposed doses, and this is likely to underlie its efficacy in patients with Parkinson's disease. MAO-B inhibition after single doses is > 90%, and long lasting, allowing once daily dosing.

The submitted pharmacodynamic studies do not provide any basis for expecting safinamide to have a very narrow therapeutic window even though there were some inconsistent results across the dose range of 50 mg/day to 200 mg/day suggesting a narrow therapeutic window, or borderline efficacy in some patient groups (particularly ESPD). In LSPD, only doses of 50 mg/day and 100 mg/day were assessed.

Other possible mechanism of action such as effect on neuronal excitability, sodium channel block was not adequately substantiated through the submitted clinical dossier. Safinamide has not shown to have any known analgesic properties. Safinamide has only a weak potential for enhancing the pressor response to dietary tyramine.

Safinamide should be avoided in subjects with congenital short QT syndrome due to mild QT shortening effect.

Efficacy

Study 016

Study 016 was a randomised, placebo-controlled Phase III study that assessed safinamide 50 mg/day and safinamide 100 mg/day in comparison to placebo in the treatment of LSPD, as add-on therapy to levodopa.

The study was positive, showing a clinically modest but statistically significant improvement in the primary endpoint, daily 'on' time without troublesome dyskinesia. The mean total daily 'on' time without troublesome dyskinesia during the 18 h diary recording time in all three treatment groups. By Week 24, the increase was approximately 55% higher in the safinamide 50 mg/day and safinamide 100 mg/day groups, compared to placebo. The values cited for the increase in mean 'on' time without troublesome dyskinesia differed slightly in the Study Synopsis, SCE and Clinical Overview, but in the SCE, the mean (SD) increase in the placebo group was 0.97 (2.375) h; in the 50 mg/day group, it was 1.37 (2.745) h; and in the 100 mg/day group, it was 1.36 (2.625 h). The MMRM LS-means differences from placebo were 0.51 h for the 50 mg/day dose group, and 0.55 h for the 100 mg/day dose group. That is, about 30 to 35 minutes of 'on' time was gained with active treatment, about one twentieth of the patients' total 'on' time (approximately 10 h per day).

Secondary endpoints were generally consistent with the primary endpoint, with formal superiority over placebo demonstrated for decrease in 'off' time, UPDRS-III and CGI-C.

In general, the efficacy results for safinamide 100 mg/day were slightly better than results for 50 mg/day, which supports the sponsor's recommendation to start at 50 mg/day and increase to 100 mg/day as needed and tolerated.

Study 27919 (SETTLE Study)

Study 27929 was a randomised, placebo-controlled Phase III study that assessed safinamide as add-on therapy to levodopa in subjects with LSPD. It assessed an adjustable dose of safinamide (within the range 50 to 100 mg/day) in comparison to placebo. The primary endpoint was the change in total daily 'on' time without troublesome dyskinesia. This improved in both treatment groups, but the improvement was significantly greater in the active treatment group ($p < 0.001$ by ANCOVA). From a baseline value of about 9.5 h (mean 9.3 in safinamide group, 9.06 in the placebo group), the safinamide group had a mean (SD) change in daily on time of 1.42 h (2.80), while the placebo group had a mean (SD) change of 0.57 h (2.47). The LS mean (SE) difference between the groups was 0.96 h (0.21), indicating an attributable increase in daily on time with safinamide of about one hour.

A number of secondary analyses and secondary endpoints were consistent with these positive findings. Two achieved formal superiority: reduction in 'off' time, and UPDRS-III scores. At Week 24, the mean (SD) change from baseline in UPDRS-III was -3.43 (7.72) for the safinamide group, compared to -1.83 (8.23) for the placebo group. The reduction in the safinamide group (LS mean difference [SE] was estimated to be -1.82 [0.61], which was significant ($p = 0.003$).

Overall, this study adds to Study 016 in showing a small but robust benefit when safinamide 50-100 mg is used as add-on therapy to levodopa in patients with LSPD.

Extension study in LSPD, Study 018

Study 018 was a 78 week, double blind extension of Study 016, in which patients continued to take the same treatment and dose they received in Study 016 (safinamide 50 mg/day, safinamide 100 mg/day or placebo), along with the same dose of levodopa. Increases in the dose of the patient's levodopa or addition of any other antiparkinsonian treatments, excluding other MAO inhibitors, were permitted, if needed.

The total duration of Studies 016 and 018 combined was 102 weeks.

The primary efficacy variable (different from the one used in the parent study) was the mean change in the Dyskinesia Rating Scale (DRS) during 'on' time from Baseline (Study 016) to endpoint (last visit in Study 018). The Delegate agrees with the clinical evaluator that the original endpoint would have been more appropriate for the extension study. In the proposed PI *only* endpoints that were continued from the parent study, focussing on the original endpoint is described.

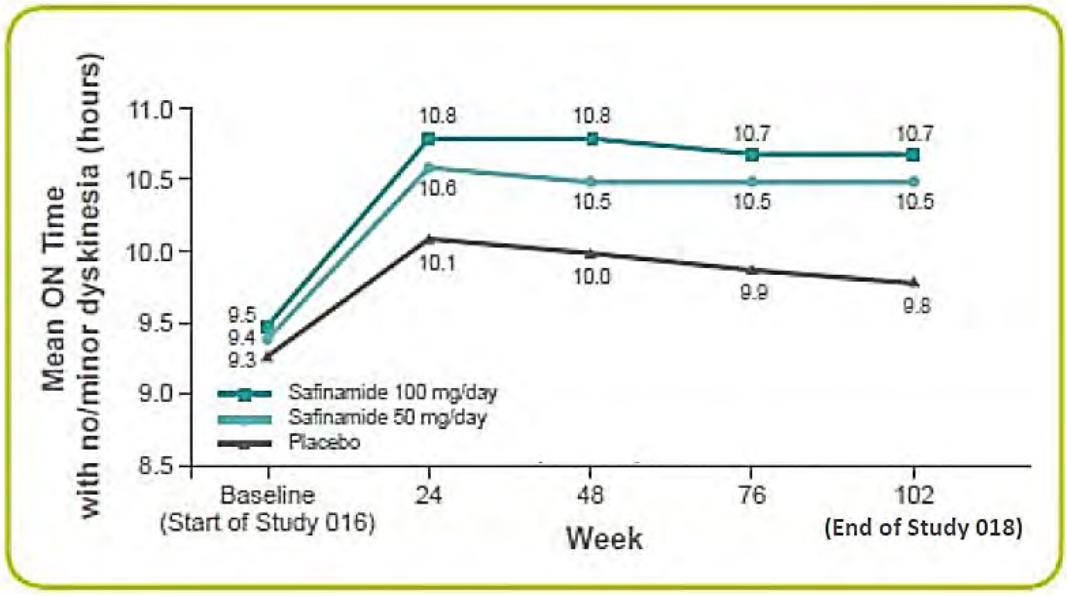
Secondary efficacy variables were largely similar to the parent study and were listed in a hierarchical fashion. The first secondary endpoint was the same as the primary endpoint in the parent study (change in 'on' time without troublesome dyskinesia.

The primary endpoint was negative. At the Study 016 Baseline, the mean (SD) DRS scores for the placebo, safinamide 50 mg/day, and safinamide 100 mg/day groups were 3.4 (3.93), 3.9 (3.89), and 3.7 (4.07), respectively. DRS scores improved slightly in the active groups but remained largely unchanged in the placebo group: a percentage reduction of 31% was observed for the safinamide 50 mg/day group and 27% for the safinamide 100 mg/day group, versus a 3% reduction in the placebo group. The changes in DRS for the active treatment groups were not statistically significantly different from the placebo group (p = 0.2125 for the safinamide 50 mg/day group and p = 0.1469 for the safinamide 100 mg/day group).

The original primary efficacy variable from the parent study showed a more convincing treatment response, with continued benefit observed over the course of Study 018, as shown in the figure (Figure 4) below (from the proposed PI). This benefit was statistically significant: the safinamide 50 mg/day and the safinamide 100 mg/day groups had a significantly greater mean increase from the 016 Baseline (LS mean, 1.01 h for the safinamide 50 mg/day group (p = 0.0031) and 1.18 h for the safinamide 100 mg/day group (p = 0.0002)) compared with the placebo group (LS mean, 0.34 h). The difference from placebo was broadly consistent across the two studies (and numerically improved over time as 'on' time worsened slightly in the placebo group), indicating persistence of efficacy over the long term.

Other endpoints were also generally favourable, and consistent with the original study.

Figure 4: Results for the primary efficacy variable mean on time with no/minor dyskinesia (h)



The *Diary Responder Rate* was higher with active treatment, and appeared broadly consistent over time.

For *UPDRS-IV,* the results were mixed. The reduction (improvement) in mean UPDRS-IV scores from Baseline to Week 78 for the ITT population was significantly greater in the safinamide 100 mg/day group (LS mean, -0.90 (p = 0.0003)), but not in the safinamide 50 mg/day group (LS mean, -0.35 (p = 0.5100)), compared with placebo (LS mean, -0.22).

The *time to develop troublesome dyskinesia* showed no consistent dose trend and no significant differences between groups. The *time to develop any dyskinesia* did not show a treatment benefit, and was longest in the placebo group (427.14 minutes), followed by the safinamide 100 mg/day group (409.86 minutes) and safinamide 50 mg/day (306.96 minutes) group. The differences between groups were not significant.

Changes in the UPDRS-II scores from Baseline to Week 78, which reflect ability to perform ADLs, favoured the higher dose of safinamide.

For *changes in levodopa dose***,** a slightly but significantly higher proportion of subjects in the safinamide 100 mg/day group had a reduction in their levodopa dose, compared to the placebo group. The safinamide 50 mg/day dose group did not show a significant difference from placebo. Other secondary and tertiary endpoints were broadly consistent with the key results mentioned here.

Overall, this extension study was consistent with the parent study, and showed continued benefit for safinamide in improving 'on' time without troublesome dyskinesia, as well as improving many other aspects of the patient's function. The study did not achieve its primary endpoint, however, in reducing dyskinesia ratings while 'on', and it did not delay the development of dyskinesia. In this respect, safinamide appears similar to most other effective PD treatments, which often increase the risk of dyskinesia in patients with fluctuating disease.

Pooled analysis of LSPD data

The sponsor also performed pooled analyses in LS patients with Parkinson's disease (n = 1188), with data from Studies 016 and 27919 (SETTLE), using ANCOVA and LOCF analyses for change in 'on' time. Both the 50 mg/day and 100 mg/day doses were significantly superior to placebo in improving 'on' time, as expected from the fact that the contributing studies were positive. The magnitude of benefit in 'on' time was lower in the 50 mg/day (0.50, $p < 0.05$) than the 100 mg/day (0.88, $p < 0.001$). Results were broadly consistent across subgroups and for a number of analyses of secondary endpoints.

Evaluator conclusions on clinical efficacy

The results from LSPD studies were more convincing, showing an improvement in 'on' time of about 30 min to one hour, when safinamide was added to stable doses of levodopa.

Safety

Overall, apart from the expected tolerability issues common to most Parkinson's disease therapies, safinamide is not associated with any major safety concerns.

In total 2468 patients were exposed to safinamide as compared to placebo which had 1159. No pivotal studies were primarily focussed on safety.

A high proportion of subjects had AEs, including placebo recipients. In the ESPD, the incidence of AEs was actually lower among safinamide than placebo (70.3% versus 73.0%). In the LSPD, there was a minor excess of AEs in safinamide recipients (82.4% versus 78.3%). No notable increase in open-label extensions (73.1%). In ES patients with Parkinson's disease, dyskinesia was clearly more common with safinamide than placebo (24.3% versus 12.9%) but the difference was less marked for most other AEs.

The overall incidence of patients experiencing TEAEs in the combined safinamide (76.1%) and placebo (75.8%) groups was similar, with no difference in the proportion of patients experiencing severe TEAEs. The incidence of SAEs was also similar between safinamide and placebo in both ESPD (6.9% versus 5.0%) and LSPD (12.9% versus 11.5%) datasets. Mortality rates for safinamide and placebo were similar with safinamide and placebo (safinamide 1.5 versus placebo 2.5 deaths/100 person-years).

In patients with LSPD, dyskinesia, Parkinson's disease (worsening), and falls were the 3 most frequently-reported TEAEs in safinamide treated subjects that also had at ≥ 2% higher incidence than placebo. The difference was most marked for dyskinesia: in LS patients with Parkinson's disease, dyskinesia was reported 24.3% of safinamide recipients, compared to 12.9% of the placebo group, but it was rated as severe in only 1.9% of safinamide and 1.8% of placebo patients. A total of 8 patients on safinamide (1.1%) and one patient on placebo (0.2%) discontinued treatment due to dyskinesia. Discontinuations due to AEs were relatively infrequent in the placebo-controlled studies, and broadly similar in safinamide recipients and placebo recipients.

More serious idiosyncratic reactions appeared to be rare. The incidence of adverse events of hepatotoxicity, cardiovascular events, and hypertensive crisis was low and similar in the safinamide and placebo groups. Only one subject experienced a suspected serotonin syndrome.

A monitoring program was conducted in over 2000 patients in placebo-controlled trials, evaluating the ocular safety of safinamide, including visual acuity, colour vision, visual field, fundus examination, optical coherence tomography (in a selected subset). This program did not detect any significant differences in the incidence of ocular abnormalities between safinamide and placebo recipients. The proposed PI has adequate wording to reflect on experience of safinamide in special populations.

Risk management plan

There are no major objections to approval by the RMP evaluator. The messages in the PI are same or of similar intent to those in the EU Summary of Product Characteristics (SmPC).

A post-commercialisation observational safety /drug utilisation study is proposed to investigate the safety of safinamide in groups likely to be exposed to safinamide that were not well studied during the clinical trials and is appropriate. This is acceptable in relation to the nature of the safety concerns.

No additional risk minimisation activities are proposed, which is acceptable in relation to the nature of the safety concerns. The RMP evaluator has recommended the following conditions of registration:

> *Implement EU-RMP (version 05; date 16 February 2017; DLP 24 August 2016) with Australian Specific Annex (version 2.0, date March 2018), included in submission number PM-2017-01877-1-1, and any future updates as a condition of registration.*
>
> *The following wording is recommended for the PSUR requirement:*
>
> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and*

processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As Xadago is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration.

The following wording is recommended for the condition of registration:

Safinamide mesilate (Xadago) is to be included in the Black Triangle Scheme. The PI and CMI for [Xadago] must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Risk-benefit analysis

Delegate's considerations

Overall PK of safinamide is well characterised in the clinical program without posing any substantial issues. Drug-drug interaction studies did not detect any clinically significant interactions. Safinamide exposure is increased more substantially in patients with moderate hepatic impairment which is appropriately addressed in product information.

Safinamide 200 mg/day dose which was primary dose of analysis, failed to show any efficacy in this setting and there is unexplained discrepancy between the 200 mg/day dose and the 100 mg/day dose.

Two Phase III studies in mid to late Parkinson's disease have demonstrated efficacy of safinamide with fixed doses of 50 mg/day or 100 mg/day or flexible dosing in the range 50 to 100 mg/day. In both studies, an improvement in 'on' time without troublesome dyskinesia was observed, amounting to about 30 to 60 minutes. Many secondary endpoints also showed an improvement on active treatment, including a small improvement in UPDRS-III. Responses to 100 mg/day were generally superior to 50 mg/day.

Safinamide has not shown any major safety concern apart from expected tolerability issues common to most Parkinson's disease therapies such as dyskinesia. No major objections to approval by the RMP evaluator. Drug utilisation study to investigate the safety of safinamide in groups likely to be exposed to safinamide that were not well studied during the clinical trials is ongoing and expected to report in 2019.

Initial indication proposed by the sponsor had no mention of motor fluctuation or stage of disease to start safinamide as an adjunctive therapy. After the sponsor's responses to TGA's questions, the sponsor has agreed to include motor fluctuation in the indication. There is still some ambiguity over whether to include classification of the disease such as mid-late stage Parkinson's disease in the indication. But having included levodopa as a baseline therapy and safinamide to be used only in the evident of motor fluctuation, value of putting 'mid-late' stage of disease seems comparatively less important.

Stable dose of levodopa before starting safinamide has been emphasised by the clinical evaluator. Levodopa has both short term and long term effect and it can possibly take a month for full effects. Also, to ascertain treatment effect (benefit/harm) due to change in levodopa dose or addition of safinamide will be difficult. In addition, this drug could be prescribed by general practitioners who may not be familiar with the desirability of a stable baseline levodopa dose. Taking all the above into consideration making it explicit in the indication will reflect the importance of stable baseline levodopa dosing before starting adjunctive safinamide.

Apart from the expected tolerability issues common to most Parkinson's disease therapies, safinamide is not associated with any major safety concerns. Overall the safety of safinamide was considered acceptable, as incidences of adverse events under safinamide treatment seemed quite low as compared to placebo.

Deficiencies of the data

- Comparison to currently approved MAO-B inhibitors
- Lack of dose effect seen with 200mg in ES patients with Parkinson's disease
- Long term use > 3 years.

Conditions of registration

As Xadago is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration.

The following study reports must be submitted to the TGA, in addition to those identified and/or agreed in the RMP/ASA, as soon as possible after completion, for evaluation as Category 1 submission(s):

1. Final Study report of Drug Utilisation Study, cat. 3 (European, (Study ID Z7219N02))

Conclusion

Overall safinamide is approval as the quality, nonclinical and clinical evaluators (subjected to indication wording changes) have all recommended approval. The Delegate considers that sufficient data and justification have been provided to support the registration of safinamide on quality, safety and efficacy grounds for the treatment of adult patients with fluctuating idiopathic Parkinson's disease (PD) as add-on therapy to a regimen that includes stable dose of levodopa (L-DOPA), (alone, or in combination with other PD medications).

Summary of issues

1. Inclusion or omission of 'mid-late stage' wording in the indication.
2. Stable dose of levodopa while commencing on safinamide.
3. Dose escalation from 50 mg/day to 100 mg/day *after 2 weeks* if clinically warranted.

Proposed action

The Delegate had no reason to say, at this time, that the application for safinamide should not be approved for registration.

Any approval is subject to taking into account all issues arising from the advisory Committee on Medicines (ACM) deliberations and finalising matters pertaining to the PI, to the satisfaction of the TGA.

Request for ACM's advice

The committee is requested to provide advice on the following specific issue:

1. What are ACM's views on the efficacy and to what extent is there sufficient clinical trial evidence to support the proposed indication for safinamide? Please also

comment on whether there is clinical need to explicitly include in the indication 'stable dose' of levodopa and 'mid-late PD'.

2. Is it needed to specify *2 weeks* before escalating dose from 50 mg/day to 100 mg/day?
3. Does the ACM consider that the safety of safinamide (Xadago) in the proposed new indication is sufficiently well characterised and communicated in the PI?
4. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor's comments regarding each of the questions posed to the ACM for advice are provided below.

Proposed indication

From a clinical perspective, the key diagnostic feature for considering safinamide treatment is that the patient is on levodopa, either alone or in combination with other PD medications, and experiencing fluctuations. There is no clinical need to explicitly include either 'stable dose' or 'mid-late PD' in the indication.

Stable dose

The clinical evaluator and Delegate have commented that it may take a month for the full effects of levodopa dose to be apparent in an individual patient. Whilst this is acknowledged for levodopa alone, current clinical practice is for levodopa to be is administered in combination with a peripheral dopa-decarboxylase inhibitor such as carbidopa or benserazide. Combining levodopa with these medicines reduces the amount of levodopa required and provides an earlier response to therapy. According to the Australian PI for Sinemet (levodopa/carbidopa AUST R 171665, 171666), a response has been observed in one day, and sometimes after one dose, and fully effective doses are usually reached within seven days as compared to weeks or months with levodopa alone. Similarly for Madopar (levodopa/benserazide AUST R 13742-7, 43517), the product information states that the effective dose may be reached in as little as four days. The time to achieve clinical benefit is further illustrated by the dosage adjustment periods recommended for these levodopa/dopa-decarboxylase inhibitor combination products which may be increased every day, every other day or at most weekly.

As stated above, levodopa/dopa-decarboxylase inhibitor combination products are more commonly used than levodopa alone. The full effect of these combination products can be observed in a matter of days as opposed to the one month timeframe stated by the clinical evaluator and Delegate. The one month timeframe for levodopa alone is not reflective of current clinical practice and using this as the basis for specifying a 'stable levodopa dose' in the Xadago indication is not clinically justified.

There is also concern that including reference to a stable dose of levodopa in the Xadago indication may cause confusion about appropriate clinical management of patients experiencing fluctuations. As noted in the Section 4.4 *Special Warnings and Precautions for Use* of the proposed Xadago PI, safinamide, like other add-on therapies for Parkinson's disease, may potentiate the side effects of levodopa and/or other dopaminergic drugs. To mitigate this risk, a reduction in the patient's daily levodopa dosage or the dosage of another dopaminergic drug may be appropriate. Specifying that a stable levodopa dose is required for Xadago treatment may cause confusion and suggest that adjusting levodopa dosage according to individual patient response is not appropriate.

With regard to use by general practitioners as described the clinical evaluator and the Delegate, the sponsor acknowledges that they may also prescribe Xadago. However, initiation of a new therapy is most likely to be done by a specialist in Parkinson's disease,

who is familiar with the desirability of a stable baseline levodopa dose. Prescriptions by General Practitioners (GPs) are generally repeat prescriptions following specialist initiation. For those GPs who do initiate add-on therapy in Parkinson's disease, they are also familiar with the desirability of a stable baseline prior to initiation of a new therapy.

The concerns raised by the clinical evaluator and the Delegate surrounding stable doses and add on therapy could apply to many different medications and disease states. This situation is not specific to Xadago. As previously stated by the sponsor in our responses to the clinical evaluation report, a similar product, rasagiline (Azilect AUST R 172457 and 170172) which is also used as an add-on to levodopa/decarboxylase inhibitor therapy in patients with Parkinson's disease, does not specify in the indication that 'stable' levodopa/decarboxylase inhibitor doses are required prior to the initiation of rasagiline. Similarly, the indication for entacapone (Comtan AUST R 68463) used as an add-on to levodopa/decarboxylase inhibitor therapy does not state 'stable' in the indication. The sponsor believes it is important, where appropriate, to have similar indications across products that are used in essentially the same situations and same patient populations.

For the reasons discussed above, the sponsor believes that the term 'stable' is unnecessary in the wording of the indication for Xadago.

Mid to late stage

The sponsor agrees with the opinion of the clinical evaluator that the term 'mid to late stage' is not necessary in the indication if the target group is restricted to patients with motor fluctuations. Restricting the patient population to those experiencing fluctuations would, by default, exclude patients with early stage disease. The Delegate has also commented that '*... having included levodopa as a baseline therapy and safinamide to be used only in the evident of motor fluctuations, value of putting 'mid-late' stage of disease seems comparatively less important*.'

It is also important to note that for neurodegenerative diseases and specifically for Parkinson's disease, the expression and rate of progression between onset and advanced phases is highly variable. Presence and severity of symptoms over time varies widely amongst patients which makes it difficult to define limits for disease severity gradation.

As there is no clear definition or distinction between the stages of Parkinson's disease, the term 'mid to late stage' is open to subjective interpretation and clinical uncertainty. In contrast, the term 'fluctuations' term provides a clear clinical sign to identify the patient population suitable for treatment with Xadago and was considered by the clinical evaluator to be the most important term for inclusion in the indication.

The sponsor believes that the indication proposed provides a concise, clearly defined and clinically relevant description of the patient population for Xadago and that inclusion of the term 'mid to late' would not provide any additional information or benefit to the prescribing physician.

Dose escalation from 50 mg/day to 100 mg/day after 2 weeks if clinically warranted

The proposed dosage for Xadago is:

> *Xadago treatment should be started at 50 mg/day. The dose may be increased to 100 mg/day after two weeks on the basis of individual clinical ne*ed.

As discussed in the sponsor's response to the second round clinical evaluation report, the 2 week time period is in accordance with the dosage regime used in the pivotal SETTLE study (Study 27919). In this study, subjects in the safinamide group, started at a dose of 50 mg/day and the dose was increased to 100 mg/day on Day 14, if well tolerated.

Inclusion of this timeframe gives physicians an important guide as to when to consider dose escalation. Without this information, patients may continue on the 50 mg dose for several months before being reassessed and therefore the full benefit of safinamide

therapy may not be achieved. The table below summarises the increased benefit of the 100 mg/day dose, showing statistically significant changes for more outcomes for the 100 mg/day dose compared with the 50 mg/day dose.

Table 16: Analysis of benefits of 100 mg/day dose over 50 mg/day

	NW-016 **24 weeks**			**016/018** **2 years**			**27919 (SETTLE)** **24 weeks**	
	P	Safinamide (S) mg/day		P	S mg/day		P	S mg/day
		50	100		50	100		50-100
UPDRS III - Motor Examination (while ON): ***decrease indicates improvement of PD symptoms***								
*LS Diff v Placebo	-	-1.8	-2.6	-	-1.05	-2.13	-	-1.82 (0.61)
p value	-	0.0138[b]	0.000 06[b]	-	0.1791[b]	0.0063[b]	-	0.003[d]
UPDRS II - Activities of Daily Living (while ON): ***decrease indicates improvement of PD symptoms***								
*LS Diff v Placebo	-	-0.5	-1.0	-	-0.52	-1.06	-	-0.43 (0.30)
p value	-	0.1253[b]	0.0060[b]	-	0.1857[b]	0.0068[b]	-	0.149 [d]
PDQ-39 - Parkinson's disease Questionnaire								
*LS Diff v Placebo	-	-4.6	-16.5	-	-10.48	-18.36	-	-2.33
p value	-	0.5603[g]	0.0360 [g]	-	0.1837 [h]	0.0195 [h]	-	0.006[e]

*Least squares difference versus placebo of change from baseline. P=placebo; S= safinamide

Furthermore, inclusion of the 2 week timeframe into the Dosage and Method of Administration section of the Australian PI is in-line with the approved dosage in the US Prescribing Information, which states:

> *The recommended starting dosage of Xadago is 50 mg administered orally once daily (at the same time of day), without regard to meals. After two weeks, the dosage may be increased to 100 mg once daily, based on individual need and tolerability.*

Safety of safinamide in the proposed indication

The Delegate has also asked the ACM to consider if the safety of safinamide (Xadago) in the proposed new indication is sufficiently well characterised and communicated in the PI.

In relation to safety, the overall summary of the clinical evaluator was '*apart from the expected tolerability issues common to most PD therapies, safinamide is not associated with any major safety concerns.*'

The Delegate has provided the same conclusion and also stated that the '*Proposed PI has adequate wording to reflect on experience of safinamide in special populations.*'

The RMP evaluator has commented that 'The messages in the PI are same or of similar intent to those in the SmPC.'

The proposed Australia PI for Xadago clearly identifies the treatment emergent adverse events with an incidence of ≥2% from the two pivotal studies and provides a comprehensive list, in standard MedDRA terms;[18] of the adverse effects reported during clinical trials and considered related to safinamide treatment. All known warnings and precautions are clearly stated.

Overall, the sponsor believes that the safety of safinamide has been sufficiently well characterised and communicated in the PI.

Response to the TGA's quality evaluation

A separate response is being prepared and will be provided to the TGA in relation to outstanding quality issue on particle size limits. The sponsor anticipates that this response will address the TGA's concerns.

Discussion of clinical data

Both the clinical evaluation reports and the Delegate's summary provide considerable discussion regarding the clinical studies of safinamide in early stage Parkinson's disease patients where Xadago was used as add-on therapy to a dopamine agonist. The sponsor would like to clarify for the ACM that the efficacy data from these studies are *not relevant to the indication requested for Xadago* and, as previously advised to the TGA in our initial cover letter and in responses to the first round and second round clinical evaluation reports, these *studies were provided as additional, supporting safety data only*.

Conclusion

The sponsor considered that the data presented by the sponsor provides sufficient justification to support the registration of safinamide on quality, safety and efficacy grounds for the treatment of adult patients with fluctuating idiopathic Parkinson's disease as add-on therapy to a regimen that includes levodopa (L-DOPA), (alone, or in combination with other Parkinson's disease medications).

[18] MedDRA or Medical Dictionary for Regulatory Activities is a rich and highly specific standardised medical terminology developed by ICH to facilitate sharing of regulatory information internationally for medical products used by humans. It is used for registration, documentation and safety monitoring of medical products both before and after a product has been authorised for sale. Products covered by the scope of MedDRA include pharmaceuticals, vaccines and drug-device combination products.

Advisory committee considerations[19]

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Xadago film-coated tablets containing 50 mg and 100 mg of safinamide to have an overall positive benefit-risk profile for the amended indication:

> *Xadago is indicated for the treatment of adult patients with mid to late stage idiopathic Parkinson's disease (PD) with motor fluctuations, as add-on therapy to a regimen that includes a stable levodopa (L-DOPA) dose.*

In providing this advice the ACM noted the following:

- Efficacy of safinamide in early stage Parkinson's disease has not been sufficiently demonstrated.
- Study 016 was a Phase III study assessing the efficacy and safety of two doses of safinamide (50 mg daily and 100 mg daily) in comparison to placebo. The primary efficacy variable was the mean daily 'on' time without troublesome dyskinesia over 18 h. Safinamide demonstrated a modest but statistically significant improvement in the primary outcome over placebo of approximately 0.5 h (in both safinamide dose groups).
- Study 27919 (SETTLE) was a Phase III study assessing the efficacy and safety of an adjustable dose of safinamide (within the range 50 to 100 mg daily) in comparison to placebo. The primary efficacy parameter was the change in daily 'on' time without troublesome dyskinesia from Baseline to Week 24. Improvement was significantly greater in the safinamide treatment group compared to placebo, indicating an attributable increase in daily on time with safinamide of about one hour.
- Incidence of treatment emergent adverse events and serious adverse events were similar between the treatment groups and placebo groups.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- Rephrasing section in PI under 'Special Warnings and Precautions for Use' regarding add-on therapy to a dopamine-agonist to read: '*Limited data are available for safinamide as add-on therapy to a dopamine-agonist in the absence of levodopa. Randomised, controlled studies have been performed; however while safinamide was found to be safe and well tolerated, efficacy was not demonstrated*.'

[19] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. ***What are ACM's views on the efficacy and to what extent is there sufficient clinical trial evidence to support the proposed indication for safinamide? Please also comment on whether there is clinical need to explicitly include in the indication - 'stable dose' of levodopa and 'mid-late Parkinson's disease.***

The ACM considered that there is sufficient evidence to support efficacy of safinamide in what is referred to as 'mid to late stage' Parkinson's disease. In particular, the ACM were of the view that safinamide should only be used in patients with motor fluctuations. Noting that there is no consistently accepted method for staging Parkinson's disease qualifications to the indication to reflect the inclusion criteria of the supporting clinical trials are both technically appropriate and clinically useful. The ACM were of the view that specification of 'adult patients', 'mid to late stage', 'with motor fluctuations', and 'stable levodopa dose' should all be included in the indication wording.

2. ***Is it needed to specify 2 weeks before escalating dose from 50 mg/day to 100 mg/day?***

The ACM noted that there is unclear evidence of a predictable dose-response relationship between the 50 mg and 100 mg daily doses. Only some patients would benefit from the higher dose.

The two week interval to up-titration arises from the context of the dose escalation in the SETTLE study, where the dose was increased on Day 14 to from 50 mg to 100 mg daily if well tolerated. The ACM advised that escalating the dose before two weeks would be premature and providing guidance on the interval before escalation would be useful to prescribers.

The committee suggested consideration of including a similar timeframe for subsequent down-titration (if further improvement has not been demonstrated), and a stopping rule for clinical non-response.

3. ***Does the ACM consider that the safety of safinamide (Xadago) in the proposed new indication is sufficiently well characterised and communicated in the PI?***

The ACM noted that while no clear safety signals manifested in the context of the studies, the safety profile of safinamide in clinical use in Australia is not yet known. The ACM advised that potential toxicities and serious adverse events identified as requiring risk management activities should also be specified in the PI.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Xadago safinamide (as mesilate) 100 mg film-coated tablet blister pack and Xadago safinamide (as mesilate) 50 mg film coated tablet blister pack. The approved indication(s) for these therapeutic good(s) is:

> *Xadago is indicated for the treatment of adult patients with fluctuating idiopathic Parkinson's disease (PD) as add-on therapy to a regimen that includes levodopa (L-DOPA).*

Specific conditions of registration applying to these goods

1. Safinamide mesilate (Xadago) is to be included in the Black Triangle Scheme. The PI and CMI for Xadago must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
2. The Xadago EU-Risk Management Plan (RMP) (version 05; date 16 February 2017; DLP 24 August 2016), with Australian Specific Annex (version 2.0, date March 2018), included with submission PM-2017-01877-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Xadago approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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