▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

Australian Product Information - XADAGO® (safinamide)

1. NAME OF THE MEDICINE

Safinamide (as mesilate)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Xadago® tablets contain 50 or 100 mg safinamide (as mesilate).

For the full list of excipients, see Section LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Xadago® 50 mg Tablets: Orange to copper, round, biconcave, immediate release, film-coated tablets (7 mm diameter) with metallic gloss and “50” embossed on one side. Each tablet contains 50 mg safinamide (as mesilate).

Xadago® 100 mg Tablets: Orange to copper, round, biconcave, immediate release, film-coated tablets (9 mm diameter) with metallic gloss and “100” embossed on one side. Each tablet contains 100 mg safinamide (as mesilate).

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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).

4.2 DOSE AND METHOD OF ADMINISTRATION

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.

Discontinuation:

Xadago® 50 mg can be discontinued without down titration.
Xadago® 100 mg should be tapered by decreasing the dose to 50 mg for one week prior to discontinuation.

Paediatric Patients

The safety and efficacy of safinamide in children and adolescents under 18 years of age have not been established. No data are available.

Elderly Patients

No dosage adjustment is required for patients over 75 years of age.

Renal Impairment

No dosage adjustment is required for patients with renal impairment.

Hepatic Impairment

No dose adjustment is required for patients with mild hepatic impairment. For patients with moderate hepatic impairment, the lower dose of 50 mg/day is recommended. If patients progress from moderate to severe hepatic impairment, treatment with Xadago® should be stopped. Safinamide is contraindicated in patients with severe hepatic impairment (see **4.3 CONTRAINDICATIONS** and **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Tyramine-containing Foods

Xadago® can be used without any dietary tyramine restrictions (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance (safinamide) or to any of the tablet excipients (see **6.1 LIST OF EXCIPIENTS**)
- Concomitant treatment with other monoamine oxidase (MAO) inhibitors. At least 7 days must elapse between discontinuation of safinamide and initiation of treatment with another MAO inhibitor.
- Concomitant treatment with pethidine. At least 7 days must elapse between discontinuation of safinamide and initiation of treatment with pethidine.
- Severe hepatic impairment (see **4.2 DOSE AND METHOD OF ADMINISTRATION** and **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**)
- Albinism, retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serotonin syndrome

The development of serotonin syndrome has been reported in patients on concomitant treatment with MAO inhibitors (including selective MAO-B inhibitors), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, tetracyclic antidepressants, triazolopyridine antidepressants, cyclobenzaprine, opioid drugs and methylphenidate, amphetamine and their derivatives (see **4.3 CONTRAINDICATIONS** and **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

Serotonin syndrome symptoms may include mental status changes (e.g. agitation, hallucinations, delirium, and coma), autonomic instability (e.g. tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, and hyperthermia), neuromuscular symptoms (e.g. tremor, rigidity, myoclonus, hyperreflexia, and incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhoea).

Hepatic impairment

Exercise caution when initiating treatment in patients with moderate hepatic impairment. If patients progress from moderate to severe hepatic impairment, treatment with Xadago® should be stopped. Safinamide is contraindicated in patients with severe hepatic impairment. (See also **4.2 DOSE AND METHOD OF ADMINISTRATION, 4.3 CONTRAINDICATIONS** and **5.2 PHARMACOKINETIC PROPERTIES**)

Retinal pathology

Xadago® should not be administered to patients with ophthalmological history that would put them at increased risk for potential retinal effects (e.g. family history of hereditary retinal disease, or history of uveitis) (see **4.3 CONTRAINDICATIONS** and **5.3 PRECLINICAL SAFETY DATA**). In clinical trials no retinal degeneration was noted in patients at the maximum human dose.

Impulse control disorders

Impulse control disorders (ICDs) can occur in patients treated with dopamine agonists and/or dopaminergic treatments. Safinamide treatment has not been associated with any increase in the appearance of ICDs. However some reports of ICDs have been observed with other MAO-inhibitors.

Patients and carers should be made aware of the behavioural symptoms of ICDs that were observed in patients treated with other MAO-inhibitors including cases of compulsions, obsessive thoughts, pathological gambling, increased libido, hyper-sexuality, impulsive behaviour and compulsive spending or buying. Patients may not recognise these behaviours as abnormal. It is therefore important for prescribers to specifically ask patients or their caregivers about the development of new or increased ICD behavioural symptoms.

Dopaminergic side effects

Safinamide may potentiate the side effects of levodopa and/or other dopaminergic drugs. Pre-existing dyskinesia may be exacerbated. This effect was not seen when safinamide was used as an adjunct to a dopamine agonist in non-fluctuating PD patients. In clinical studies, dyskinesia was generally mild to moderate in intensity, with very few patients reporting severe dyskinesia. There was no increase in troublesome dyskinesias. Reducing the patient's daily levodopa dosage or the dosage of another dopaminergic drug may mitigate dyskinesia.

Tyramine/safinamide interaction

Safinamide potentiation of the tyramine pressor effect was investigated in one intravenous and two short term oral tyramine challenge studies. Results of these studies and home monitoring of blood pressure after meals during chronic dosing in two therapeutic trials in PD patients, did not detect any clinically important increases in blood pressure. In addition, three therapeutic studies performed in PD patients without any tyramine restriction, did not detect any evidence of tyramine potentiation. Xadago® can be used without any dietary tyramine restrictions.

Add-on therapy to a single dopamine-agonist

Limited data are available for safinamide as add-on therapy to a single dopamine-agonist.

Randomised, controlled studies have been performed; however while safinamide was found to be safe and well tolerated, efficacy results were inconclusive.

Paediatric use

The safety and efficacy of safinamide in children and adolescents under 18 years of age have not been established.

Effect on laboratory tests

Xadago® has no known effect on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Monoamine oxidase (MAO) inhibitors and products with MAO inhibition activity

Xadago® must not be administered concomitantly with other MAO inhibitors or products which have MAO inhibition activity as there is a risk of non-selective MAO inhibition that may lead to a hypertensive crisis (see **4.3 CONTRAINDICATIONS**). At least 7 days must elapse between discontinuation of safinamide and initiation of treatment with another MAO inhibitor.

Pethidine

Serious adverse reactions have been reported with the concomitant use of pethidine and MAO inhibitors. As this may be a class-effect, the concomitant administration of Xadago® and pethidine is contraindicated (see **4.3 CONTRAINDICTIONS**). At least 7 days must elapse between discontinuation of safinamide and initiation of treatment with pethidine.

Sympathomimetic medications

There have been reports of medicinal product interactions with the concomitant use of MAO inhibitors and sympathomimetic medicinal products. In view of the MAO inhibitory activity of safinamide, concomitant administration of Xadago® and sympathomimetics such as those present in nasal and oral decongestants or cold medicinal products containing ephedrine or pseudoephedrine, requires caution.

Dextromethorphan

There have been reports of medicinal product interactions with the concomitant use of dextromethorphan and non-selective MAO inhibitors. In view of the MAO inhibitory activity of safinamide, concomitant administration of Xadago® and dextromethorphan is not recommended. Use caution if concomitant treatment is necessary.

Serotonergic medications

Serious adverse reactions have been reported with the concomitant use of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic/tetracyclic antidepressants and MAO inhibitors, such as hypertensive crisis (high blood pressure, collapse), neuroleptic malignant syndrome (confusion, sweating, muscle rigidity, hyperthermia, CPK increase), serotonin syndrome (confusion, hypertension, muscle stiffness, hallucinations), and hypotension.

In view of the selective and reversible MAO-B inhibitory activity of safinamide, if concomitant treatment is necessary these medicinal products should be used at the lowest doses necessary, with caution for serotoninergic symptoms.

A washout period corresponding to five (5) half-lives of the SSRI used previously should be considered prior to initiating treatment with Xadago®.

Substrates of breast cancer resistance protein (BCRP)

Safinamide may transiently inhibit BCRP *in vitro*. In drug-drug interaction studies in humans, a weak interaction was observed with rosuvastatin (increases in rosuvastatin AUC between 1.25 and 2.00 fold were reported) but no significant interaction was found with diclofenac. It is recommended to monitor patients when safinamide is taken with medicinal products that are BCRP substrates (e.g. rosuvastatin, pitavastatin, pravastatin, ciprofloxacin, methotrexate, topotecan, diclofenac or glyburide).

OCT1 substrates

Safinamide inhibits OCT1 *in vitro* at clinically relevant portal vein concentrations. Therefore, caution is necessary when safinamide is taken concomitantly with medicinal products that are OCT1 substrates and have a Tmax similar to safinamide (2 hours) (e.g. metformin, aciclovir, ganciclovir) as exposure to these substrates might be increased as a consequence.

OAT3 inhibitors

The primary safinamide metabolite, 'safinamide acid' (NW-1153), is a substrate for OAT3 at clinically relevant concentrations. Medicinal products that are inhibitors of OAT3 given concomitantly with safinamide may reduce clearance of NW-1153, i.e., and thus may increase its systemic exposure. The systemic exposure of NW-1153 is low (1/10 of parent safinamide). This potential increase is most likely of no clinical relevance as NW-1153, the first product in the metabolic pathway, is further transformed to secondary and tertiary metabolites.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility studies in female rats showed reduced number of implantations and corpora lutea at exposures in excess of 3 times the anticipated human exposure. Male rats showed minor abnormal morphology and reduced speed of sperm cells at exposures in excess of 1.4 times the anticipated human exposure. Male rat fertility was not affected. The clinical relevance of these findings is unknown.

Use in pregnancy - Category B3

Xadago® should not be given during pregnancy. Women of childbearing potential should be advised not to become pregnant during safinamide therapy. Limited or no clinical data for safinamide on exposed pregnancies is available. Animal studies have shown reproductive toxicity when exposed to safinamide during pregnancy or lactation (see Section **5.3 PRECLINICAL SAFETY DATA**).

Use in lactation

Xadago® should not be used during breast feeding. Available pharmacodynamic/toxicological data in animals have shown excretion of safinamide in milk. In rat pups indirectly exposed to safinamide during the lactation period, skin discoloration, presumed to be caused by hyperbilirubinemia resulting from hepatobiliary toxicity, was observed. It is not known if safinamide is excreted in human milk. The potential relevance to humans in unknown; however risk to the breast-fed child cannot be excluded.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Somnolence and dizziness may occur during safinamide treatment. Patients treated with dopaminergic medications have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes has resulted in accidents. Patients may not perceive warning signs, such as excessive drowsiness, or they may report feeling alert immediately prior to the event.

Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with safinamide. If affected, patients must refrain from driving and using machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The overall safety profile of Xadago® is based on the clinical development program performed in over 3000 subjects, of whom over 500 were treated for more than 2 years.

Treatment Emergent Adverse Events (TEAEs) with an incidence of at least 2% in the Xadago® 100 mg/day and greater than placebo from the two pivotal, Phase III, randomised, double-blind, placebo-controlled, 26 week safinamide clinical trials (NW-016 and 27919 [SETTLE]) are presented in **Table 1**. The most common TEAEs associated with Xadago® treatment were dyskinesia, fall, nausea, and insomnia.

Table 1: Treatment Emergent Adverse Events with an Incidence ≥ 2% in the Xadago® 100 mg/day Group and Greater than Placebo

System Organ Class	Adverse Event Preferred Term	Xadago® 50 mg/day (N = 223) n (%)	Xadago® 100 mg/day (N = 498) n (%)	Placebo (N = 497) n (%)
Nervous System Disorders	Dyskinesia	47 (21.1)	87 (17.5)	44 (8.9)
Injury, Poisoning and Procedural Complication	Fall	8 (3.6)	31 (6.2)	19 (3.8)
Gastrointestinal Disorders	Nausea	7 (3.1)	28 (5.6)	21 (4.2)
	Dyspepsia	1 (0.4)	10 (2.0)	6 (1.2)
Psychiatric Disorders	Insomnia	3 (1.3)	20 (4.0)	12 (2.4)
Vascular Disorders	Orthostatic hypotension	5 (2.2)	10 (2.0)	7 (1.4)

The following adverse effects were reported from clinical trials performed with Xadago® and considered related to safinamide treatment.

Adverse effects are listed by MedDRA system organ class (SOC) and frequency very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Infections and infestations

Uncommon: Urinary Tract Infection

Rare: Bronchopneumonia, furuncle, nasopharyngitis, pyoderma, rhinitis, tooth infection, viral infection

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Uncommon: Basal Cell Carcinoma

Rare: Acrochordon, melanocytic naevus, seborrhoeic keratosis, skin papilloma

Blood and lymphatic system disorders

Uncommon: Anaemia, leukopenia, red blood cell abnormality

Rare: Eosinophilia, lymphopenia

Metabolism and nutrition disorders

Uncommon: Decreased appetite, hypertriglyceridaemia, increased appetite, hypercholesterolaemia, hyperglycaemia

Rare: Cachexia, hyperkalaemia

Psychiatric disorders

Common: Insomnia

Uncommon: Hallucination, depression, abnormal dreams, anxiety, confusional state, affect lability, libido increased, psychotic disorder, restlessness, sleep disorder

Rare: Compulsions, delirium, disorientation, illusion, impulsive behaviour, loss of libido, obsessive thoughts, paranoia, premature ejaculation, sleep attacks, social phobia, suicidal ideation

Nervous system disorders

Common: Dyskinesia, somnolence, dizziness, headache, Parkinson's disease

Uncommon: Paraesthesia, balance disorder, hypoaesthesia, dystonia, head discomfort, dysarthria, syncope, cognitive disorder

Rare: Coordination abnormal, disturbance in attention, dysgeusia, hyporeflexia, radicular pain, Restless Legs Syndrome, sedation

Eye Disorders

Common: Cataract

Uncommon: Vision blurred, scotoma, diplopia, photophobia, retinal disorder, conjunctivitis, glaucoma

Rare: Amblyopia, chromatopsia, diabetic retinopathy, erythropsia, eye haemorrhage, eye pain, eyelid oedema, hypermetropia, keratitis, lacrimation increased, night blindness, papilloedema, presbyopia, strabismus

Ear and Labyrinth disorders

Uncommon: Vertigo

Cardiac disorders

Uncommon: Palpitations, tachycardia, sinus bradycardia, arrhythmia

Rare: Myocardial infarction

Vascular disorders

Common: Orthostatic hypotension

Uncommon: Hypertension, hypotension, varicose vein

Rare: Arterial spasm, arteriosclerosis, hypertensive crisis

Respiratory, thoracic and mediastinal disorders

Uncommon: Cough, dyspnoea, rhinorrhoea

Rare: Bronchospasm, dysphonia, oropharyngeal pain, oropharyngeal spasm

Gastrointestinal disorders

Common: Nausea

Uncommon: Constipation, dyspepsia, vomiting, dry mouth, diarrhoea, abdominal pain, gastritis, flatulence, abdominal distension, salivary hypersecretion, gastrooesophageal reflux disease, aphthous stomatitis

Rare: Peptic ulcer, retching, upper gastrointestinal haemorrhage

Hepatobilary disorders

Rare: Hyperbilirubinaemia

Skin and subcutaneous tissue disorders

Uncommon: Hyperhidrosis, pruritus generalised, photosensitivity reaction, erythema

Rare: Alopecia, blister, dermatitis contact, dermatosis, ecchymosis, lichenoid keratosis, night sweats, pain of skin, pigmentation disorder, psoriasis, seborrhoeic dermatitis

Musculoskeletal and connective tissue disorders

Uncommon: Back pain, arthralgia, muscle spasms, muscle rigidity, pain in extremity, muscular weakness, sensation of heaviness

Rare: Ankylosing spondylitis, flank pain, joint swelling, musculoskeletal pain, myalgia, neck pain, osteoarthritis, synovial cyst

Renal and urinary disorders

Uncommon: Nocturia, dysuria

Rare: Micturition urgency, polyuria, pyuria, urinary hesitation

Reproductive system and breast disorders

Uncommon: Erectile dysfunction

Rare: Benign prostatic hyperplasia, breast disorder, breast pain

General disorders and administration site conditions

Uncommon: Fatigue, asthenia, gait disturbance, oedema peripheral, pain, feeling hot

Rare: Drug effect decreased, drug intolerance, feeling cold, malaise, pyrexia, xerosis

Investigations

Uncommon: Weight decreased, weight increased, blood creatine phosphokinase increased, blood triglycerides increased, blood glucose increased, blood urea increased, blood alkaline phosphatase increased, blood bicarbonate increased, blood creatinine increased, electrocardiogram QT prolonged, liver function test abnormal, urine analysis abnormal, blood pressure increased, blood pressure decreased, ophthalmic diagnostic procedures abnormal

Rare: Blood calcium decreased, blood potassium decreased, blood cholesterol decreased, body temperature increased, cardiac murmur, cardiac stress test abnormal, haematocrit decreased, haemoglobin decreased, international normalised ratio decreased, lymphocyte count decreased, platelet count decreased, very low density lipoprotein increased

Injury, poisoning and procedural complications

Common: Fall

Uncommon: Foot Fracture

Rare: Contusion, fat embolism, head injury, mouth injury, skeletal injury

Social Circumstances

Rare: Gambling

Post-Marketing Data

In addition to adverse events reported in clinical trials, the following adverse reactions have been identified during post-approval of use of Xadago®. As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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.

Adverse Event Reporting

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems

4.9 OVERDOSE

The expected pattern of events or symptoms following intentional or accidental overdose with Xadago® would be those related to its pharmacodynamic profile: MAO-B inhibition with activity-dependent inhibition of Na+ channels. The symptoms of an excessive MAO-B inhibition (increase in dopamine level) could include hypertension, postural hypotension, hallucinations, agitation, nausea, vomiting, and dyskinesia.

There is no known antidote to safinamide or any specific treatment for a safinamide overdose. If an important overdose should occur, Xadago® treatment should be discontinued and supportive treatment should be administered as clinically indicated.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Safinamide is an α-aminoamide derivative that acts through both dopaminergic and non-dopaminergic mechanisms of action. Safinamide is a highly selective and reversible monoamine oxidase B (MAO-B) inhibitor that causes an increase in extracellular levels of dopamine in the striatum. MAO-B is inhibited with more than 1000-fold selectivity over MAO-A. In clinical studies, complete inhibition (>90%) of MAO-B was measured at doses >20 mg. Safinamide is also associated with state- and use- dependent inhibition of voltage-gated sodium (Na^+) channels, calcium (Ca^{2+}) channel modulation and inhibition of glutamate release. An excess of glutamate has been identified to contribute to neuronal death in the substantia nigra as well as to the genesis of motor fluctuations in Parkinson's disease. In *in-vivo* rat models, safinamide reduced striatal glutamatergic hyperactivity. It is unknown whether these mechanisms are relevant to use in humans.

Clinical trials

The efficacy of Xadago® as an add-on therapy to a stable dose of levodopa (L-dopa), alone or in combination with other PD medications, was established in two pivotal, Phase III, randomised, double-blind, placebo-controlled, multi-centre clinical trials conducted over 26 weeks (NW-016 and 27919 [SETTLE]). Long term efficacy was established in a Phase III, double-blind, placebo-controlled, 18-month (78-week) extension to NW-016 (NW-018). Clinical trials of safinamide as add-on therapy to a single dopamine agonist have also been performed, however efficacy results were inconclusive.

In NW-016 and SETTLE, the primary efficacy measure was the change (increase) in daily ON time without troublesome dyskinesia from baseline to endpoint, based on 18-hour diaries that were completed for at least 3 days before assessment. ON time was defined as time when PD medication was providing benefit with regard to mobility, slowness and stiffness. Secondary efficacy parameters included change in OFF time; Unified Parkinson's Disease Rating Scale (UPDRS) section III – Motor Examination

Changes in non-motor symptoms, including UPDRS section II - Activities of Daily Living and PD Questionnaire (PDQ-39), which measures eight dimensions of health: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily pain were also assessed.

In NW-016 patients were randomly assigned to receive safinamide, 50 mg (n=223) or 100 mg per day, (n=224), or placebo (n=222). At baseline the patients' mean duration of PD was approximately 8 years (range 0 to 27.3 years), Hoehn and Yahr stage was similar in both the safinamide and placebo groups (mean 2.8, range 1.0 to 4.0) and average daily OFF time was approximately 5 hours (range 0 to 13 hours). Patients were taking 4-10 levodopa doses per day and the mean daily dose was 605 mg. Other PD medicinal products were concomitantly taken by the following percentage of patients: DA-Agonists (60.8%), COMT-inhibitors (24.4%), Anticholinergic (37.1%) and Amantadine (13.9%).

In SETTLE patients were randomly assigned to receive safinamide, (n=274) or placebo (n=275). Treatment in the safinamide group started at 50 mg/day; in the majority of patients the daily dose was increased to 100

mg/day after two weeks. At baseline the patients' mean duration of PD was approximately 9 years (range 0 to 31 years), Hoehn and Yahr stage was similar in the both the safinamide and placebo groups (mean 2.5, range 1.0 to 4.0). Average daily OFF time was approximately 5.3 hours (range 0 to 12.5 hours). Patients were taking 3-10 levodopa doses per day and the mean daily dose of L-dopa was 777 mg. Other PD medicinal products were concomitantly taken by the following percentage of patients: DA-Agonists (74.3%), COMT-inhibitors (17.9%), Anticholinergic (17.3%) and Amantadine (30.2%).

In both studies, safinamide treatment significantly increased ON time without troublesome dyskinesia compared to placebo treatment (**Table 2**). The time course of improvement in mean daily ON time showed greater improvement with Xadago® compared to baseline at all post-baseline time-points (Figure 1 and 2). In addition data from NW-018, the 18-month (78-week) extension to NW-016, show that improvement in ON time was maintained long-term (Figure 1).

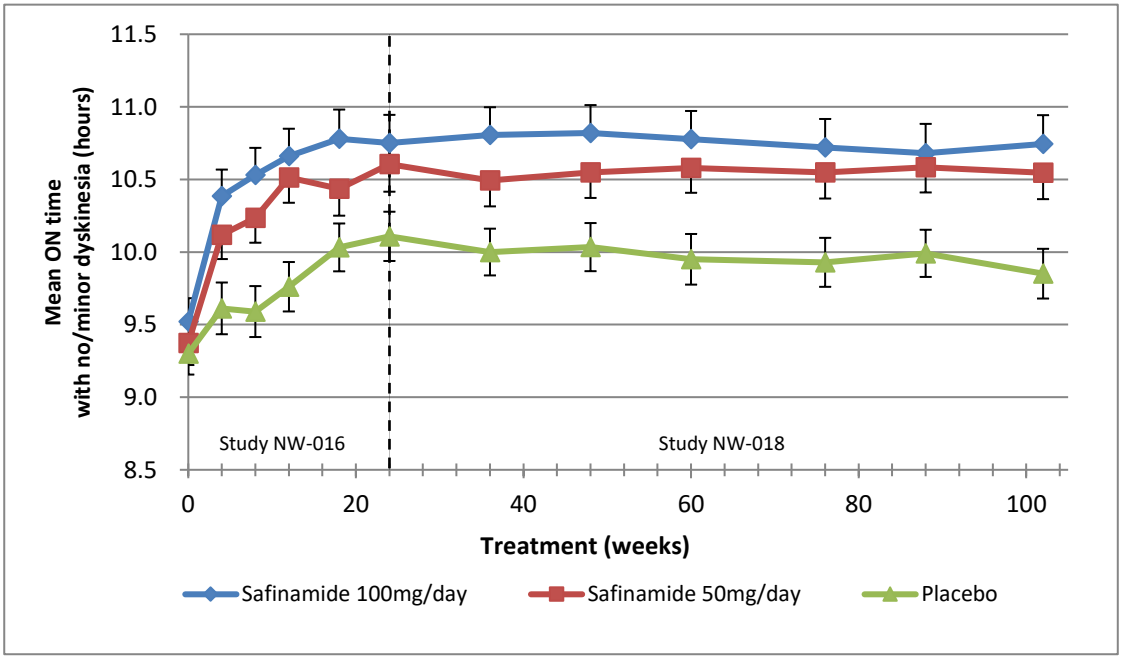


Figure 1: **Mean daily ON time with no/minor dyskinesia from NW-016 study baseline to end of NW-018 (18 month extension study)**

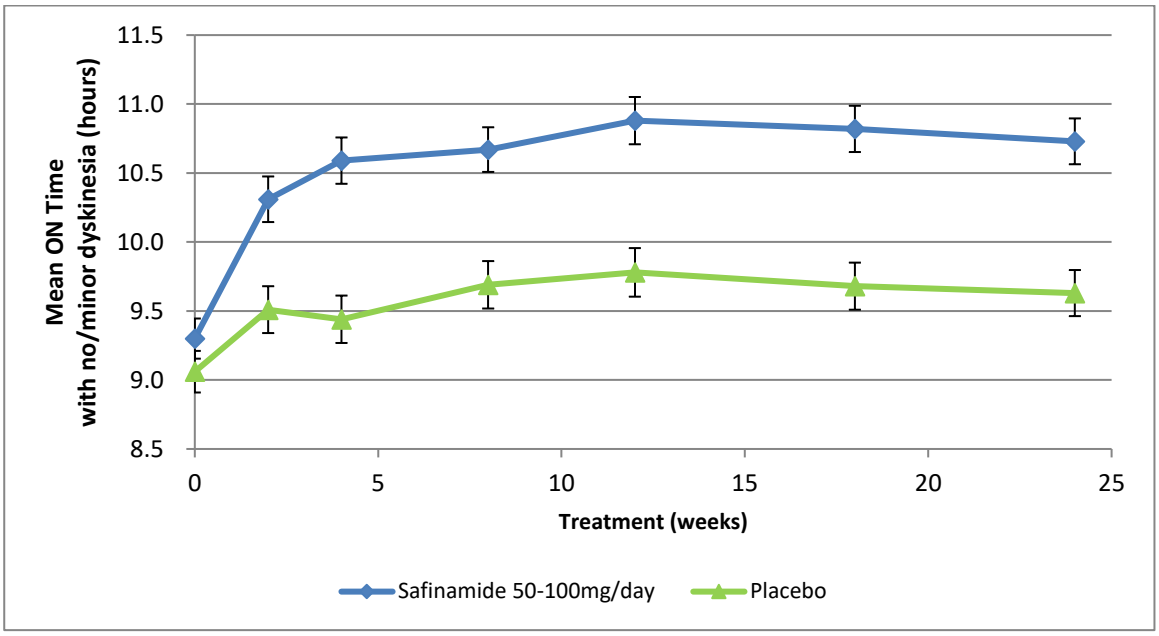


Figure 2: Mean daily ON time with no/minor dyskinesia from SETTLE study baseline to end

In NW-016, mean (SD) change in daily ON time without troublesome dyskinesia after 24 weeks (6 months) was +1.37 (SD: 2.745) hours for safinamide 50 mg/day, +1.36 (2.625) hours for safinamide 100 mg/day and +0.97 (2.375) hours for placebo (least-squares mean difference: 50 mg/day safinamide: +0.51 hours, 95% CI, 0.07-0.94 hours; p = 0.0223; 100 mg/day safinamide: +0.55 hours, 95% CI, 0.12-0.99, p = 0.0130). The increase in daily ON time without troublesome dyskinesia for both safinamide doses compared to placebo was maintained at the end of NW-018, the 18-month extension to NW-016; compared to baseline, the mean (SD) daily change in ON time after 2 years was +1.15 (SD: 2.75) hours for safinamide 50 mg/day; +1.19 (2.88) hours for safinamide 100 mg/day, and +0.56 (2.51) hours for placebo (least-squares mean difference: 50 mg/day safinamide: +0.67 hour, 95% CI, 0.23-1.11 hours; p = 0.0031; 100 mg/day safinamide: +0.83 hour, 95% CI, 0.39-1.27, p = 0.0002).

In SETTLE, mean (SD) change in daily ON time without troublesome dyskinesia after 24 weeks (6 months) was +1.42 (2.80) hours for safinamide, from a baseline of 9.30 (2.41) hours, compared to +0.57 (2.47) hours for placebo, from a baseline of 9.06 (2.50) hours (least-squares mean difference, 0.96 hour; 95% CI, 0.56-1.37 hours; p < 0.001). In both NW-016 and SETTLE the increase in ON time was accompanied by a similar significant reduction in OFF time and a reduction in UPDRS section III - Motor Examination score assessed during ON time (**Table 2**).

Assessment of non-motor symptoms in clinical studies demonstrated a reduction (improvement) in UPDRS section II – Activities of daily living; the difference was statistically significant compared to placebo in NW-016 and NW-018 (100 mg/day safinamide group) (p=0.0060 and p=0.0068) (**Table 2**).

The PDQ-39 questionnaire summary index score showed a greater improvement for safinamide compared with placebo. This difference was statistically significant compared to placebo in SETTLE (p = 0.006) and for the 100mg/day safinamide group in NW-016(p=0.0360) and NW-018 (p=0.0195) (**Table 2**).

Table 2: Efficacy Assessments – Xadago® as Add-on to Levodopa ITT Population

	NW-016 24 weeks			016/018 2 years			27919 (SETTLE) 24 weeks	
	Placebo	Safinamide (mg/day)		Placebo	Safinamide (mg/day)		Placebo	Safinamide mg/day
		50	100		50	100		50-100
Randomised (n)	222	223	224	222	223	224	275	274
Age (years)	59.4 (9.41)	60.1 (9.65)	60.1 (9.19)	59.9 (9.36)	60.6 (9.64)	60.5 (9.15)	62.1 (8.9)	61.7 (9.0)
PD Duration (years)	8.29 (3.759)	7.94 (3.910)	8.15 (3.788)	8.83 (3.775)	8.50 (3.902)	8.70 (3.800)	9.0 (4.9)	8.9 (4.4)
ON time without troublesome dyskinesia (hours)								
Baseline	9.30 (2.155)	9.37 (2.259)	9.52 (2.426)	9.30 (2.155)	9.37 (2.259)	9.52 (2.426)	9.06 (2.50)	9.30 (2.41)
Change from Baseline LS Mean (SE)	0.72 (n/a)	1.23 (n/a)	1.28 (n/a)	0.34 (n/a)	1.01 (n/a)	1.18 (n/a)	0.56 (0.15)	1.52 (0.15)
LS Diff v Placebo	-	0.51	0.55	-	0.67	0.83	-	0.96 (0.21)
95% CI	-	[0.07, 0.94]	[0.12, 0.99]	-	[0.23, 1.11]	[0.39, 1.27]	-	[0.56, 1.37]
p-value	-	0.0223[a]	0.0130[a]	-	0.0031[c]	0.0002[c]	-	<0.001[d]
OFF time (hours)								
Baseline	5.3 (2.06)	5.2 (2.08)	5.2 (2.16)	5.3 (2.06)	5.2 (2.08)	5.2 (2.16)	5.38 (2.01)	5.34 (1.97)
Change from Baseline LS Mean (SE)	-0.7 (n/a)	-1.3 (n/a)	-1.3 (n/a)	-0.74 (n/a)	-1.36 (n/a)	-1.49 (n/a)	-0.62 (0.14)	-1.65 (0.14)
LS Diff v Placebo	-	-0.6	-0.6	-	-0.62	-0.75	-	-1.03 (0.19)
95% CI	-	[-0.9, -0.2]	[-1.0, -0.2]	-	[-0.98, -0.25]	[-1.11, -0.38]	-	[-1.40, -0.67]
p-value	-	0.0043[b]	0.0034[b]	-	0.0011[c]	< 0.0001[c]	-	<0.001[d]

UPDRS III - Motor Examination (while ON): decrease indicates improvement of PD symptoms								
Baseline	28.7 (12.02)	27.3 (12.66)	28.3 (13.30)	28.7 (12.02)	27.3 (12.66)	28.3 (13.30)	23.05 (12.65)	22.26 (11.66)
Change from Baseline LS Mean (SE)	-4.3 (n/a)	-6.1 (n/a)	-6.9 (n/a)	-3.94 (n/a)	-4.98 (n/a)	-6.06 (n/a)	-1.70 (0.46)	-3.52 (0.46)
LS Diff v Placebo	-	-1.8	-2.6	-	-1.05	-2.13	-	-1.82 (0.61)
95% CI	-	[-3.3, -0.4]	[-4.1, -1.1]	-	[-2.58, 0.48]	[-3.65, -0.60]	-	[-3.01, -0.62]
p-value	-	0.0138[b]	0.0006[b]	-	0.1791[b]	0.0063[b]	-	0.003[d]
UPDRS II - Activities of Daily Living (while ON): *decrease indicates improvement of PD symptoms*								
Baseline	12.3 (5.92)	11.8 (5.66)	12.1 (5.82)	12.3 (5.92)	11.8 (5.66)	12.1 (5.82)	10.43 (6.29)	9.97 (5.53)
Change from Baseline LS Mean (SE)	-1.2 (n/a)	-1.7 (n/a)	-2.2 (n/a)	-0.91 (n/a)	-1.43 (n/a)	-1.97 (n/a)	-0.79 (0.23)	-1.22 (0.23)
LS Diff v Placebo	-	-0.5	-1.0	-	-0.52	-1.06	-	-0.43 (0.30)
95% CI	-	[-1.2, 0.2]	[-1.7, -0.3]	-	[-1.29, 0.25]	[-1.83, -0.29]	-	[-1.02, 0.16]
p-value	-	0.1253[b]	0.0060[b]	-	0.1857[b]	0.0068[b]	-	0.149[d]
PDQ-39 - Parkinson's Disease Questionnaire								
Change from Baseline LS Mean (SE)	-11.9	-16.4	-28.4	-13.65	-24.12	-32.01	-0.68 (10.51)	-3.17 (10.86)
LS Diff v Placebo	-	-4.6	-16.5	-	-10.48	-18.36	-	-2.33
95% CI	-	[-20.0,10.9]	[-31.9,-1.1]	-	[-25.94,4.98]	[-33.75, -2.97]	-	(-3.98, -0.68)
p-value	-	0.5603[g]	0.0360[g]	-	0.1837[h]	0.0195[h]	-	0.006[e]

Abbreviations: LS, least squares; SD, standard deviation; PD, Parkinson's Disease; CI, Confidence interval; SE, Standard Error

[a] Target dose of 10 0mg/day; [b] Treatments were compared using a repeated measures model, based upon the change from Baseline, [c] Treatments compared using an ANCOVA with terms for treatment and centre and Baseline as a covariate. [d] Treatments compared using an ANCOVA, [e] Parametric ANCOVA model is based on the change from baseline to endpoint with fixed effects for treatment, region, and baseline value as a covariate. [f] Treatments compared with placebo using an ANCOVA with the model containing Baseline, treatment, and pooled centre. [g] Treatments were compared using an ANCOVA with baseline as a covariate and treatment and centre and main effects. [h] Treatments were compared using an ANCOVA model on change from baseline with model containing baseline, pooled centre, and treatment.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Safinamide is rapidly absorbed after single and multiple oral dosing under fasting conditions; Tmax is reached 1.8-2.8 h after dosing. Absolute bioavailability is high (95%), showing that safinamide is almost completely absorbed after oral administration and first pass metabolism is negligible. The high absorption classifies safinamide as a highly permeable substance.

Food Effect

A slight delay in Tmax was observed in the fed state relative to the fasted condition, but there was no effect on safinamide $AUC_{0-\infty}$ or Cmax. Xadago® may be administered with or without food.

Patients with Hepatic Impairment

Safinamide exposure in patients with mild hepatic impairment increased marginally (30% in AUC). In patients with moderate hepatic impairment, safinamide exposure increased by approximately 80% (see **4.3 CONTRAINDICATIONS** and **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Patients with Renal Impairment

Safinamide exposure was comparable in patients with moderate or severe renal impairment and patients with normal renal function. The pharmacokinetics of safinamide are not affected by impaired renal function.

Distribution

The volume of distribution (Vss) is approximately 165 L which is 2.5-fold of body volume indicating extensive extravascular distribution of safinamide. Total clearance was determined to be 4.6 L/h classifying safinamide as a low clearance substance. Plasma protein binding of safinamide is 88-90%.

Metabolism

In humans, safinamide is almost exclusively eliminated via metabolism (~5% of the drug is eliminated unchanged, mainly in urine), through three main metabolic pathways. One pathway involves hydrolytic oxidation of the amide moiety leading to the primary metabolite 'safinamide acid' (NW-1153). Another pathway is oxidative cleavage of the ether bond forming 'Odebenzylated safinamide' (NW-1199). Finally, the 'N-dealkylated acid' (NW-1689) is formed by oxidative cleavage of the amine bond of either safinamide or the primary safinamide acid metabolite (NW-1153). The 'N-dealkylated acid' (NW-1689) undergoes further conjugation with glucuronic acid yielding its acyl glucuronide. NW-1689 is the main circulating metabolite in human plasma, exceeding the exposure of the parent (161% of parent). NW-1689 AG and NW-1153 account for about 18% and 11% of the parent drug exposure, respectively. None of the metabolites has pharmacological activity.

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

Safinamide does not appear to significantly induce or inhibit enzymes at clinically relevant systemic concentrations. *In vitro* metabolism studies have indicated that there is no meaningful induction or inhibition of cytochrome P450, CYP2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A3/5 at concentrations which are relevant (Cmax of free safinamide 0.4 µM at 100 mg/day) in man. Dedicated drug-drug interaction studies performed with ketoconazole, L-dopa and CYP1A2 and CYP3A4 substrates (caffeine and midazolam), did not detect any clinically significant effects on the pharmacokinetics of safinamide, or L-dopa, caffeine and midazolam.

Excretion

Safinamide undergoes almost complete metabolic transformation and the primary route of excretion is through the kidney. After oral administration of ^{14}C-labelled safinamide, substance-related radioactivity was excreted in urine (76%) and to a low extent in faeces (1.5%) after 192 hours. The terminal elimination half-life of total radioactivity was approximately 80 hours.

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

There was no effect on the clearance of safinamide in patients with Parkinson's disease (PD) receiving safinamide as add on therapy to chronic levodopa (L-Dopa) and/or Dopamine Agonists (DA-Agonists).

Linearity/non-linearity

The pharmacokinetics of safinamide are linear after single and repeated doses. No time-dependency was observed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Safinamide was negative for genotoxicity in *in vitro* (Ames, mouse lymphoma) and *in vivo* (mouse micronucleus) assays.

Carcinogenicity

Carcinogenicity studies were conducted for up to two years in mice and rats, at doses of 50, 100 and 200 mg/kg/day and 25, 50 and 100 mg/kg/day, respectively. Study results showed no evidence of tumorigenic potential related to safinamide at systemic exposures up to 2.8 to 3.5 times respectively, the anticipated systemic exposure (based on AUC) in patients given the maximal therapeutic dose.

Retinal Degeneration

Retinal degeneration and loss of photoreceptor cells were observed in albino and pigmented rats administered safinamide orally in toxicity studies of between 2 weeks and 6 months duration. In albino rats administered safinamide orally for two years, retinal scarring and cataracts were observed at all doses tested. No retinal degeneration was noted in monkeys, despite higher systemic exposure than in rodents.

Embryofoetal Studies

Foetal abnormalities have been observed in rats following oral administration of safinamide (0, 50, 100 or 150 mg/kg/day) throughout organogenesis. The lowest dose tested is approximately twice that of the maximum recommended human dose (MRHD) on an AUC basis. When safinamide was administered to

pregnant rats in combination with levodopa/carbidopa (80/20 mg/kg/day), the dose causing developmental toxicity was lower than when safinamide was administered by itself (25 mg/kg/day).

No development toxicity was observed in rabbits up to the highest oral dose of safinamide tested (100 mg/kg/day). However, when safinamide was administered in combination with levodopa/carbidopa there was an increased incidence of embryofoetal death and cardiac and skeletal malformations.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose, crospovidone, magnesium stearate, colloidal anhydrous silica, Opadry complete film coating system 02F59058 Clear (PING # 111420), Candurin Orange amber (PING # 106848) and Candurin Gold sheen (PING # 106846).

Safinamide mesilate is a white to off-white crystalline powder. Safinamide mesilate is freely soluble in water, methanol and dimethyl sulfoxide. Safinamide mesilate is sparingly soluble in ethanol and is practically insoluble in ethyl acetate. In aqueous buffers that span a pH range of 1.2 to 7.5, safinamide mesilate is highly soluble at pH 1.2 and 4.5, but shows low solubility (<0.4 mg/mL) at pH 6.8 and 7.5.

6.2 INCOMPATIBILITIES

See **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

6.3 SHELF LIFE

Four (4) years.

The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

Xadago® tablets are supplied in PVC/PVDC/Aluminium blister packs containing 30 tablets. A starter pack containing 10 tablets may also be available.

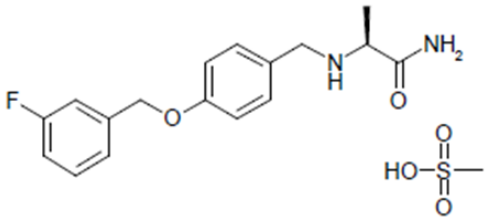
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The molecular formula of safinamide mesilate is C17H19FN2O2•CH4O3S, the molecular weight is 398.45 g/mol and the chemical structure is:



CAS number

The chemical abstracts service (CAS) registry number of safinamide mesilate is 202825-46-5

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (S4): Prescription Only Medicine

8. SPONSOR

Atnahs Pharma Australia Pty Ltd
Level 10 / 10 Shelley Street,
Sydney, NSW, 2000, Australia
Ph: 1800 899 005

9. DATE OF FIRST APPROVAL

2 November 2018

10. DATE OF REVISION

6 March 2025

Section changed	Summary of new information
4.8	Details of Sponsor changed from Seqirus to Atnahs.

Xadago is a registered trademark of Zambon S.p.A.

Under Licence from Newron Pharmaceuticals S.p.A