

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Xadago 50 mg film-coated tablets  
Xadago 100 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### Xadago 50 mg film-coated tablets

Each film-coated tablet contains safinamide methanesulfonate equivalent to 50 mg safinamide.

### Xadago 100 mg film-coated tablets

Each film-coated tablet contains safinamide methanesulfonate equivalent to 100 mg safinamide.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

### Xadago 50 mg film-coated tablets

Orange to copper, round, biconcave, film-coated tablet of 7 mm diameter with metallic gloss, embossed with the strength “50” on one side of the tablet.

### Xadago 100 mg film-coated tablets

Orange to copper, round, biconcave, film-coated tablet of 9 mm diameter with metallic gloss, embossed with the strength “100” on one side of the tablet.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Xadago is indicated 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.

### 4.2 Posology and method of administration

#### Posology

Treatment with safinamide should be started at 50 mg per day. This daily dose may be increased to 100 mg/day on the basis of individual clinical need.

If a dose is missed the next dose should be taken at the usual time the next day.

#### *Elderly*

No change in dose is required for elderly patients.

Experience of use of safinamide in patients over 75 years of age is limited.

#### *Hepatic impairment*

Safinamide use in patients with severe hepatic impairment is contraindicated (see section 4.3). No dose adjustment is required in patients with mild hepatic impairment. The lower dose of 50 mg/day is recommended for patients with moderate hepatic impairment. If patients progress from moderate to severe hepatic impairment safinamide should be stopped (see section 4.4).

#### *Renal impairment*

No change in dose is required for patients with renal impairment.

#### *Paediatric population*

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

#### Method of administration

For oral use.

Safinamide should be taken with water.

Safinamide may be taken with or without food.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

Concomitant treatment with other monoamine oxidase (MAO) inhibitors (see sections 4.4 and 4.5).

Concomitant treatment with pethidine (see sections 4.4 and 4.5).

Use in patients with severe hepatic impairment (see section 4.2).

Use in patients with albinism, retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy (see sections 4.4 and 5.3).

### **4.4 Special warnings and precautions for use**

#### General warning

In general, safinamide may be used with selective serotonin re-uptake inhibitors (SSRIs) at the lowest effective dose, with caution for serotonergic symptoms. In particular, the concomitant use of safinamide and fluoxetine or fluvoxamine should be avoided, or if concomitant treatment is necessary these medicinal products should be used at low doses (see section 4.5). A washout period corresponding to 5 half-lives of the SSRI used previously should be considered prior to initiating treatment with safinamide.

At least 7 days must elapse between discontinuation of safinamide and initiation of treatment with MAO inhibitors or pethidine (see section 4.3 and 4.5).

When safinamide is co-administered with products that are BCRP substrates, please refer to the SmPC for that particular medicinal product.

#### Hepatic impairment

Caution should be exercised when initiating treatment with safinamide in patients with moderate hepatic impairment. In case patients progress from moderate to severe hepatic impairment, treatment with safinamide should be stopped (see sections 4.2, 4.3 and 5.2).

#### Potential for retinal degeneration in patients with prior history of retinal disease

Safinamide 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 sections 4.3 and 5.3.

#### Impulse control disorders (ICDs)

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

Patients and carers should be made aware of the behavioural symptoms of ICDs that were observed in patients treated with MAO-inhibitors, including cases of compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying.

#### Dopaminergic side effects

Safinamide used as an adjunct to levodopa may potentiate the side effects of levodopa, and pre-existing dyskinesia may be exacerbated, requiring a decrease of levodopa. This effect was not seen when safinamide was used as an adjunct to dopamine agonists in early stage PD patients.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### *In vivo and in vitro pharmacodynamic drug interactions*

##### *MAO inhibitors and pethidine*

Safinamide must not be administered along with other MAO inhibitors (including moclobemide) as there may be a risk of non-selective MAO inhibition that may lead to a hypertensive crisis (see section 4.3).

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 safinamide and pethidine is contraindicated (see section 4.3).

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 safinamide and sympathomimetics, such as those present in nasal and oral decongestants or cold medicinal products containing ephedrine or pseudoephedrine, requires caution (see section 4.4).

##### *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, the concomitant administration of safinamide and dextromethorphan is not recommended, or if concomitant treatment is necessary, it should be used with caution (see section 4.4).

##### *Antidepressants*

The concomitant use of safinamide and fluoxetine or fluvoxamine should be avoided (see section 4.4), this precaution is based on the occurrence of serious adverse reactions (e.g. serotonin syndrome), although rare, that have occurred when SSRIs and dextromethorphan have been used with MAO inhibitors. If necessary, the concomitant use of these medicinal products should be at the lowest effective dose. A washout period corresponding to 5 half-lives of the SSRI used previously should be considered prior to initiating treatment with safinamide.

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 (see section 4.4). In view of the selective and reversible MAO-B inhibitory activity of safinamide, antidepressants may be administered but used at the lowest doses necessary.

#### In vivo and in vitro pharmacokinetic drug interactions

Safinamide may transiently inhibit BCRP *in vitro*. In drug-drug-interaction studies in human, a weak interaction was observed with rosuvastatin (AUC increase between 1.25 and 2.00 fold) but no significant interaction was found with diclofenac.

It is recommended to monitor patients when safinamide is taken with medicinal products that are BCRP substrates (e.g., rosuvastatin, pitavastatin, pravastatin, ciprofloxacin, methotrexate, toptecan, diclofenac or glyburide) and to refer to their SmPCs to determine if a dose adjustment is needed.

Safinamide is almost exclusively eliminated via metabolism, largely by high capacity amidases that have not yet been characterized. Safinamide is eliminated mainly in the urine. In human liver microsomes (HLM), the N-dealkylation step appears to be catalysed by CYP3A4, as safinamide clearance in HLM was inhibited by ketoconazole by 90%.

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  $t_{max}$  similar to safinamide (2 hours) (e.g. metformin, aciclovir, ganciclovir) as exposure to these substrates might be increased as a consequence.

The metabolite 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.

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Women of childbearing potential

Safinamide should not be given to women of childbearing potential unless adequate contraception is practiced.

#### Pregnancy

There are no or limited amount of data from the use of safinamide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Xadago is not recommended during pregnancy and in women of childbearing potential not using contraception.

#### Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of safinamide in milk (for details see 5.3).

A risk for the breast-fed child cannot be excluded. Xadago should not be used during breast-feeding.

## Fertility

Animal studies indicate that safinamide treatment is associated with adverse reactions on female rat reproductive performance and sperm quality. Male rat fertility is not affected (see section 5.3).

### **4.7 Effects on ability to drive and use machines**

Somnolence and dizziness may occur during safinamide treatment, therefore patients should be cautioned about using hazardous machines, including motor vehicles, until they are reasonably certain that safinamide does not affect them adversely.

### **4.8 Undesirable effects**

#### Summary of the safety profile

Dyskinesia was the most common adverse reaction reported in safinamide patients when used in combination with L-dopa alone or in combination with other PD treatments.

Serious adverse reactions are known to occur with the concomitant use of SSRIs, 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. With MAO-inhibitors there have been reports of drug interactions with concomitant use of sympathomimetic medicinal products.

Impulse control disorders; pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments.

#### Tabulated list of adverse reactions

The tabulation below includes all adverse reactions in clinical trials where adverse reactions were considered related.

Adverse reactions are ranked under headings of frequency using the following conventions: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

<b>System Organ Class</b>	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>
Infections and infestations			Urinary tract infection	Bronchopneumonia, furuncle, nasopharyngitis, pyoderma, rhinitis, tooth infection, viral infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Basal cell carcinoma	Acrochordon, melanocytic naevus, seborrhoeic keratosis, skin papilloma
Blood and lymphatic system disorders			Anaemia, leukopenia, red blood cell	Eosinophilia, lymphopenia

System Organ Class	Very common	Common	Uncommon	Rare
			abnormality	
Metabolism and nutrition disorders			Decreased appetite, hypertriglyceridaemia, increased appetite, hypercholesterolaemia, hyperglycaemia,	Cachexia, hyperkalaemia
Psychiatric disorders		Insomnia	Hallucination, depression, abnormal dreams, anxiety, confusional state, affect lability, libido increased, psychotic disorder, restlessness, sleep disorder	Compulsions, delirium, disorientation, illusion, impulsive behaviour, loss of libido, obsessive thoughts, paranoia, premature ejaculation, sleep attacks, social phobia, suicidal ideation
Nervous system disorders		Dyskinesia somnolence, dizziness, headache, Parkinson's disease	Paraesthesia, balance disorder, hypoaesthesia, dystonia, head discomfort, dysarthria, syncope, cognitive disorder	Coordination abnormal, disturbance in attention, dysgeusia, hyporeflexia, radicular pain, Restless Legs Syndrome, sedation
Eye disorders		Cataract	Vision blurred, scotoma, diplopia, photophobia, retinal disorder, conjunctivitis, glaucoma	Amblyopia, chromatopsia, diabetic retinopathy, erythroptosis, eye haemorrhage, eye pain, eyelid oedema, hypermetropia, keratitis, lacrimation increased, night blindness, papilloedema, presbyopia, strabismus
Ear and labyrinth disorders			Vertigo	
Cardiac disorders			Palpitations, tachycardia, sinus bradycardia, arrhythmia	Myocardial infarction
Vascular disorders		Orthostatic hypotension	Hypertension, hypotension, varicose vein	Arterial spasm, arteriosclerosis, hypertensive crisis
Respiratory, thoracic and mediastinal			Cough, dyspnoea, rhinorrhoea	Bronchospasm, dysphonia, oropharyngeal pain,

<b>System Organ Class</b>	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>
disorders				oropharyngeal spasm
Gastrointestinal disorders		Nausea	Constipation, dyspepsia, vomiting, dry mouth, diarrhoea, abdominal pain, gastritis, flatulence, abdominal distension, salivary hypersecretion, gastrooesophageal reflux disease, aphthous stomatitis	Peptic ulcer, retching, upper gastrointestinal haemorrhage
Hepatobiliary disorders				Hyperbilirubinaemia
Skin and subcutaneous tissue disorders			Hyperhidrosis, pruritus generalised, photosensitivity reaction, erythema	Alopecia, blister, dermatitis contact, dermatosis, ecchymosis, lichenoid keratosis, night sweats, pain of skin, pigmentation disorder, psoriasis, seborrhoeic dermatitis
Musculoskeletal and connective tissue disorders			Back pain, arthralgia, muscle spasms, muscle rigidity, pain in extremity, muscular weakness, sensation of heaviness	Ankylosing spondylitis, flank pain, joint swelling, musculoskeletal pain, myalgia, neck pain, osteoarthritis, synovial cyst
Renal and urinary disorders			Nocturia, dysuria	Micturition urgency, polyuria, pyuria, urinary hesitation
Reproductive system and breast disorders			Erectile dysfunction	Benign prostatic hyperplasia, breast disorder, breast pain
General disorders and administration site conditions			Fatigue, asthenia, gait disturbance, oedema peripheral, pain, feeling hot	Drug effect decreased, drug intolerance, feeling cold, malaise, pyrexia, xerosis

System Organ Class	Very common	Common	Uncommon	Rare
Investigations			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	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		Fall	Foot fracture	Contusion, fat embolism, head injury, mouth injury, skeletal injury
Social circumstances				Gambling

#### Description of selected adverse reactions

Dyskinesia occurred early in treatment, was rated “severe”, led to discontinuation in very few patients (approx. 1.5%), and did not require reduction of dose in any patient.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via [the national reporting system listed in Appendix V](#).

## 4.9 Overdose

In one patient suspected of consuming more than the daily prescribed dose of 100 mg for one month, symptoms of confusion, sleepiness, forgetfulness and dilated pupils were reported. These symptoms resolved on discontinuing the medicinal product, without sequelae.

The expected pattern of events or symptoms following intentional or accidental overdose with Safinamide would be those related to its pharmacodynamic profile: MAO-B inhibition with activity-dependent inhibition of Na<sup>+</sup> 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 safinamide overdose. If an important overdose occurs, safinamide treatment should be discontinued and supportive treatment should be administered as clinically indicated.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Anti-Parkinson-Drugs, monoamine oxidase -B inhibitors, ATC code: N04BD03.

#### Mechanism of action

Safinamide acts through both dopaminergic and non-dopaminergic mechanisms of action. Safinamide is a highly selective and reversible MAO-B inhibitor causing an increase in extracellular levels of dopamine in the striatum. Safinamide is associated with state-dependent inhibition of voltage-gated sodium (Na<sup>+</sup>) channels, and modulation of stimulated release of glutamate. To what extent the non-dopaminergic effects contribute to the overall effect has not been established.

#### Pharmacodynamic effects

Population PK models developed from studies in patients with Parkinson's disease indicate that the pharmacokinetic and pharmacodynamics effects of safinamide were not dependent on age, gender, weight, renal function and exposure to levodopa, indicating that dose adjustments will not be required based on these variables.

Pooled analyses of adverse event data from placebo controlled studies in Parkinson's disease patients indicate that the concomitant administration of safinamide together with a broad category of commonly used medicinal products in this patient population (antihypertensive, beta-blockers, cholesterol lowering, non-steroidal anti-inflammatory medicinal products, proton pump inhibitors, antidepressants, etc.) was not associated with an increased risk for adverse events. Studies were not stratified for co-medication, and no randomized interaction studies were performed for these medicinal products.

#### Clinical efficacy

##### *Studies in mid- to late-stage PD patients*

The efficacy of safinamide as add-on treatment in mid-to late-stage PD (LSPD) patients with motor fluctuations, currently receiving L-dopa alone or in combination with other PD medicinal products, was evaluated in two double-blind, placebo-controlled studies: Study SETTLE (Study 27919; 50-100 mg/day; 24 weeks), and Study 016/018 (50 and 100 mg/day; 2-year, double-blind, placebo-controlled study).

The primary efficacy parameter was the change from baseline to endpoint in 'ON Time without troublesome dyskinesia'.

Secondary efficacy parameters included OFF Time, UPDRS II and III (Unified Parkinson's Disease Rating Scale – sections II and III), and CGI-C (Clinical Global Impression of Change)

Both the SETTLE and 016/018 studies indicated significant superiority of safinamide, compared to placebo, at the target doses of 50 and 100 mg/day for the primary, and selected secondary, efficacy

variables, as summarized in the table below. The effect on ON Time was maintained at the end of the 24-month double-blind treatment period for both safinamide doses as compared to placebo.

Study	016 (24 weeks)			016/018 (2 years)			27919 (SETTLE) (24 weeks)	
	Placebo	Safinamide		Placebo	Safinamide		Placebo	Safinamide
		50	100		50	100		50-100 (d)
<b>Dose (mg/day) (a)</b>								
<b>Randomized</b>	222	223	224	222	223	224	275	274
<b>Age (years) (b)</b>	59.4 (9.5)	60.1 (9.7)	60.1 (9.2)	59.4 (9.5)	60.1 (9.7)	60.1 (9.2)	62.1 (9.0)	61.7 (9.0)
<b>PD Duration (years) (b)</b>	8.4 (3.8)	7.9 (3.9)	8.2 (3.8)	8.4 (3.8)	7.9 (3.9)	8.2 (3.8)	9.0 (4.9)	8.9 (4.4)
<b>ON time without troublesome dyskinesia (hrs) (c)</b>								
Baseline (b)	9.3 (2.2)	9.4 (2.2)	9.6 (2.5)	9.3 (2.2)	9.4 (2.2)	9.6 (2.5)	9.1 (2.5)	9.3 (2.4)
Change LSM (SE)	0.5 (0.2)	1.0 (0.2)	1.2 (0.2)	0.8 (0.2)	1.4 (0.2)	1.5 (0.2)	0.6 (0.1)	1.4 (0.1)
LS Diff vs Placebo		0.5	0.7		0.6	0.7		0.9
95% CI		[0.1, 0.9]	[0.3, 1.0]		[0.1, 1.0]	[0.2, 1.1]		[0.6, 1.2]
p-value		0.0054	0.0002		0.0110	0.0028		<0.000 1
<b>OFF time (hrs) (c)</b>								
Baseline (b)	5.3 (2.1)	5.2 (2.0)	5.2 (2.2)	5.3 (2.1)	5.2 (2.2)	5.2 (2.1)	5.4 (2.0)	5.3 (2.0)
Change LSM (SE)	-0.8 (0.20)	-1.4 (0.20)	-1.5 (0.20)	-1.0 (0.20)	-1.5 (0.19)	-1.6 (0.19)	-0.5 (0.10)	-1.5 (0.10)
LS Diff vs Placebo		-0.6	-0.7		-0.5	-0.6		-1.0
95% CI		[-0.9, -0.3]	[-1.0, -0.4]		[-0.8, -0.2]	[-0.9, -0.3]		[-1.3, -0.7]
p-value		0.0002	<0.000 1		0.0028	0.0003		<0.000 1
<b>UPDRS III (c)</b>								
Baseline (b)	28.6 (12.0)	27.3 (12.8)	28.4 (13.5)	28.6 (12.0)	27.3 (12.8)	28.4 (13.5)	23.0 (12.8)	22.3 (11.8)
Change LSM (SE)	-4.5 (0.83)	-6.1 (0.82)	-6.8 (0.82)	-4.4 (0.85)	-5.6 (0.84)	-6.5 (0.84)	-2.6 (0.34)	-3.5 (0.34)
LS Diff vs Placebo		-1.6	-2.3		-1.2	-2.1		-0.9
95% CI		[-3.0, -0.2]	[-3.7, -0.9]		[-2.6, 0.2]	[-3.5, -0.6]		[-1.8, 0.0]
p-value		0.0207	0.0010		0.0939	0.0047		0.0514
<b>UPDRS II (c)</b>								
Baseline (b)	12.2 (5.9)	11.8 (5.7)	12.1 (5.9)	12.2 (5.9)	11.8 (5.7)	12.1 (5.9)	10.4 (6.3)	10.0 (5.6)
Change LSM (SE)	-1.2 (0.4)	-1.9 (0.4)	-2.3 (0.4)	-1.4 (0.3)	-2.0 (0.3)	-2.5 (0.3)	-0.8 (0.2)	-1.2 (0.2)
LS Diff vs Placebo		-0.7	-1.1		-0.6	-1.1		-0.4
95% CI		[-1.3, -0.0]	[-1.7, -0.5]		[-1.3, 0.0]	[-1.8, -0.4]		[-0.9, 0.0]
p-value		0.0367	0.0007		0.0676	0.0010		0.0564
<b>Responder analyses (post-hoc) (e) n(%)</b>								

Study	016 (24 weeks)			016/018 (2 years)			27919 (SETTLE) (24 weeks)	
	Placebo	Safinamide		Placebo	Safinamide		Placebo	Safinamide
		50	100		50	100		50-100 (d)
ON time increase $\geq$ 60 minutes	93 (43.9)	119 (54.8)	121 (56.0)	100 (47.2)	125 (57.6)	117 (54.2)	116 (42.5)	152 (56.3)
p-value		0.0233	0.0122		0.0308	0.1481		0.0013
$\geq$ 60 minutes increase ON time and decrease in OFF time and $\geq$ 30% improvement UPDRS III	32 (15.1)	52 (24.0)	56 (25.9)	28 (13.2)	43 (19.8)	42 (19.4)	24 (8.8)	49 (18.1)
p-value		0.0216	0.0061		0.0671	0.0827		0.0017
CGI-C: patients who were much/very much improved	42 (19.8)	72 (33.2)	78 (36.1)	46 (21.7)	62 (28.6)	64 (29.6)	26 (9.5)	66 (24.4)
p-value (f)		0.0017	0.0002		0.0962	0.0575		<0.0001

(a) Daily targeted dose, (b) Mean (SD), (c) analysis population (mITT); MMRM model for change from Baseline to Endpoint includes treatment, region, and visit as fixed effects, and baseline value as a covariate; (d) target dose of 100 mg/day; (e) analysis population (mITT); data are presented as the number (percentage) of patients in each group meeting the responder definition (f) chi-square test of the odds ratio of the treatment groups compared to placebo using a logistic regression model, with fixed effects for treatment and country.  
SE Standard Error, SD Standard deviation, LSM Least Square Mean, LS Diff. Least Square Difference vs Placebo  
mITT Population: Study 016/018 - Placebo (n=212), safinamide 50 mg/day (n=217) and 100 mg/day (n=216), and SETTLE - Placebo (n=270), safinamide 50-100 mg/day (n=273).

### Paediatric population

The pharmacodynamic effects of safinamide have not been assessed in children and adolescents.

## 5.2 Pharmacokinetic properties

### Absorption

Safinamide absorption is rapid after single and multiple oral dosing, reaching  $T_{max}$  in the time range 1.8-2.8 h after dosing under fasting conditions. 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.

### 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. 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%.

### Biotransformation

In humans, safinamide is almost exclusively eliminated via metabolism (urinary excretion of unchanged safinamide was <10%) mediated principally through high capacity amidases, that have not yet been characterized. *In vitro* experiments indicated that inhibition of amidases in human hepatocytes led to complete suppression of the NW-1153 formation. Amidase present in blood, plasma, serum, simulated gastric fluid and simulated intestinal fluid as well as human carboxylesterases hCE-1 and hCE-2 are not responsible for the biotransformation of safinamide to NW-1153. The amidase FAAH was able to catalyse the formation of NW-1153 at low rates only. Therefore, other amidases are likely to be involved in the conversion to NW-1153. Safinamide's metabolism is not dependent on Cytochrome P450 (CYP) based enzymes.

Metabolite structure elucidation revealed three metabolic pathways of safinamide. The principal pathway involves hydrolytic oxidation of the amide moiety leading to the primary metabolite 'safinamide acid' (NW-1153). Another pathway involves oxidative cleavage of the ether bond forming 'O-debenzylated safinamide' (NW-1199). Finally the 'N-dealkylated acid' (NW-1689) is formed by oxidative cleavage of the amine bond of either safinamide (minor) or the primary safinamide acid metabolite (NW-1153) (major). The 'N-dealkylated acid' (NW-1689) undergoes conjugation with glucuronic acid yielding its acyl glucuronide. None of these metabolites are pharmacologically active.

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 ( $C_{max}$  of free safinamide 0.4  $\mu$ M 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.

A mass balance study showed that the plasma  $AUC_{0-24h}$  of the unchanged  $^{14}C$ -safinamide accounted for approximately 30% of the total radioactivity  $AUC_{0-24h}$ , indicative of an extensive metabolism.

### Transporters

Preliminary *in vitro* studies have shown that safinamide is not a substrate for the transporters P-gp, BCRP, OAT1B1, OAT1B3, OATP1A2 or OAT2P1. Metabolite NW-1153 is not a substrate for OCT2, or OAT1, but it is substrate for OAT3. This interaction has the potential to reduce the clearance of NW-1153 and increase its exposure; however the systemic exposure of NW-1153 is low (1/10 of parent safinamide), and as it is metabolised to secondary and tertiary metabolites, it is unlikely to be of any clinical relevance.

Safinamide transiently inhibits BCRP in the small intestine (see section 4.5). At concentrations of 50 $\mu$ M, safinamide inhibited OATP1A2 and OATP2P1. The relevant plasma concentrations of safinamide are substantially lower, therefore a clinically relevant interaction with co-administered substrates of these transporters is unlikely. NW-1153 is not an inhibitor of OCT2, MATE1, or MATE2-K up to concentrations of 5 $\mu$ M.

### Linearity/non-linearity

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

### Elimination

Safinamide undergoes almost complete metabolic transformation (<10% of the administered dose was found unchanged in urine). Substance-related radioactivity was largely excreted in urine (76%) and only 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.

#### Patients with hepatic impairment

Safinamide exposure in patients with mild hepatic disease increased marginally (30% in AUC), while in patients with moderate hepatic impairment exposure increased by approximately 80% (see section 4.2).

#### Patients with renal impairment

Moderate or severe renal impairment did not alter the exposure to safinamide, compared to healthy subjects (see section 4.2).

### **5.3 Preclinical safety data**

Retinal degeneration was observed in rodents after repeated safinamide dosing resulting in systemic exposure below the anticipated systemic exposure in patients given the maximal therapeutic dose. No retinal degeneration was noted in monkeys despite higher systemic exposure than in rodents or in patients at the maximum human dose.

Long-term studies in animals have shown convulsions (1.6 to 12.8 times human clinical exposure, based on plasma AUC). Liver hypertrophy and fatty changes were seen only in rodent livers at exposures similar to humans. Phospholipidosis was seen mainly in the lungs in rodents (at exposures similar to humans) and monkeys (at exposures greater than 12 fold higher than human).

Safinamide did not present genotoxic potential in *in vivo* and in several *in vitro* systems using bacteria or mammalian cells.

The results obtained from carcinogenicity studies in mice and rats showed no evidence of tumorigenic potential related to safinamide at systemic exposures up to 2.3 to 4.0 times respectively, the anticipated systemic exposure in patients given the maximal therapeutic dose.

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.

In embryo-foetal developmental studies in rats and rabbits malformations were induced at safinamide exposures 2 and 3-fold above human clinical exposure, respectively. The combination of safinamide with levodopa/carbidopa resulted in additive effects in the embryo-foetal development studies with a higher incidence of foetal skeletal abnormalities than seen with either treatment alone.

In a pre- and postnatal developmental rat study, pup mortality, absence of milk in the stomach and neonatal hepatotoxicity were observed at dose levels similar to the anticipated clinical exposure. Toxic effects on the liver and accompanying symptoms as yellow/orange skin and skull, in pups exposed to safinamide during lactation are mediated mainly via in utero exposure, whereas exposure via the mother's milk had only a minor influence.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Microcrystalline cellulose  
Crospovidone type A  
Magnesium stearate  
Silica, colloidal anhydrous

Film-coating

Hypromellose  
Macrogol (6000)  
Titanium dioxide (E171)  
Iron oxide red (E172)  
Mica (E555)

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

4 years

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**

PVC/PVDC/Aluminium blister packs of 14, 28, 30, 90 and 100 tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements for disposal.

**7 MARKETING AUTHORISATION HOLDER**

Zambon S.p.A.  
Via Lillo del Duca 10  
20091 Bresso (MI) - Italy  
Tel: +39 02 665241  
Fax: +39 02 66501492  
Email: info.zambonspa@zambongroup.com

**8 MARKETING AUTHORISATION NUMBER(S)**

Xadago 50 mg film-coated tablets

EU/1/14/984/001  
EU/1/14/984/002  
EU/1/14/984/003  
EU/1/14/984/004

EU/1/14/984/005

Xadago 100 mg film-coated tablets

EU/1/14/984/006

EU/1/14/984/007

EU/1/14/984/008

EU/1/14/984/009

EU/1/14/984/010

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 24 February 2015

Date of latest renewal: 19 September 2019

**10 DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

### Name and address of the manufacturer responsible for batch release

Catalent Germany Schorndorf GmbH  
Steinbeisstrasse 2  
D-73614 Schorndorf  
Germany

Zambon S.p.A.  
Via della Chimica, 9  
36100 Vicenza  
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to medical prescription

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON –film-coated tablets**

**1. NAME OF THE MEDICINAL PRODUCT**

Xadago 50 mg film-coated tablets  
safinamide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains safinamide methanesulfonate equivalent to 50 mg safinamide.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 film-coated tablets  
28 film-coated tablets  
30 film-coated tablets  
90 film-coated tablets  
100 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Zambon S.p.A.  
Via Lillo del Duca 10  
20091 Bresso (MI) - Italy

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/984/001  
EU/1/14/984/002  
EU/1/14/984/003  
EU/1/14/984/004  
EU/1/14/984/005

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

xadago 50 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

Xadago 50 mg tablets  
safinamide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Zambon S.p.A.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON – film-coated tablets**

**1. NAME OF THE MEDICINAL PRODUCT**

Xadago 100 mg film-coated tablets  
safinamide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains safinamide methansulfonate equivalent to 100 mg safinamide.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 film-coated tablets  
28 film-coated tablets  
30 film-coated tablets  
90 film-coated tablets  
100 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Zambon S.p.A.  
Via Lillo del Duca 10  
20091 Bresso (MI) - Italy

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/984/006  
EU/1/14/984/007  
EU/1/14/984/008  
EU/1/14/984/009  
EU/1/14/984/010

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

xadago 100 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

Xadago 100 mg tablets  
safinamide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Zambon S.p.A.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### **Xadago 50 mg film-coated tablets** **Xadago 100 mg film-coated tablets** safinamide

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

### **What is in this leaflet**

1. What Xadago is and what it is used for
2. What you need to know before you take Xadago
3. How to take Xadago
4. Possible side effects
5. How to store Xadago
6. Contents of the pack and other information

#### **1. What Xadago is and what it is used for**

Xadago is a medicine that contains the active substance safinamide. It acts to increase the level of a substance called dopamine in the brain, which is involved in the control of movement and is present in reduced amounts in the brain of patients with Parkinson's disease. Xadago is used for the treatment of Parkinson's disease in adults.

In mid- to late-stage patients experiencing sudden switches between being "ON" and able to move and being "OFF" and having difficulties moving about, Xadago is added to a stable dose of the medicine called levodopa alone or in combination with other medicines for Parkinson's disease.

#### **2. What you need to know before you take Xadago**

##### **Do not take Xadago**

- If you are allergic to safinamide or any of the other ingredients of this medicine (listed in section 6).
- If you are taking any of the following medicines:
  - Monoamine oxidase (MAO) inhibitors such as selegiline, rasagiline, moclobemide, phenelzine, isocarboxazid, tranylcypromine (e.g. for treatment of Parkinson's disease or depression, or used for any other condition).
  - Pethidine (a strong pain killer).  
You must wait at least 7 days after stopping Xadago treatment before starting treatment with MAO inhibitors or pethidine.
- If you have been told that you have severe liver problems
- If you have an eye condition which might put you at risk of potential damage to your retina (the light sensitive layers at the back of your eyes), e.g. albinism (lack of pigment in your skin and eyes), retinal degeneration (loss of cells from light sensitive layer at the back of the eye), or

uveitis (inflammation inside of the eye), inherited retinopathy (inherited disorders of the vision), or severe progressive diabetic retinopathy (a progressive decrease of the vision due to diabetes).

### **Warnings and precautions**

Talk to your doctor before taking Xadago

- If you have liver problems
- Patients and carers should be made aware that certain compulsive behaviours such as compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying have been reported with other medicines for Parkinson's disease.
- Uncontrollable jerky movements may occur or worsen when Xadago is used together with levodopa.

### **Children and adolescents**

Xadago is not recommended for use in children and adolescents, below 18 years old due to the lack of data on safety and efficacy in this population.

### **Other medicines and Xadago**

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines. Ask your doctor for advice before taking any of the following medicines together with Xadago:

- Cold or cough remedies containing dextromethorphan, ephedrine or pseudoephedrine
- Medicines called selective serotonin reuptake inhibitors (SSRIs) typically used to treat anxiety disorders, and some personality disorders (e.g. fluoxetine or fluvoxamine)
- Medicines called serotonin–norepinephrine reuptake inhibitors (SNRIs), used in the treatment of major depression and other mood disorders, such as venlafaxine
- Medicines for high cholesterol such as rosuvastatin, pitavastatin, pravastatin
- Fluoroquinolone antibiotic such as ciprofloxacin
- Medicines that affect the immune system such as methotrexate
- Medicines to treat metastatic carcinoma such as topotecan
- Medicine to treat pain and inflammation such as diclofenac
- Medicines to treat type 2 diabetes such as glyburide, metformin
- Medicines to treat virus infection such as aciclovir, ganciclovir

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

#### Pregnancy

Xadago should not be used during pregnancy or by women of childbearing potential not practicing adequate contraception.

#### Breast Feeding

Xadago is likely to be excreted in breast milk. Xadago should not be used during breast-feeding.

### **Driving and using machines**

Somnolence and dizziness may occur during safinamide treatment; you should be cautious about operating hazardous machines or driving, until you are reasonably certain that Xadago does not affect you in any way.

Ask your doctor for advice prior to driving or using machines.

### 3. How to take Xadago

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended starting dose of Xadago is one 50 mg tablet that may be increased to one 100 mg tablet, taken once daily preferably in the morning by mouth with water. Xadago may be taken with or without food.

If you suffer from moderately reduced liver function, you should not take more than 50 mg a day; your doctor will advise if this applies to you.

#### **If you take more Xadago than you should**

If you have taken too many Xadago tablets, you may develop raised blood pressure, anxiety, confusion, forgetfulness, sleepiness, lightheadedness; feel sick or be sick; dilated pupils or develop involuntary jerky movements. Contact your doctor immediately and take the Xadago pack with you.

#### **If you forget to take Xadago**

Do not take a double dose to make up for a forgotten dose. Skip the missed dose and take the next dose at the time you normally take it.

#### **If you stop taking Xadago**

Do not stop taking Xadago without first talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

### 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Seek medical advice in case of hypertensive crisis (very high blood pressure, collapse), neuroleptic malignant syndrome (confusion, sweating, muscle rigidity, hyperthermia, increase level of enzyme creatine kinase in your blood), serotonin syndrome (confusion, hypertension, muscle stiffness, hallucinations), and hypotension.

The following side effects have been reported in patients at a mid- to late-stage of Parkinson's disease (patients taking safinamide as add-on to levodopa alone or in combination with other medicines for Parkinson's disease):

**Common** (may affect up to 1 in 10 people): insomnia, difficulty in performing voluntary movements, feeling sleepy, dizziness, headache, worsening of Parkinson's disease, clouding of the lens of the eye, fall in blood pressure when rising to a standing position, nausea, falling.

**Uncommon** (may affect up to 1 in 100 people): urine infection, skin cancer, low iron in your blood, low white cell count, red blood cell abnormality, decreased appetite, high fat in blood, increased appetite, high blood sugar, seeing things that are not there, feeling sad, abnormal dreams, fear and worry, confusional state, mood swings, increased interest in sex, abnormal thinking and perception, restlessness, sleep disorder, numbness, unsteadiness, loss of sensation, sustained abnormal muscle contraction, head discomfort, difficulty in speaking, fainting, memory impairment, blurring of vision, blind spot, double vision, aversion to light, disorders of the light sensitive layer at the back of your eye, redness of the eyes, increased pressure in the eye, sensation of room spinning, feeling of heart beating, fast heartbeat, irregular heartbeat, slowed heartbeat, high blood pressure, low blood pressure, veins that have become large and twisted, cough, difficult breathing, runny nose, constipation, heartburn, vomiting, dry mouth, diarrhoea, abdominal pain, burning stomach, wind, feeling full, drooling, mouth ulcer, sweating, itching, sensitive to light, redness of the skin, back pain, joint pain, cramps, stiffness, pain in legs or arms, muscle weakness, sensation of heaviness, increased urination at

night, pain upon urination, difficulty in having sex in males, fatigue, feeling weak, unsteady walking, swelling of your feet, pain, feeling hot, weight loss, weight gain, abnormal blood tests, high fat in your blood, increased sugar in your blood, abnormal ECG, liver function test abnormal, abnormal urine tests, blood pressure decreased, blood pressure increased, abnormal eye test, fracture of your foot.

**Rare** (may affect up to 1 in 1000 people): pneumonia, skin infection, sore throat, nasal allergy, tooth infection, viral infection, non-cancerous skin conditions/growth, white blood cell abnormalities, severe loss of weight and weakness, increased potassium in blood, uncontrollable urges, clouding of consciousness, disorientation, wrong perception of images, reduced interest in sex, thoughts that you cannot get rid of, feeling that someone is out to get you, premature ejaculation, uncontrollable urge to sleep, fear of social situations, thoughts of suicide, clumsiness, easily distracted, loss of taste, weak/slow reflexes, radiating pain in the legs, continuous desire to move your legs, feeling sleepy, eye abnormalities, progressive diminution of vision due to diabetes, increased tears, night blindness, cross eyed, heart attack, tightening/narrowing of blood vessel, severe high blood pressure, tightening of the chest, difficulty in speaking, difficulty in/painful swallowing, peptic ulcer, retching, stomach bleeding, jaundice, loss of hair, blister, skin allergy, skin conditions, bruising, scaly skin, night sweats, pain of skin, discolouration of the skin, psoriasis, flaky skin, inflammation of spinal joints due to an autoimmune disorder, pain in your sides, swelling of joints, musculoskeletal pain, muscular pain, neck pain, joint pain, cyst in the joint, uncontrollable urge to urinate, increased urination, passing of pus cells in urine, urinary hesitation, prostate problem, breast pain, drug effect decreased, drug intolerance, feeling cold, feeling unwell, fever, dryness of skin, eye and mouth, abnormal blood tests, heart murmur, abnormal heart tests, bruising/swelling after injury, blood vessel blockage due to fat, head injury, mouth injury, skeletal injury, gambling.

### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

## **5. How to store Xadago**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after “EXP”  
The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## **6. Contents of the pack and other information**

### **What Xadago contains**

- The active substance is safinamide. Each tablet contains 50 mg or 100 mg of safinamide (as methansulfonate).
- The other ingredients are:
  - Tablet core: microcrystalline cellulose, crospovidone type A, magnesium stearate, silica colloidal anhydrous
  - Tablet coating: hypromellose, macrogol (6000), titanium dioxide (E171), iron oxide red (E172), mica (E555).

### **What Xadago looks like and contents of the pack**

Xadago 50 mg are orange to copper, round, biconcave film-coated tablets of 7 mm diameter with metallic gloss, embossed with “50” on one side of the tablet.

Xadago 100 mg are orange to copper, round, biconcave film-coated tablets 9 mm diameter with metallic gloss, embossed with “100” on one side of the tablet.

Xadago is supplied in packs containing 14, 28, 30, 90 or 100 film coated tablets.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

Zambon S.p.A.  
Via Lillo del Duca 10  
20091 Bresso (MI)  
Italy  
Tel: +39 02665241  
Fax: +39 02 66501492  
Email: info.zambonspa@zambongroup.com

### **Manufacturer**

Catalent Germany Schorndorf GmbH  
Steinbeisstrasse 2  
D- 73614 Schorndorf  
Germany

Zambon S.p.A.  
Via della Chimica, 9  
36100 Vicenza  
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien/  
Luxembourg/Luxemburg**  
Zambon N.V./S.A.  
Tél/Tel: + 32 2 777 02 00

**France**  
Zambon France S.A.  
Tél: + 33 (0)1 58 04 41 41

**България/ Eesti/  
Ireland/Ísland/Κύπρος/Latvija/ Malta/Polska/  
România**  
Zambon S.p.A.  
Тел./Tel/Τηλ/Šimi: + 39 02665241

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Zambon Italia S.r.l.  
Tel: + 39 02665241

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Tlf/Puh/Tel: + 46 10 33 50 800

**Nederland**  
Zambon Nederland B.V.  
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Tel: + 34 93 544 64 00

**Česká republika**

Desitin Pharma spol. s r.o.  
Tel: + 420 222 245 375

**Ελλάδα**

Innovis Pharma A.E.B.E.  
Τηλ:+ 30 216 200 5600

**Magyarország**

Richter Gedeon Nyrt.  
Tel.: +36 1 505 7032

**Hrvatska/Slovenija**

SALUS, Veletrgovina, d.o.o.  
Tel: + 386 1 5899 100

**Slovenská republika**

Desitin Pharma s.r.o.  
Tel: + 421 2 5556 3810

**Lietuva**

UAB „Norameda“  
Tel: + 370 5 2306499

**This leaflet was last revised in .**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.