**SCHEDULING STATUS**

S4

## 1. NAME OF THE MEDICINE

**XADAGO 50 mg film-coated tablets**

**XADAGO 100 mg film-coated tablets**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**XADAGO 50 mg**

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

**XADAGO 100 mg**

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

Sugar free.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets

**XADAGO 50 mg**

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**

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 medicines in mid-to late-stage fluctuating patients.

## 4.2 Posology and method of administration

**Posology**

Treatment with XADAGO 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.

**Special populations**

*Elderly patients*

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*

XADAGO 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, XADAGO 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 XADAGO in children and adolescents under 18 years of age have not been established. No data are available.

**Method of administration**

For oral use.

XADAGO should be taken with water.

XADAGO may be taken with or without food.

## 4.3 Contraindications

- Hypersensitivity to safinamide 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 serotoninergic symptoms. In particular, the concomitant use of safinamide and fluoxetine or fluvoxamine should be avoided, or if concomitant treatment is necessary these medicines 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 professional information (PI) for that particular medicine.

**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 XADAGO should be stopped (see sections 4.2, 4.3 and 5.2).

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

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 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 (refer to levodopa Professional Information for further information). This effect was not seen when safinamide was used as an adjunct to dopamine agonists in early-stage PD patients.

In addition, Dopamine dysregulation syndrome (DDS) has been reported in literature reports in patients treated with carbidopa/levodopa. Although Safinamide (contained in XADAGO) never showed this risk both alone nor when administered with carbidopa/levodopa, patients and caregivers should be warned of the potential risk of developing DDS when Xadago is co-administered with carbidopa/levodopa.
Dopamine Dysregulation Syndrome (DDS) is an addictive disorder seen in some patients treated with carbidopa/ levodopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias.

## 4.5 Interaction with other medicines and other forms of interaction

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

*MAO inhibitors and pethidine*
XADAGO 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 interactions with the concomitant use of MAO inhibitors and sympathomimetic medicines. 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 and flu medicines containing ephedrine or pseudoephedrine, requires caution (see section 4.4).

*Dextromethorphan*
There have been reports of 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 XADAGO 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 (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. If necessary, the concomitant use of these medicines 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 XADAGO.
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.
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 interactions**

Safinamide may transiently inhibit BCRP *in vitro*. In interaction studies in human, a weak interaction was observed with rosuvastatin (AUC increase between 1,25 and 2,00-fold) but no significant interaction was found with diclofenac. It is recommended to monitor patients when safinamide is taken with medicinal products that are BCRP substrates (e.g., rosuvastatin, pitavastatin, pravastatin, ciprofloxacin, methotrexate, topotecan, diclofenac or glyburide) and to refer to their professional information 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 characterised. 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 medicines 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.

Medicines that are inhibitors of OAT3 given concomitantly with XADAGO 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**

XADAGO 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 XADAGO 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.

**Breastfeeding**

Available pharmacodynamic/toxicological data in animals have shown excretion of safinamide in milk (for details see section 5.3).
A risk for the breastfed child cannot be excluded. XADAGO should not be used during breastfeeding.

**Fertility:**

Animal studies indicate that XADAGO 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 XADAGO does not affect them adversely.

## 4.8 Undesirable effects

**Summary of the safety profile**

Dyskinesia was the most common adverse reaction reported in XADAGO 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 interactions with concomitant use of sympathomimetic medicines.

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 (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data).

| **System Organ Class** | **Very common** | **Common** | **Uncommon** | **Rare** |
|---|---|---|---|---|
| Infections and infestations | | | Urinary tract infection | Broncho-pneumonia, furuncle, nasopharyngitis, pyoderma, rhinitis, tooth infection, viral infection |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | Basal cell carcinoma | Acrochordon, Melanocytic naevus, Seborrheic keratosis, skin papilloma |
| Blood and lymphatic system disorders | | | Anaemia, leukopenia, red blood cell abnormality | Eosinophilia, lymphopenia |
| Metabolism and nutrition disorders | | | Decreased appetite, hyper-triglyceridemia, | Cachexia, hyperkalaemia |

| | | | | |
|---|---|---|---|---|
| | | | increased appetite, hyper-cholesterolaemia, hyperglycaemia | |
| 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 | Abnormal Coordination, disturbance in attention, dysgeusia, hyporeflexia, radicular pain, Restless Legs Syndrome, sedation |
| Eye disorders | | Cataract | Vision blurred, scotoma, diplopia, photophobia, | Amblyopia, chromatopsia, |

| | | | | |
|---|---|---|---|---|
| | | | retinal disorder, conjunctivitis, glaucoma | diabetic retinopathy, erythropsia, eye haemorrhage, eye pain, eyelid oedema, hypermetropia, keratitis, increased lacrimation, night blindness, papilloedema, presbyopia, strabismus |
| Ear and labyrinth disorders | | | Vertigo | |
| Cardiac disorders | | | Palpitations, tachycardia, sinus bradycardia, dysrhythmia | Myocardial infarction |
| Vascular disorders | | Orthostatic hypotension | Hypertension, hypotension, varicose vein | Arterial spasm, arteriosclerosis, hypertensive crisis |
| Respiratory, thoracic and mediastinal disorders | | | Cough, dyspnoea, rhinorrhoea | Bronchospasm, dysphonia, oropharyngeal pain, oropharyngeal spasm |

| | | | | |
|---|---|---|---|---|
| Gastrointestinal disorders | | Nausea | Constipation, dyspepsia, vomiting, dry mouth, diarrhoea, abdominal pain, gastritis, flatulence, abdominal distension, salivary hypersecretion, gastroesophageal reflux disease, aphthous stomatitis | Peptic ulcer, retching, upper gastrointestinal haemorrhage |
| Hepatobiliary disorders | | | | Hyper-bilirubinaemia |
| 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 |
| Investigations | | | Weight decreased, weight increased, blood creatine phosphokinase increased, blood triglycerides increased, blood glucose increased, | Blood calcium decreased, blood potassium decreased, blood cholesterol decreased, body temperature increased, cardiac murmur, |

| | | | | |
|---|---|---|---|---|
| | | | 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 | 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.

**Post marketing experience**

The following adverse reactions have been identified during post approval use of safinamide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: Hypersensitivity: A post marketing report describes a patient who developed a hypersensitivity reaction consisting of swelling of the tongue and gingiva, dyspnea and skin rash. The symptoms resolved shortly after XADAGO was discontinued, but reappeared following rechallenge a month later.

**Reporting of suspected adverse reactions:**

Reporting suspected adverse reactions after authorisation of XADAGO is important. It allows continued monitoring of the benefit/risk balance of XADAGO. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

## 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 XADAGO, 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 $Na^+$ 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 XADAGO or any specific treatment for XADAGO overdose. If an important overdose occurs, XADAGO treatment should be discontinued and supportive treatment should be administered as clinically indicated.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Category and class: A 5.4.1 Anti-Parkinsonism preparations.
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 ($Na^+$) 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 medicines in this patient population (antihypertensive, beta-blockers cholesterol lowering, non-steroidal anti-inflammatory medicines, proton pump inhibitors, antidepressants, etc.) was not associated with an increased risk for adverse events. Studies were not stratified for co-medication, and no randomised interaction studies were performed for these medicines.

**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 medicines, 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)** | |
|---|---|---|---|---|---|---|---|---|
| **Dose (mg/day)** (a) | **Placebo** | **Safinamide** | | **Placebo** | **Safinamide** | | **Placebo** | **Safinamide** |
| | | **50** | **100** | | **50** | **100** | | **50-100 (d)** |
| **Randomized** | 222 | 223 | 224 | 222 | 223 | 224 | 275 | 274 |
| **Age (years)** (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) |
| **PD Duration (years)** (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) |
| **ON time without troublesome dyskinesia (hrs) (c)** | | | | | | | | |
| 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 | | 0,005 | 0,0002 | | 0,011 | 0,002 | | <0,0001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 4 | | | 0 | 8 | | |
| **OFF time (hrs) (c)** | | | | | | | | |
| 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 | <0,0001 | | 0,0028 | 0,0003 | | <0,0001 |
| **UPDRS III (c)** | | | | | | | | |
| 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 |
| **UPDRS II (c)** | | | | | | | | |
| 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 | -2,3 (0,4) | -1,4 | -2,0 | -2,5 | -0,8 | -1,2 (0,2) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | (0,4) | | (0,3) | (0,3) | (0,3) | (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 |
| **Responder analyses (post-hoc) (e) n(%)** | | | | | | | | |
| ON time increase ≥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 |
| ≥60 minutes increase ON time and decrease in OFF time and ≥ 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.

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

**Distribution**

The volume of distribution ($V_{ss}$) is approximately 165 L which is 2,5-fold of body volume indicating extensive extravascular distribution of safinamide. 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 µM at 100 mg/day) in man. Dedicated 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 µM, 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 µM.

**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.

**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).

**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 and loss of photoreceptor cells were observed in albino and pigmented rats after repeated safinamide oral dosing resulting in systemic exposure below the anticipated systemic exposure in patients given the maximal therapeutic dose. 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 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).

*Genotoxicity*

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

*Carcinogenicity*

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.

*Impairment of 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.

*Embryofoetal Studies*

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 (80/20 mg/kg/day) 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**

Crospovidone type A

Magnesium stearate

Microcrystalline cellulose

Silica, colloidal anhydrous

**Tablet coating**

Hypromellose

Iron oxide red (E172)

Macrogol (6000)

Mica (E555)

Titanium dioxide (E171)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Store at or below 30 °C.

Keep blister strips in carton until required for use.

### 6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

No special requirements for disposal.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand 1685,
South Africa
Customer Care: 0860 ADCOCK / 232625

## 8. REGISTRATION NUMBERS

XADAGO 50 mg: 55/5.4.1/0806
XADAGO 100 mg: 55/5.4.1/0807

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 January 2023

## 10. DATE OF REVISION OF THE TEXT

adcock ingram

PI 6298015 08/2023

**SCHEDULING STATUS**

S4

**XADAGO 50 mg film-coated tablets**

**XADAGO 100 mg film-coated tablets**

Safinamide

Sugar free

**Read all of this leaflet carefully before you start taking XADAGO.**

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- XADAGO has been prescribed for your personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

**What is in this leaflet**



## 1. What XADAGO is and what it is used for

XADAGO contains the active substance safinamide. XADAGO 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 hypersensitive (allergic) to safinamide or any of the other ingredients of XADAGO (listed in section 6 of this leaflet).
- If you have a history of an allergic reaction to safinamide. Signs of an allergic reaction to safinamide could include swelling of your tongue, mouth or trouble breathing. Ask your healthcare provider if you are not sure if you have had an allergic reaction to safinamide in the past.
- 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 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**

Tell your doctor before taking XADAGO:

- If you have any 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 (see section 4).
- Uncontrollable jerky movements may occur or worsen when XADAGO is used together with levodopa. Also, when using XADAGO together with levodopa, tell your doctor if you or your family/carer notices you are developing addiction-like symptoms leading to craving for large doses of levodopa and other medicines used to treat Parkinson's disease.

**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**

Always tell your health care provider if you are taking any other medicine. (This includes complementary or traditional 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 fungal infections such as ketoconazole
- Medicines to treat type 2 diabetes such as glyburide, metformin
- Medicines to treat viral infection such as aciclovir, ganciclovir

**XADAGO with food and drink**

XADAGO may be taken with or without food.

**Pregnancy and breastfeeding**

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other health care provider for advice before taking XADAGO.

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

XADAGO is likely to be excreted in breast milk. XADAGO should not be used during breastfeeding.

**Driving and using machines**

Somnolence and dizziness may occur during XADAGO 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

Do not share any medicines prescribed for you with any other person.

Always take XADAGO 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.

Your doctor will tell your how long your treatment with XADAGO will last.

If you have the impression that the effect of XADAGO is too strong or too weak, tell your doctor or pharmacist.

**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, light-headedness; feel sick or be sick; dilated pupils or develop involuntary jerky movements. In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre. Take this leaflet and your remaining tablets with you so the doctor can see what you have taken.

**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.

## 4. Possible side effects

XADAGO can have side effects.

Not all side effects reported for XADAGO are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking XADAGO, please consult your doctor, pharmacist or other health care provider for advice.

If any of the following happens, stop taking XADAGO and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Swelling of the hands, feet, ankles, face, lips, tongue and mouth or throat, which may cause difficulty in swallowing or breathing.
- Rash or itching.
- Fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to XADAGO. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- hypertensive crisis (very high blood pressure, collapse)
- neuroleptic malignant syndrome (confusion, sweating, muscle stiffness, higher than normal body temperature, increase level of enzyme creatine kinase in your blood)
- serotonin syndrome (confusion, hypertension, muscle stiffness, hallucinations), and
- hypotension (low blood pressure).

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

*Side effects that may occur frequently:*

- 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

*Side effects that may occur less frequently:*

- urinary tract 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, varicose veins (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
- the inability to get or keep an erection in men (erectile dysfunction)
- 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, abnormal liver function tests, abnormal urine tests, decreased blood pressure, increased blood pressure, abnormal eye test
- fracture of your foot

*Other side effects that may also occur:*

- 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
- 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 arising from social circumstances
- Immune system related hypersensitivity reaction

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

**Reporting of side effects**

If you get 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 to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of XADAGO.

## 5. How to store XADAGO

- Store at or below 30 °C.
- Keep blister strips in carton until required for use.
- STORE ALL MEDICINES OUT OF REACH OF CHILDREN.
- Do not use after the expiry date printed on the carton.
- Return all unused medicine to your pharmacist.
- Do not dispose of unused medicine in drains and sewerage systems (e.g. toilets).

## 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 methanesulfonate).

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 available in PVC/PVDC/Aluminium blister packs of 14, 28, 30, 90 or 100 tablets.

Not all pack sizes may be marketed.

**Holder of certificate of registration**

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand 1685

South Africa

Customer Care: 0860 ADCOCK / 232625

**This leaflet was last revised in:**

**Registration numbers**

XADAGO 50 mg: 55/5.4.1/0806

XADAGO 100 mg: 55/5.4.1/0807

adcock ingram

PIL 6298015 08/2023

**PASIËNT INLIGTINGSBLAD**

**SKEDULERINGSTATUS**

S4

**XADAGO 50 mg filmbedekte tablette**

**XADAGO 100 mg filmbedekte tablette**

Safinamied

Suikervry

**Lees die hele voubiljet noukeurig deur voordat u XADAGO begin neem.**

- Bewaar hierdie voubiljet. U sal dit dalk weer moet lees.
- Indien u verdere vrae het, raadpleeg asseblief u dokter, apteker, verpleegkundige of ander gesondheidsorg kundige.
- XADAGO is aan u persoonlik voorgeskryf en u moet nie u medisyne met ander mense deel nie. Dit kan hulle benadeel, selfs al ervaar hul dieselfde simptome as u.

**Wat in hierdie voubiljet is**



## 1. Wat XADAGO is en waarvoor dit gebruik word

XADAGO bevat die aktiewe bestanddeel safinamied. XADAGO verhoog die vlak van 'n stof genaamd dopamien in die brein, wat betrokke is by die beheer van beweging en teenwoordig is in verminderde hoeveelhede in die brein van pasiënte met Parkinson se siekte. XADAGO word gebruik vir die behandeling van Parkinson se siekte by volwassenes. By pasiënte in middel- tot laat-stadium wat skielike oorskakelings ervaar tussen die tye waar hul "AAN" is en kan beweeg en wanneer hulle “AF” is en probleme ondervind om rond te

beweeg, word XADAGO by 'n stabiele dosis van die medisyne genaamd levodopa gevoeg, alleen of in kombinasie met ander medisyne vir Parkinson se siekte.

**2. Wat u moet weet voordat u XADAGO neem**

**Moenie XADAGO neem nie:**

- Indien u hipersensitief (allergies) is vir safinamied of enige van die ander bestanddele van XADAGO (gelys in afdeling 6 van hierdie voubiljet).
- Indien u 'n geskiedenis van 'n allergiese reaksie op safinamied het. Tekens van 'n allergiese reaksie op safinamied kan swelling van u tong, mond of probleme met asemhaling insluit. Raadpleeg u gesondheidsorg kundige indien u nie seker is of u 'n allergiese reaksie op safinamied in die verlede gehad het nie.
- Indien u enige van die volgende medisyne gebruik:
  - Monoamienoksidase (MAO) inhibeerders soos selegilien, rasagilien, moklobemied, fenelsien, isokarboksasied, tranielsipromien (bv. vir behandeling van Parkinson se siekte of depressie, of gebruik vir enige ander toestand).
  - Petidien ('n sterk pynstiller)

  U moet ten minste 7 dae wag nadat u XADAGO-behandeling gestaak is voordat u met MAO-inhibeerders of petidien begin.
- Indien u ernstige lewerprobleme het.
- Indien u 'n oogtoestand het wat u in gevaar kan stel vir potensiële skade aan u retina (die lig-sensitiewe lae aan die agterkant van u oë), bv. albinisme (gebrek aan pigment in u vel en oë), retinale degenerasie (verlies van selle van die lig-sensitiewe laag aan die agterkant van die oog), of uveïtis (ontsteking binne-in die oog), oorgeërfde retinopatie (oorgeërfde versteurings van die visie), of ernstige progressiewe diabetiese retinopatie ('n progressiewe afname van die visie as gevolg van diabetes).

**Waarskuwings en voorsorgmaatreëls**

Lig u dokter in voordat u XADAGO neem:

- Indien u enige lewerprobleme het.
- Pasiënte en versorgers moet bewus gemaak word daarvan dat sekere kompulsiewe gedrag soos kompulsies, obsessiewe gedagtes, patologiese dobbelary, verhoogde libido, hiperseksualiteit, impulsiewe gedrag en kompulsiewe besteding of koop van

goedere aangemeld is saam met ander medisyne vir Parkinson se siekte (sien afdeling 4).

- Onbeheerbare rukkerige bewegings kan voorkom of vererger wanneer XADAGO saam met levodopa gebruik word. Ook, wanneer XADAGO saam met levodopa gebruik word, raadpleeg u dokter in indien u of u gesin/versorger agterkom dat u verslawingstipe simptome ontwikkel wat lei tot drang na groot dosisse levodopa en ander medisyne wat gebruik word om Parkinson se siekte te behandel.

**Kinders en adolessente**

XADAGO word nie aanbeveel vir gebruik by kinders en adolessente jonger as 18 jaar nie weens die gebrek aan data oor veiligheid en doeltreffendheid in hierdie populasie.

**Ander medisyne en XADAGO**

Lig altyd u gesondheidsorg kundige in indien u enige ander medisyne gebruik. (Dit sluit komplementêre of tradisionele medisyne in.)

Vra u dokter vir advies voordat enige van die volgende medisyne saam met XADAGO geneem word:

- Verkoue- of hoesmiddels wat dekstrometorfaan, efedrien of pseudoefedrien bevat
- Medisyne genoem selektiewe serotonienheropname-inhibeerders (SSHI's) wat tipies gebruik word om angsversteurings te behandel, en sommige persoonlikheidsversteurings (bv. fluoksetien of fluvoksamien)
- Medisyne genoem serotonien-norepinefrien heropname inhibeerders (SNHI's), wat gebruik word in die behandeling van ernstige depressie en ander gemoedsversteurings, soos venlafaksien
- Medisyne vir hoë cholesterol soos rosuvastatien, pitavastatien, pravastatien
- Fluorokinoloon-antibiotikum soos siprofloksasien
- Medisyne wat die immuunstelsel aantas soos metotreksaat
- Medisyne om metastatiese karsinoom te behandel soos topotekan
- Medisyne om pyn en inflammasie te behandel soos diklofenak
- Medisyne om swaminfeksies te behandel soos ketokonasool
- Medisyne om tipe 2-diabetes te behandel soos gliburied, metformien
- Medisyne om virale infeksie te behandel soos asiklovir, gansiklovir

**XADAGO met kos en drank**
XADAGO kan met of sonder kos geneem word.

**Swangerskap en borsvoeding**
Indien u swanger is of u baba borsvoed, raadpleeg asseblief u dokter, apteker of ander gesondheidsorg kundige vir advies voordat u XADAGO neem.

XADAGO moet nie tydens swangerskap gebruik word of deur vroue van vrugbare potensiaal wat nie voldoende voorbehoeding gebruik nie.

XADAGO sal waarskynlik in borsmelk uitgeskei word. XADAGO moet nie tydens borsvoeding gebruik word nie.

**Bestuur van 'n voertuig en hantering van masjinerie**
Lomerigheid en duiseligheid kan tydens XADAGO-behandeling voorkom; u moet versigtig wees met die hantering van gevaarlike masjiene of bestuur van 'n voertuig, totdat u redelik seker is dat XADAGO u op geen manier beïnvloed nie.
Vra u dokter vir advies voordat u 'n voertuig bestuur of masjiene hanteer.

**3. Hoe om XADAGO te neem**
Moenie enige medisyne wat aan u voorgeskryf is met enige ander persoon deel nie.
Neem XADAGO altyd presies soos u dokter vir u gesê het. Bevestig met u dokter indien u nie seker is nie.

Die aanbevole aanvangsdosis van XADAGO is een 50 mg tablet, wat verhoog kan word tot een 100 mg tablet, een keer per dag, verkieslik soggens per mond met water. XADAGO kan met of sonder kos geneem word.

Indien u aan matige verminderde lewerfunksie ly, moet u nie meer as 50 mg per dag neem nie; u dokter sal u inlig of dit op u van toepassing is.

U dokter sal u inlig hoe lank u behandeling met XADAGO sal duur.

Datum van goedkeuring: 24 Januarie 2023

Indien u die indruk het dat die effek van XADAGO te sterk of te swak is, lig u dokter of apteker in.

**Indien u meer XADAGO neem as wat u moes**
Indien u te veel XADAGO-tablette geneem het, kan u verhoogde bloeddruk, angs, verwarring, vergeetagtigheid, slaperigheid, lighoofdigheid ontwikkel; naar voel of braak; verwyde pupille of onwillekeurige rukbewegings ontwikkel. In die geval van oordosis, raadpleeg u dokter of apteker. Indien nie een beskikbaar is nie, kontak die naaste hospitaal of gifhulpsentrum. Neem hierdie voubiljet en u oorblywende tablette saam sodat die dokter kan sien wat u geneem het.

**Indien u vergeet om XADAGO te neem**
Moenie 'n dubbele dosis neem om 'n vergete dosis in te haal nie. Slaan die vergete dosis oor en neem die volgende dosis op die tyd wat u dit gewoonlik neem.

**Indien u XADAGO staak**
Moenie XADAGO staak sonder om eers u dokter te raadpleeg nie.

**4. Moontlike newe-effekte**
XADAGO kan newe-effekte hê.
Nie alle newe-effekte wat vir XADAGO aangemeld is, is in hierdie voubiljet ingesluit nie. Indien u algemene gesondheid verswak of indien u enige nadelige effekte ervaar terwyl u XADAGO neem, raadpleeg asseblief u dokter, apteker of ander gesondheidsorg kundige vir advies.

Indien enige van die volgende gebeur, staak XADAGO en lig u dokter dadelik in of gaan na die ongevalle-afdeling by u naaste hospitaal:

- Swelling van die hande, voete, enkels, gesig, lippe, tong en mond of keel, wat probleme kan veroorsaak om te sluk of asem te haal.
- Veluitslag of jeuk.
- Floutes.

Hierdie is alles baie ernstige newe-effekte. Indien u dit ervaar, het u dalk 'n ernstige allergiese reaksie op XADAGO gehad. U benodig dalk dringende mediese aandag of hospitalisasie.

Lig u dokter dadelik in of gaan na die ongevalle-afdeling by u naaste hospitaal indien u enige van die volgende opmerk:

- hipertensiewe krisis (baie hoë bloeddruk, ineenstorting)
- kwaadaardige neuroleptiese sindroom (verwarring, sweet, spierstyfheid, hoër as normale liggaamstemperatuur, verhoogde vlak van ensiem kreatienkinase in u bloed)
- serotoniensindroom (verwarring, hipertensie, spierstyfheid, hallusinasies), en
- hipotensie (lae bloeddruk).

Hierdie is alles ernstige newe-effekte. U benodig dalk dringende mediese hulp.

Lig u dokter in indien u enige van die volgende opmerk:

*Newe-effekte wat algemeen mag voorkom:*

- slapeloosheid
- probleme om vrywillige bewegings uit te voer
- voel slaperig
- duiseligheid
- hoofpyn
- verergering van Parkinson se siekte
- vertroebeling van die lens van die oog
- daling in bloeddruk wanneer u regop staan
- naarheid

*Newe-effekte wat minder algemeen kan voorkom:*

- urienweginfeksie
- velkanker
- lae yster in u bloed, lae witseltelling, rooibloedselle abnormaliteit
- verminderde eetlus, hoë vet in bloed, verhoogde eetlus, hoë bloedsuiker

- sien dinge wat nie daar is nie, voel hartseer, abnormale drome, vrees en bekommernis, verwarde toestand, buierigheid, verhoogde belangstelling in seks, abnormale denke en persepsie, rusteloosheid, slaapversteuring
- gevoelloosheid, onbestendigheid, verlies van sensasie, volgehoue abnormale spiersametrekking, ongemak van die kop, sukkel om te praat, floutes, geheue inkorting
- versteuring van visie, blindekol, dubbelvisie, lig-sensitiwiteit, versteurings van die lig-sensitiewe laag aan die agterkant van u oog, rooiheid van die oë, verhoogde druk in die oog
- sensasie van vertrek wat draai
- voel u hart klop, vinnige hartklop, onreëlmatige hartklop, vertraagde hartklop
- hoë bloeddruk, lae bloeddruk, spatare (are wat groot geword het en gedraai het)
- hoes, moeilike asemhaling, loopneus
- hardlywigheid, sooibrand, braking, droë mond, diarree, buikpyn, brandende maag, winde, vol gevoel, kwyl, mondsere
- sweet, jeuk, sensitief vir lig, rooiheid van die vel
- rugpyn, gewrigspyn, krampe, styfheid, pyn in bene of arms, spierswakheid, u voel swaar
- verhoogde urinering in die nag, pyn tydens urinering
- die onvermoë om 'n ereksie te kry of te behou by mans (erektiele disfunksie)
- moegheid, swak gevoel, onstabiele stap, swelling van u voete, pyn, warm voel
- gewigsverlies, gewigstoename, abnormale bloedtoetse, hoë vet in u bloed, verhoogde suiker in u bloed, abnormale EKG, abnormale lewerfunksietoetse, abnormale urientoetse, verlaagde bloeddruk, verhoogde bloeddruk, abnormale oogtoets
- fraktuur van u voet

*Ander newe-effekte wat ook mag voorkom:*

- longontsteking, velinfeksie, seer keel, neusallergie, tandinfeksie, virusinfeksie
- nie-kankeragtige veltoestande/groeisels
- witbloedselafwykings
- ernstige gewigsverlies en swakheid, verhoogde kalium in bloed
- onbeheerbare drange, vertroebeling van bewussyn, disoriëntasie, verkeerde persepsie van beelde, verminderde belangstelling in seks, gedagtes waarvan u nie ontslae kan

raak nie, gevoel dat iemand daarop uit is om u te benadeel, voortydige ejakulasie, onbeheerbare drang om te slaap, vrees vir sosiale situasies, gedagtes van selfdood
- lomp, maklik afleibaar, verlies aan smaak, swak/stadige reflekse, stralende pyn in die bene, voortdurende begeerte om u bene te beweeg, slaperig voel
- oogafwykings, progressiewe vermindering van visie as gevolg van diabetes, verhoogde trane, nagblindheid, oë wat oor mekaar kyk
- hartaanval
- toetrek/vernouing van bloedvat, erge hoë bloeddruk
- toetrek van die bors, probleme om te praat, probleme met/pynlike sluk
- peptiese ulkus, brakingsbewegings, maagbloeding
- geelsug
- verlies van hare, blase, velallergie, veltoestande, kneusing, skubberige vel, nagsweet, pynlike vel, verkleuring van die vel, psoriase, skilferige vel
- ontsteking van ruggraatgewrigte as gevolg van 'n outo-immuunafwyking, pyn in u sye, swelling van gewrigte, muskuloskeletale pyn, spierpyn, nekpyn, gewrigspyn, sist in die gewrig
- onbeheerbare drang om te urineer, verhoogde urinering, uitskeiding van etterselle in urien, urinêre huiwering
- prostaatprobleem, borspyn
- voel koud, voel onwel, koors, droë vel, oë en mond
- abnormale bloedtoetse, hartgesuis, abnormale harttoetse
- kneusing/swelling na besering, bloedvatblokkasie as gevolg van vet, kopbesering, mondbesering, skeletbesering
- dobbel wat voortspruit uit sosiale omstandighede
- Immuunstelselverwante hipersensitiwiteitsreaksie

Indien u enige newe-effekte opmerk wat nie in hierdie voubiljet genoem word nie, stel asseblief u dokter of apteker in kennis.

**Aanmelding van newe-effekte**

Indien u newe-effekte ervaar, raadpleeg u dokter of apteker. Dit sluit enige moontlike newe-effekte in wat nie in hierdie voubiljet gelys word nie. U kan ook newe-effekte by SAHPRA

aanmeld via die vorm “6.04 Adverse Drug Reaction Reporting Form”, wat aanlyn gevind word onder SAHPRA se publikasies: https://www.sahpra.org.za/Publications/Index/8. Deur newe-effekte aan te meld, kan u help om meer inligting oor die veiligheid van XADAGO te verskaf.

**5. Hoe om XADAGO te bêre**

- Bêre teen of benede 30 °C.
- Hou stulpstrokies in karton totdat dit benodig word vir gebruik.
- BÊRE ALLE MEDISYNE BUITE BEREIK VAN KINDERS.
- Moet nie gebruik na die vervaldatum wat op die karton gedruk is nie.
- Neem alle ongebruikte medisyne terug na u apteker.
- Moenie ongebruikte medisyne in afvoerpype en rioolstelsels (bv. toilette) weggooi nie.

**6. Inhoud van die verpakking en ander inligting**

**Wat XADAGO bevat**

Die aktiewe bestanddeel is safinamied. Elke tablet bevat 50 mg of 100 mg safinamied (as metaansulfonaat).

Die ander bestanddele is:

- Tabletkern: mikrokristallyne sellulose, kruispovidoon tipe A, magnesiumstearaat, kolloïdale watervrye silika.
- Tabletbedekking: hipromellose, makrogol (6000), titaandioksied (E171), ysteroksiedrooi (E172), mika (E555).

**Hoe XADAGO lyk en die inhoud van die verpakking**

XADAGO 50 mg is oranje tot koper, ronde, bikonkawe filmbedekte tablette van 7 mm deursnee met metaalglans, gebosseleer met "50" aan die een kant van die tablet.
XADAGO 100 mg is oranje tot koper, ronde, bikonkawe filmbedekte tablette van 9 mm deursnee met metaalglans, gebosseleer met “100” aan die een kant van die tablet.

XADAGO is beskikbaar in PVC/PVDC/Aluminium stulpverpakkings van 14, 28, 30, 90 of 100 tablette.

Datum van goedkeuring: 24 Januarie 2023

Nie alle verpakkingsgroottes word dalk bemark nie.

**Houer van Sertifikaat van Registrasie**

Adcock Ingram Limited

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Midrand 1685

South Africa

Kliëntediens: 0860 ADCOCK / 232625

**Hierdie voubiljet is mees onlangs hersien op:**

**Registrasienommers**

XADAGO 50 mg: 55/5.4.1/0806

XADAGO 100 mg: 55/5.4.1/0807

adcock ingram

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