New Medicine Recommendation

Safinamide (Xadago®) 50mg and 100mg film-coated tablets for Treatment of adult patients with idiopathic Parkinson's disease

Recommendation:

Black

Safinamide is not recommended for the treatment of patients with Parkinson's disease

Evidence to support efficacy is not adequate to support a recommendation to prescribe.

The drug is more expensive than others in its class and a favourable cost/benefit profile cannot be calculated for the drug.

There are established options for treating patients at the late stage of their condition including two drugs currently supported that fall into the MAO-B category.

Summary of supporting evidence

- Study primary endpoints of change in daily ON time without troublesome dyskinesias at 24 weeks met in 2 pivotal studies
    - 0.51 (CI95% 0.07; 0.9, p=0.0223) and 0.55 hours (CI95% 0.12; 0.99, p=0.013) for the 50 mg and 100 mg safinamide dose, respectively in study 016[20] and
    - 0.96 hrs for 50mg-100mg safinamide versus placebo (CI95% 0.56; 1.37; p <0.001) in the SETTLE study.[21]
- Secondary endpoints met and were consistent with primary endpoints in both pivotal studies
    - Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor) scores were significantly improved in both 50 and 100 mg/day groups compared to placebo (LS mean changes: 50 mg/day: 21.8 [95% CI, 23.3 to 20.4; P=0.0138]; and 100 mg/day: 22.6 in hours [95% CI, 24.1 to 21.1; P=0.0006]) in study 016.[20]
    - Statistically significant improvements in health-related quality of life and functioning, as assessed by the PDQ-39 and EQ-5D scales, were observed in the SETTLE study.[21]
- The EMEA stated that the efficacy of safinamide was favourable in the comparison to historical data of other treatments such as pramipexole or rasagiline.[19]
- Adverse event rates only slightly raised from placebo especially at the 100mg dose i.e. 78.3% for placebo, 88.5% for 50mg and 79.3% for 100mg safinamide.[19]
- Serious adverse events occurred in 12.9% of late stage PD patients compared to 11.5% for placebo. Withdrawal due to side effects was 9.1% for 50mg, and 6.1% for 100mg and 5.4% for placebo.[19]

Details of Review

Name of medicine (generic & brand name):

Safinamide (Xadago®)

Strengths and forms:

50mg and 100mg film-coated tablets[1]

Dose and administration:

50mg OD increased to 100mg OD based on individual clinical need.[1]

BNF therapeutic class / mode of action: Drugs used in parkinsonism and related disorder α-aminoamide derivative:

- Selective and reversible inhibitor of MAO-B (without inhibition of MAO-A) ➔ inhibition of dopamine uptake
- Selective sodium and calcium channel antagonist ➔ antagonism of glutamate release. [2]

Licensed indication(s):

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[1]

Proposed use:

Within licensed indication

Course and cost:

50mg x 30=£69.00; 100mg x 30=£69.00 annual cost: £839.50 (50-100mg OD)[2]

Current standard of care/comparator therapies:

MAO-B inhibitors - rasagiline, selegiline

Relevant NICE guidance:

Not yet reviewed by NICE.

NICE CG35 (Parkinson's disease in over 20s: diagnosis and management) June 2006, briefly indicates which drug classes should be used in late stage Parkinson's Disease (PD), indicating MAO-B inhibitors as potential first line choices:

1.5.1.1 It is not possible to identify a universal first-choice drug therapy for people with later PD.

The choice of adjuvant drug first prescribed should take into account:

- clinical and lifestyle characteristics
- patient preference, after the patient has been informed of the short- and long-term benefits and drawbacks of the drug classes.[3]

Options for adjuvant pharmacotherapy in later PD

Adjuvant therapy for later PD	First-choice option	Symptom control	Risk of side effects	
			Motor complications	Other adverse events

Dopamine agonists	Yes	Moderate degree of symptom control	Evidence of reduced motor complications	Evidence of increased other adverse events
COMT inhibitors	Yes	Moderate degree of symptom control	Evidence of reduced motor complications	Evidence of increased other adverse events
MAO-B inhibitors	Yes	Moderate degree of symptom control	Evidence of reduced motor complications	Evidence of increased other adverse events
Amantadine	No	Non-significant result	Evidence of reduced motor complications	Evidence of increased other adverse events
Apomorphine	No	Limited degree of symptom control	Evidence of reduced motor complications	Evidence of increased other adverse events

In the NICE guideline, 'early disease' refers to PD in people who have developed functional disability and require symptomatic therapy. 'Later disease' refers to PD in people on levodopa who have developed motor complications. Safinamide is only indicated as add-on therapy to a stable dose of levodopa.

Disease Background

Idiopathic Parkinson's disease (PD) is an adult-onset neurodegenerative disorder that is prevalent worldwide. Incidence increases sharply with age, with approximately 1 in 200 people over 70 years of age suffering from the disease.[4] PD is clinically characterised by resting tremor, bradykinesia, rigidity and gait disturbances. Progressive clinical impairment occurs, usually over a 10- to 15-year period, reflecting the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, resulting in a significant loss of dopamine (DA) in the striatum.[5] DA replacement therapy remains the backbone of antiparkinson therapy.[6] As PD progresses, further symptoms appear that either do not respond to dopaminergic replacement therapy or are related to levodopa treatment. Disabling dyskinesias and motor fluctuations are often referred to as DA-related symptoms of PD, even though these complications are likely to be a consequence of underlying nigrostriatal degeneration, revealed by exposure to dopaminergic treatment.[5]

Current treatment options

Current symptomatic treatment relies on levodopa, DA agonists, monoamine oxidase B (MAO-B) inhibitors, and catechol- O -methyltransferase (COMT) inhibitors that compensate for the deficit in the nigrostriatal dopaminergic input pathways. MAO-B inhibitors increase levels of dopamine at the synapses, improving PD motor symptoms and may be used to reduce motor fluctuations in patients with later disease.[7] The SIGN guideline for PD reviewed the evidence base for MAO-B inhibitors, concluding that their use in patients with motor fluctuations resulted in significant reductions of Unified Parkinson's Disease Rating Scale (UPDRS) total scores.[8] There is also evidence that some MAO-B inhibitors are neuroprotective.[5]

The first MAO-B inhibitor to be widely used for PD was **selegiline**, which irreversibly binds to MAO-B. Selegiline improves overall symptom control compared with placebo but effects on dyskinesias are unclear, with dyskinesias being worsened in one study and unaffected in another.[9,10,11] Less favourably, at high doses, selegiline loses its selectivity, also inhibiting MAO-A,[12,13] and being structurally related to amphetamine is metabolised to methamphetamine-based compounds, implicated in cardiovascular toxicity, including hypertension.[12]

Rasagiline is an irreversible MAO-B inhibitor that is more selective than selegiline.[14] It is not structurally related to amphetamine and therefore does not exhibit the cardiovascular side effects associated with selegiline. The efficacy of rasagiline has been demonstrated as an

adjunct to levodopa and as monotherapy for early-stage PD.[11,15,16,17] Despite selectivity of rasagiline for MAO-B, its manufacturer recommends virtually all dietary and drug restrictions required for nonselective MAO inhibitors.[18]

Safinamide is the subject of this New Medicine Assessment. It is a new highly selective and reversible MAO-B inhibitor, licensed for the treatment of adult patients with idiopathic PD as add-on therapy to L-dopa alone, or in combination with other PD medication in mid to late stage fluctuating patients. Safinamide acts through both dopaminergic and non-dopaminergic mechanisms. It is associated with state-dependent inhibition of voltage-gated sodium channels, and modulation of stimulated release of glutamate. To what extent the non-dopaminergic effects contribute to the overall effect has not been established.[1]

Summary of efficacy data in proposed use:

Pivotal studies

Data from two pivotal 24-week, randomised, parallel, double blind, placebo-controlled studies were provided to the EMEA in support of safinamide's indication "as add-on to L-dopa, alone or in combination with other PD medication, in mid- to late-stage PD patients with motor fluctuations".[19] The studies were: **Study 016**[20] (n=669) and the **SETTLE** study[21] (n=549). In addition, **study 018**,[22] a long-term extension of study 016 was performed where blinding and placebo-control was maintained for another 18 months to a total duration of 24 months.

Patients with PD with motor fluctuations despite treatment with L-dopa -with or without other PD treatments, like anticholinergics, amantadine, DA-agonists or COMT inhibitors were included in the pivotal studies. The mean patient age was 60 years and the duration of PD ranged from 8-9 years. Patients with dementia, major psychiatric illness, and/or severe and progressive medical illnesses were also excluded from trials. Both studies lacked an active comparator. The primary endpoint was change in daily ON time without troublesome dyskinesias at 24 weeks, as recorded in the patient's diary. The measured baseline ON time ranged from 9.06 to 9.52 hours over the study arms.[19]

In studies 016 and 018 there were two fixed dose arms (safinamide 50 mg or 100mg/day) whereas in SETTLE there was a flexible dose range 50-100 mg/day. The majority of subjects in the SETLLE Study received the 100 mg dose.

Study 016 results

In study 016, the mean change from baseline to Week 24 of the ON-time without troublesome dyskinesias (primary endpoint) was 0.72, 1.23 and 1.28 hour for placebo, safinamide 50 mg and 100 mg, respectively. Differences versus placebo were 0.51 (CI95% 0.07; 0.9, p=0.0223) and 0.55 hours (CI95% 0.12; 0.99, p=0.013) for the 50 mg and 100 mg safinamide dose, respectively.

The effects on secondary endpoints were consistent with the main results. Several post-hoc defined responders rates, e.g. 30 minutes improvement in ON time (without increase in dyskinesia) and OFF time were in favour of the 100 mg dose groups i.e. 40.1 % for placebo versus and 51.8% in safinamide 100mg group, whereas no significant difference was achieved for the 50 mg dose group. Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor) scores were significantly improved in both 50 and 100 mg/day groups compared to placebo (LS mean changes: 50 mg/day: 21.8 [95% CI, 23.3 to 20.4; P=0.0138]; and 100 mg/day: 22.6 in hours [95% CI, 24.1 to 21.1; P=0.0006]).

SETTLE study results

In the **SETTLE** study, ON-time without troublesome dyskinesias at Week 24 improved by 0.56 and 1.52 hours for placebo and safinamide 50-100 mg/dose group, respectively. Difference versus placebo was 0.96 hrs (CI95% 0.56; 1.37; p <0.001). For both studies the observed effects in ON time were reflected in a reciprocal decrease in OFF-time.

Statistically significant improvements in health-related quality of life and functioning, as assessed by the PDQ-39 and EQ-5D scales, were observed. For the UPDRS-II, Dyskinesia Rating Scale and GRID-HAM-D, there was no significant difference between groups in the change from baseline in total score.[19]

Relevance of pivotal studies

As no active comparator was included in the pivotal studies, the magnitude of the observed treatment effects is difficult to appreciate. The efficacy of safinamide was favourable in the comparison to historical data of other treatments such as pramipexole or rasagiline.[19] The improvements of 0.51h or 1h in ON time, respectively, were deemed clinically relevant in this population of advanced patients with motor-fluctuations, however the claims with respect to a beneficial effect on dyskinesias could not be substantiated by data.

Study 018

From the 669 patient cohort of study 016, 544 continued their allocated study treatment in study 018.[22] The median duration of treatment was 2.0 years from baseline of study 016. For the primary endpoint of mean change in dyskinesia score during ON-time, a worsening of 0.32 points was observed in the placebo group (baseline 3.4 points). For the safinamide 50 mg group an improvement of 0.19 points (baseline 3.9) was observed. For safinamide 100 mg/day a 0.28 points improvement (from baseline 3.7 points) was observed. The extension study did not meet the primary end point in the overall population; the differences were not statistically significant and were considered only indicative for efficacy. The L-dopa dose increased by 18%, 10% and 5 % in the placebo, 50 mg and 100mg/day group, respectively, which further illustrated maintenance of efficacy regarding the effect on improvement of motor symptoms.

Summary of safety data:

In total, 3169 study subjects participated in the clinical development program of safinamide and of this study population, 2013 patients with PD received safinamide.[19] 1036 patients with mid to late stage PD were exposed to safinamide in clinical trials, of these 734 received safinamide for more than 1 year and 169 patients received safinamide for more than 4 years.[19] In late stage PD patients (for whom the drug is licensed), adverse events tended to occur more often for dosages of 50 mg safinamide per day (88.5%) compared to 100 mg safinamide per day (79.3%). The adverse event rate for placebo treated patients was 78.3%.

The most frequently observed types of adverse events among late stage PD patients were: nervous system disorders (38-60%), gastro-intestinal disorders (22-27%), infections and infestations (18-22%), musculoskeletal disorders (20-30%), and eye disorders (16-27%).[19] 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,[1] in the clinical study programme they occurred in 12.9-31.3% of late stage PD patients.[19]

Serious adverse events occurred in 12.9% of late stage PD patients compared to 11.5% for placebo. Withdrawal due to side effects was 9.1% for 50mg, and 6.1% for 100mg and 5.4% for placebo.[19]

The SPC for Safinamide (Xadago®) lists the following adverse events:[1]

Incidence of Event	Adverse Event
Very Common (≥1/10)	None listed
Common (≥1/100 to <1/10)	Insomnia, dyskinesia, somnolence, dizziness, headache, Parkinson's disease, cataract, orthostatic hypotension, nausea, fall
Uncommon (≥1/1,000 to <1/100)	Urinary tract infection, basal cell carcinoma, anaemia, leukopenia, red blood cell abnormality, decreased appetite, hypertriglyceridaemia, increased appetite, hypercholesterolaemia, hyperglycaemia, hallucination, depression, abnormal dreams, anxiety, confusional state, affect lability, libido increased, psychotic disorder, restlessness, sleep disorder, paraesthesia, balance disorder, hypoaesthesia, dystonia, head discomfort, dysarthria, syncope, cognitive disorder, vision blurred, scotoma, diplopia, photophobia, retinal disorder, conjunctivitis, glaucoma, vertigo, palpitations, tachycardia, sinus bradycardia, arrhythmia, hypertension, hypotension, varicose vein, cough, dyspnoea, rhinorrhoea, constipation, dyspepsia, vomiting, dry mouth, diarrhoea, abdominal pain, gastritis, flatulence, abdominal distension, salivary hypersecretion, gastrooesophageal reflux disease, aphthous stomatitis, hyperhidrosis, pruritus generalised, photosensitivity reaction, erythema, back pain, arthralgia, muscle spasms, muscle rigidity, pain in extremity, muscular weakness, sensation of heaviness, nocturia, dysuria, erectile dysfunction, fatigue, asthenia, gait disturbance, oedema peripheral, pain, feeling hot, 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, foot fracture
Rare (≥1/10,000 to <1/1,000)	Bronchopneumonia, furuncle, nasopharyngitis, pyoderma, rhinitis, tooth infection, viral infection, acrochordon, melanocytic naevus, seborrhoeic keratosis, skin papilloma, eosinophilia, lymphopenia, cachexia, hyperkalaemia, compulsions, delirium, disorientation, illusion, impulsive behaviour, loss of libido, obsessive thoughts, paranoia, premature ejaculation, sleep attacks, social phobia, suicidal ideation, coordination abnormal, disturbance in attention, dysgeusia, hyporeflexia, radicular pain, Restless Legs Syndrome, sedation, amblyopia, chromatopsia, diabetic retinopathy, erythropsia, eye haemorrhage, eye pain, eyelid oedema, hypermetropia, keratitis, lacrimation increased, night blindness, papilloedema, presbyopia, strabismus, myocardial infarction, arterial spasm, arteriosclerosis, hypertensive crisis, bronchospasm, dysphonia, oropharyngeal pain, oropharyngeal spasm, peptic ulcer, retching, upper gastrointestinal haemorrhage, hyperbilirubinaemia, alopecia, blister, dermatitis contact, dermatosis, ecchymosis, lichenoid keratosis, night sweats, pain of skin, pigmentation disorder, psoriasis, seborrhoeic dermatitis, ankylosing spondylitis, flank pain, joint swelling, musculoskeletal pain, myalgia, neck pain, osteoarthritis, synovial cyst, micturition urgency, polyuria, pyuria, urinary hesitation, benign prostatic hyperplasia, breast disorder, breast pain, drug effect decreased, drug intolerance, feeling cold, malaise, pyrexia, xerosis, 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, contusion, fat embolism, head injury, mouth injury, skeletal injury, gambling

Safinamide is contraindicated in patients with severe hepatic impairment, albinism, retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy.

The use of safinamide is contraindicated with pethidine and in combination with other MAOIs and cautioned in patients taking sympathomimetics due to the potential for hypertensive crisis.[1]

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 medicinal products should be used at low doses.[1]

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.[1]

The EMEA concluded in its public assessment report that, overall, the safety of safinamide was considered acceptable, as incidences of adverse events under safinamide treatment seemed quite low as compared to placebo. In the light of the animal findings, the CHMP was of the view that even though the clinical data did not indicate a risk in PD patients, retinal deterioration should be considered as an important potential risk. This potential is followed up through routine and additional pharmacovigilance activities which also focus on the increased incidence of dyskinesia, and the potential for development of impulse control disorders.[19]

Strengths and limitations of the evidence:

Strengths:

- Safinamide has demonstrated a statistically significant effect, increasing ON-time without troublesome dyskinesias in patients with late stage PD in two large, placebo controlled trials.
- The EMEA stated that the efficacy of safinamide was favourable in the comparison to historical data of other treatments such as pramipexole or rasagiline.[19]
- The secondary endpoint in study 016, Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor) scores, were significantly improved in both 50 and 100 mg/day groups compared to placebo.
- Adverse events tended to occur more often for dosages of 50 mg safinamide per day (88.5%) compared to 100 mg safinamide per day (79.3%) compared to 78.3% for placebo.

Limitations

- In the long term study 018, the primary endpoint of mean change in dyskinesia score during ON-time appeared to support safinamide but the differences observed were not statistically significant hence additional data are required to conclude that safinamide is preferable in patients treated beyond the initial 24 week studies.
- Only patients who were compliant with therapy during the study 016, were willing to continue and were not withdrawn due to adverse events were entered in to study 018 therefore there will be some self-selection bias in the results of the extension study.
- All trials were against placebo and not comparator drugs.
- Conclusions about differences in comparison to active drug are not directly available and historical data can only infer favourability compared to active comparator.
- Despite clinical data not indicating a risk in Parkinson's disease patients, retinal deterioration is considered an important potential risk with safinamide.[19]
- Experience of use of safinamide in patients over 75 years of age is limited.[1]

Prescribing and risk management issues:

Although retinal toxicity was present in rats, and its mechanism had not been elucidated, the lack of consistent similar findings in humans diminished the concern for potential similar effect on the patients. Based on the non-clinical evidence available, retinal degeneration should be considered as an important potential risk and followed up on through routine and additional pharmacovigilance activities, as described in a risk management plan including completion of targeted follow-up questionnaires for all spontaneous reports of retinal events to determine their potential association with safinamide.[19] Safinamide is a 'black triangle' medicine - the Commission on Human Medicines (CHM) and the MHRA encourages the reporting of all suspected adverse reactions (side effects) to newer drugs and vaccines, which are denoted by the Black Triangle symbol.[23]

Commissioning considerations:

Prescribing of MOA-B inhibitors across Lancashire August 2015 to July 2016

Drug	Items	Cost	Cost/item
Selegiline	1,430	£24,660	£17.24
Rasagiline	9,473	£580,587	£61.29
TOTAL	10903	£605,247	N/A
Prescribing data for Lancashire August 2015 to July 2016			

Cost of MOA-B inhibitors

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Safinamide (Xadago®)	50-100mg OD	50mg x 30 = £69.00 100mg x 30 = £69.00	£839.50 Cost per item = £69.00
Selegiline (Eldepryl®)	5-10mg OM	5mg x 100 = £16.52 5mg x 60 = £26.50 10mg x 100 = £32.23 10mg x 30 = £27.20	Prices **unstable** Cost per item = £17.24
Rasagiline (generic)	1mg OD	1mg x 28 = £58.53	£762.98 Cost per item = £61.29
Costs based on MIMS list prices October 2016. Table does not imply therapeutic equivalence of drugs or doses.			

Anticipated patient numbers and net budget impact

PD is a common neurological condition, estimated to affect 274 per 100,000 of the population.[24]

Rasagiline has a 'stable' price of £58.53 for 28 tablets; selegiline has an 'unstable' price and, depending on product dispensed, will cost varying amounts for each prescription.

Using the rasagiline figures in the table above, it is clear that MAO-B inhibitors are prescribed approximately on a monthly basis – rasagiline costs £58.53 for 28 tablets, 1 item costs on average £61.29.

Rasagiline and selegiline combined total 10903 items per year, equivalent to 909 items per month, therefore around 909 patients are treated with MAO-B inhibitors in Lancashire.

Currently in Lancashire the spend on MAO-B inhibitors is £605,247

If, in one year 10% of patients are prescribed safinamide instead of either rasagiline or selegiline:

- 10% of selegiline is 143 items.
- 10% of rasagiline is 947 items,
- total 1090 items which would cost £75,210 if prescribed as safinamide.

A 10% reduction in selegiline and rasagiline would leave costs:

- £22,187 for selegiline and
- £522,558 for rasagiline
- Total £544,745

Calculated above, 10% of items as safinamide would cost £75,210 which is added to the selegiline and rasagiline figures giving a total cost for the year of £619, 955

- The extra spend in one year because of the 10% uptake of safinamide will be £619,955 – £605,247 = **£14, 708**

Associated additional costs or available discounts:

None identified

Productivity, service delivery, implementation:

It is anticipated that patients with mid to late stage fluctuating PD would be under the ongoing care of a specialist.

Innovation, need, equity:

Safinamide differs from the MAO-B inhibitors currently licensed for PD in its mode of inhibition (reversible rather than irreversible, limiting the potential for interactions with tyramine-rich foods and sympathomimetic and serotonergic substances) and by its additional activity on sodium channels and glutamate release. To what extent the non-dopaminergic effects contribute to the overall effect has not been established.

Appendix A - Summary of key safinamide RCTs relevant to use in mid to late Parkinson's disease

Ref	Trial design	Patients / trial subjects	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
20	Phase III, double-blind, randomised, placebo-controlled, parallel-group, multicentre trial 10-day PD treatment optimisation period → 4-week L-dopa stabilisation period → 24 week treatment period → 1-week optional taper period	Population: Adults (aged 30-80) with mid to late stage idiopathic PD of ≥3 years' duration, experiencing motor fluctuations while receiving L-dopa and other dopaminergic treatments, including dopamine agonists, COMT inhibitors, amantadine ± anticholinergics. ITT population = 669 Inclusion criteria: • Hoehn and Yahr stage I-IV during off • >1.5hours off/day • Able to accurately maintain a diary for the 10-day treatment optimisation period and the 5 days preceding each scheduled visit Exclusion criteria: • Severe, disabling peak-dose/biphasic dyskinesia • Unpredictable/widely swinging symptoms fluctuations • Dementia • Major psychiatric illness • Severe progressive medical illness • MAO inhibitors/TCA/SNRI treatment before/during the study Treatment: Placebo/safinamide 50mg OM/safinamide 100mg OM. [During the 24 week treatment period doses of safinamide could be increased/decreased, PD drugs	Change in mean daily total on time with no dyskinesia or on with non-troublesome dyskinesia (dyskinesia does not interfere with function/cause meaningful discomfort) versus placebo assessed using Hauser's patient diaries Safinamide 50mg OM = 30.6 minutes (95% CI 4.2-56.4 minutes; p = 0.0223) Safinamide 100mg OM = 33minutes (95% CI 7.2-59.4 minutes; p = 0.0130)	Change in mean daily off time versus placebo Safinamide 50mg OM = -36 minutes (95% CI -54 to -12 minutes; p = 0.0043) Safinamide 100mg OM = -36 minutes (95% CI -60 to -12 minutes; p = 0.0034) UPDRS-III (motor) scores versus placebo in the on phase Safinamide 50mg OM = -1.8 (95% CI -3.3 to -0.4; p = 0.0138) Safinamide 100mg OM = -2.6 (95% CI = -4.1—1.1; p = 0.0006) Change in UPDRS-II (ADL) from baseline: Placebo = -1.2 Safinamide 50mg OM = -1.7 (p = 0.1253) Safinamide 100mg OM = -2.2 (p = 0.0060) Change in PDQ-39 total score from baseline: Placebo = -11.9 Safinamide 50mg OM = -16.4 (p =	Level 1

		(except MAOIs) could be initiated, and L-dopa dose reduced as indicated]		0.5603) Safinamide 100mg OM = -28.4 (p = 0.0360) 10-13% of patients had their L-dopa dose reduced during the trial (no statistically significant between-group differences)	
22	Phase III, double-blind, randomised, placebo-controlled, parallel-group, multicentre extension trial Continuation in the same treatment group to which they were randomised in study [2]	Population: Patients from study [20]. ITT population = 669 (entry number = 544) Inclusion criteria: • Had completed the study • Were treatment compliant during study • Were willing to continue with trial participation • Discontinued from [20], but efficacy evaluations at weeks 12 & 24 complete Exclusion criteria: • Clinically significant AEs during study [2] • Clinically significant deterioration in motor symptoms during study [2] • MAO inhibitors/ TCA/SNRI/neuroleptic/tramadol/pethidine/ hepatic enzymes inducer or inhibitor treatment during the study [During the 18 month study doses of safinamide could be decreased/interrupted/discontinued, PD drugs could be initiated, and L-dopa dose reduced as indicated]	Mean change from baseline (at start of study [2]) in DRS total score during on time, calculated as the sum of the severities across all items collected at a particular time point Placebo = +0.32 Safinamide 50mg OM = -0.19 Safinamide 100mg OM = -0.28 Primary endpoint not met.	Mean daily total on time with no dyskinesia or on with non-troublesome dyskinesia (dyskinesia does not interfere with function/cause meaningful discomfort) from week 0 (study [20]) to week 72 Placebo = 20.4 Safinamide 50mg OM = 60.6 minutes (95% CI 13.8-66.6 minutes; p = 0.0031) Safinamide 100mg OM = 70.8 minutes (95% CI 23.4-76.2 minutes; p = 0.0002)	Level 1
NCT00627640 (Safinamide Add on to L-Dopa: A Randomized, Placebo-Controlled, 24-Week Global Trial in Patients with Parkinson's Disease (PD) and Motor Fluctuations (SETTLE)) abstract only available					

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: high quality randomised controlled trials (RCTs) with low risk of bias systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: clinical trials at moderate or high risk of bias systematic reviews or meta-analyses of such clinical trials or with inconsistent findings cohort studies case-control studies	
Level 3	Disease-oriented evidence, or evidence from: consensus guidelines expert opinion case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Midlands and Lancashire Commissioning Support Unit,
Jubilee House, Lancashire Business Park, Leyland, PR26 6TR

References

[1] Electronic Medicines Compendium, Summary of Product Characteristics for Xadago® (safinamide) https://www.medicines.org.uk/emc/medicine/31917 [accessed online on 10 October 2016]

[2] Haymarket Media Group, eMIMS online http://www.mims.co.uk/drugs/central-nervous-system/parkinson-s-disease-parkinsonism/xadago [accessed online 7 October 2016]

[3] https://www.nice.org.uk/guidance/cg35/resources/parkinsons-disease-in-over-20s-diagnosis-and-management-975388237765 [accessed online 10 October 2016]

[4] Rajput AH, Offord KP, Beard CM, Kurland LT. Epidemiology of parkinsonism: incidence, classification, and mortality. Ann Neurol 1984 ; 16 : 278 -82

[5] Onofrj M, Bonanni L & Thomas A. An expert opinion on safinamide in Parkinson's disease. Expert Opin. Investig. Drugs (2008) 17(7):1115-1125

[6] Clarke CRA. Neurological disease. In: Kumar P, Clark M, editors, Clinical medicine. 4th edition. WB Saunders, Edinburgh, UK; 1999 . p. 1062 -4

[7] The National Collaborating Centre for Chronic Conditions. Parkinson's Disease: National clinical guideline for diagnosis and management in primary and secondary care. Royal College of Physicians; 2006

[8] Scottish Intercollegiate Guidelines Network. Diagnosis and pharmacological management of Parkinson's disease: A national clinical guideline. NHS Quality Improvement Scotland; 2010

[9] Golbe LI, Lieberman AN, Muenter MD, et al. Deprenyl in the treatment of symptom fluctuations in advanced Parkinson's disease. Clin Neuropharmacol 1988; 11: 45 -55

[10] Waters CH, Sethi KD, Hauser RA, et al. Zydis selegiline reduces off time in Parkinson's disease patients with motor fluctuations: a 3-month, randomized, placebo-controlled study. Mov Disord 2004; 19: 426 -32

[11] Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006; 66 (7): 983 -95

[12] Moussa BH, Bakhle Y, Bakhle YS. Monoamine oxidase: isoforms and inhibitors in Parkinsons's disease and depressive illness. Br J Pharmacol 2006; 147: S287 -96

[13] Lew MF, Pahwa R, Leehey M, et al. Safety and efficacy of newly formulated selegiline orally disintegrating tablets as an adjunct to levodopa in the management of 'off ' episodes in patients with Parkinson's disease. Curr Med Res Opin 2007; 23: 741 -50

[14] Guay DRP. Rasagiline (TVP-1012): a new selective monoamine oxidase inhibitor for Parkinson's disease. Am J Geriatr Pharmacother 2006; 4: 330 -46

[15] Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. Arch Neurol 2002; 59: 1937 -43

[16] Rascol O, Brooks DJ, Melamed E, et al. LARGO study group. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once-daily, study): a randomised, double-blind, parallel-group trial. Lancet 2005;365:947-54. Comment in: Lancet 2005; 365: 914 -6

[17] Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. Arch Neurol 2005; 62: 241 -8

[18] Guay DRP. Rasagiline (TVP-1012): a new selective monoamine oxidase inhibitor for Parkinson's disease. Am J Geriatr Pharmacother 2006; 40: 330 -46

[19] European Medicines Agency. Xadago – European Public Assessment Report; December 2014. Accessed 23 June 2016 at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002396/WC500184967.pdf

[20] Borgohain R, Szasz J, Stanzione P et al. Randomized Trial of Safinamide Add-On to Levodopa in Parkinson's Disease With Motor Fluctuations. Movement Disorders. 2014; 29(2): 229-237

[21] Schapira A, Fox S, Hauser R et al. Safinamide add on to L-dopa: a randomized, placebo-controlled, 24-week global trial in patients with Parkinson's disease (PD) and motor fluctuations (SETTLE). 65th Annual Meeting of the American Academy of Neurology (AAN); March 16-23, 2013; San Diego Convention Centre, San Diego, CA, USA

[22] Borgohain R, Szasz J, Stanzione P et al. Two-Year, Randomized, Controlled Study of Safinamide as Add-on to Levodopa in Mid to Late Parkinson's Disease. Movement Disorders. 2014; 29(10): 1273-1280

[23] MHRA. Black Triangle Scheme - new medicines and vaccines subject to EU-wide additional monitoring. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/396808/Black_Triangle_Scheme_-_new_medicines_and_vaccines_subject_to_EU-wide_additional_monitoring.pdf [accessed online 14 October 2016]

[24] Parkinson's UK. Parkinson's prevalence in the United Kingdom (2009); 2012 https://www.parkinsons.org.uk/sites/default/files/parkinsonsprevalenceuk_0.pdf [accessed online 14 October 2016]