



Bedfordshire and Luton Joint Prescribing Committee (JPC)

**18 September 2019
Review Date September 2022**

Bulletin 277: Safinamide for Parkinson's Disease

JPC Recommendation:

A Formulary application for Safinamide for the treatment of Parkinson's Disease was considered at the September 2019 JPC meeting.

Following discussion, the Committee decided not to support the Formulary application for safinamide. The main concerns were the lack of head to head trials with appropriate comparators, safety issues (e.g. retinopathy) and cost/cost-effectiveness.

**Bedfordshire CCG
Luton CCG**

New Medicine Review Bulletin

Safinamide for the treatment of Parkinson's disease

Medicine	Safinamide (Xadago®) for the treatment of Parkinson's disease
Document status	<i>Final</i>
Date of last revision	03/09/2019, minor update 05/11/19
Proposed Sector of prescribing	Primary and Secondary Care
Introduction Summary Key points Evidence level	<p>Introduction</p> <p>The Luton & Dunstable Hospital has requested the addition of safinamide for the treatment of Parkinson's disease (in accordance with the marketing authorisation for safinamide and NICE Clinical Guideline 71 – Parkinson's Disease in Adults) to be added the Joint Bedfordshire and Luton Formulary. This review outlines the key evidence of efficacy, safety and cost for safinamide and is mainly based on NICE Evidence Summary – Parkinson's disease with motor fluctuations: safinamide, published 21 February 2019.</p> <p>Key Points:-</p> <p>The summary of product characteristics (SPC) states that safinamide (Xadago: Profile Pharma) is a highly selective and reversible MAO-B inhibitor. This differs from rasagiline and selegiline which are selective and irreversible MAO-B inhibitors (European Public Assessment Report [EPAR]: Xadago). Several other mechanisms of action of safinamide have been identified by in-vitro data, including sodium channel inhibition and reducing excessive glutamate release. However, the extent to which the non-dopaminergic effects contribute to the overall clinical effect of safinamide has not been established. The EPAR for safinamide states that no clinical effects that might be related to these mechanisms were clearly evident in clinical trials.</p> <p>The NICE evidence summary discusses 3 randomised controlled trials (RCTs) in people with Parkinson's disease of at least 3 years duration, who were taking a stable dose of levodopa and were experiencing motor fluctuations. Most people in the studies were also taking other Parkinson's disease medicines, most commonly a dopamine agonist. There is limited data on the use of safinamide as a first choice add-on treatment to levodopa.</p> <p>The main clinical benefits of safinamide at 24 weeks were an increase in 'on time' without troublesome dyskinesia (involuntary movements) of approximately 30 to 60 minutes daily, and a similar reduction in 'off time', compared with placebo. This effect was still observed at a 2-year follow-up.</p> <p>Dyskinesia was the most commonly reported adverse effect, but was usually mild and associated with an increase in on time. Contraindications and cautions for use are similar to those of other MAO-B inhibitors. There is a potential risk of retinal degeneration in people with, or a previous history of, retinal disease with safinamide.</p> <p>Safinamide is the third MAO-B inhibitor licensed in the UK as add-on treatment to levodopa in people with Parkinson's disease who are experiencing motor fluctuations. It is more expensive than other MAO-B inhibitors.</p> <p>There are no head-to-head studies comparing the efficacy and safety of safinamide with other active treatments, including other MAO-B inhibitors.</p>

	The NICE guideline on Parkinson's disease makes recommendations on the place in therapy of adjuvant treatments. The choice of treatment will depend on the person's clinical and lifestyle characteristics, and their preferences, after an informed discussion about the benefits and risks of treatment.
The intervention Mechanism of action	The summary of product characteristics (SPC) states that safinamide (Xadago: Profile Pharma) is a highly selective and reversible MAO-B inhibitor. This differs from rasagiline and selegiline which are selective and irreversible MAO-B inhibitors (European Public Assessment Report [EPAR]: Xadago). Several other mechanisms of action of safinamide have been identified by in-vitro data, including sodium channel inhibition and reducing excessive glutamate release. However, the extent to which the non-dopaminergic effects contribute to the overall clinical effect of safinamide has not been established. The EPAR for safinamide states that no clinical effects that might be related to these mechanisms were clearly evident in clinical trials. ⁽¹⁾
Licensed indication	Safinamide is indicated for the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients. ⁽²⁾
Formulation/Available Products	Film coated tablets containing safinamide methansulfonate equivalent to 50mg and 100mg safinamide. ⁽²⁾
Usual dosage	Start at 50 mg daily. The 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. <i>Hepatic impairment</i> No dosage adjustment is required in patients with mild hepatic impairment. The lower dose of 50 mg/day is recommended for patients with moderate renal impairment. Safinamide use is contra-indicated in patients with severe hepatic impairment. ⁽²⁾
Treatment alternatives/ place in therapy	Rasagiline and selegiline which are selective and irreversible MAO-B inhibitors. ⁽¹⁾ Selegiline (Eldepryl®) is a Formulary Medicine while Selegiline (Zelapar®) and Rasagiline are Non Formulary Medicines. http://www.bedsformulary.nhs.uk/ The proposed place in therapy from the requesting specialist is attached below along with the New Medicines Request.  Safinamide protocol.pdf  Safinamide DTC NMA L&D application In summary – the specialist has asked for safinamide to be added to Formulary for the following three principle reasons:- 1) Increased clinical efficacy – the clinician refers to the information included in the NICE Evidence Summary (See Evidence for use section below for more information) 2) Increase available treatment options for patients with co-morbidities The Clinician makes the following key points:- 'Safinamide can be used concomitantly with antidepressants at the lowest necessary doses, compared to rasagiline, where fluoxetine and fluvoxamine are contraindicated, and selegiline, where all antidepressants are contraindicated.' Author's response – The SPC for Safinamide states that 'concomitant use of Safinamide with fluoxetine or fluvoxamine should be avoided, or if concomitant treatment is necessary, these medicinal

	<p>products should be used at low doses. A washout period corresponding to 5 half lives of the SSRI used previously should be considered prior to initiating treatment safinamide.’ The eBNF entries relating to selegiline/rasagiline/safinamide with respect to the interactions with fluoxetine and fluvoxamine are the same.</p> <p>Selegiline is also contraindicated for use in association with levodopa in patients with concomitant severe cardiovascular disease, arterial hypertension, hyperthyroidism, phaeochromocytoma, prostatic adenoma with the appearance of residual urine, tachycardia, arrhythmias, severe angina pectoris and thyrotoxicosis, while rasagiline and safinamide have no specific caution or contra-indication in these patient groups. Author’s response - I would agree with this statement.</p> <p>Parkinson’s disease is associated with orthostatic hypotension. As per NICE guidelines regarding treatment of Parkinson’s disease, if pharmacological treatment of orthostatic hypotension in Parkinson’s disease is required, first-line therapy is midodrine, with fludrocortisone second-line. Sympathomimetics, such as midodrine, are contraindicated for use with rasagiline/selegiline, while may be used in combination with safinamide with caution. Author’s response – The eBNF interaction information relating to the safinamide/midodrine interaction states the following ‘Safinamide is predicted to increase the risk of a hypertensive crisis when given with midodrine. Manufacturer advises avoid. Severity of interaction: Severe; Evidence for interaction: Anecdotal’</p> <p>3) Increased patient safety</p> <p>There was no association with an increased frequency of impulse control disorders with safinamide use, no requirement for dietary modification, and decreased rates of hallucinations compared to the other available monoamine oxidase (MAO) inhibitors, and no cautions/contraindications in those with cardiovascular risk. Post-hoc data is suggestive of decreased analgesic therapy required in patients treated with safinamide. Author’s response – I would agree with these statements.^{2,8,9} No dietary modification is recommended for patients treated with selegiline or rasagiline. ^{8,9}</p>
National guidance	<p>NICE – NICE Guideline 71, Parkinson’s disease in adults, July 2017 – https://www.nice.org.uk/guidance/ng71 - ‘offer a choice of dopamine agonists, MAO-B inhibitors or catechol-O-methyl transferase (COMT) inhibitors as an adjunct to levodopa for people with Parkinson’s disease who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy’ NICE Parkinson’s disease Clinical Knowledge Summary (CKS). https://cks.nice.org.uk/parkinsons-disease - Safinamide (Xadago®) has been added as possible adjuvant therapy in the section on specialist management of motor symptoms, in line with the manufacturer’s Summary of Product Characteristics (SPC, 2016).</p> <p>All Wales Medicines Strategy Group – ‘In the absence of a submission from the holder of the marketing authorisation, safinamide (Xadago®) cannot be endorsed for use within NHS Wales for the treatment of adult patients with idiopathic Parkinson’s disease as add-on therapy to a stable dose of levodopa (L-dopa) alone or in combination with other Parkinson’s disease medicinal products in mid-to late-stage fluctuating patients.’.</p> <p>Scottish Medicines Consortium – ‘In the absence of a submission from the holder of the marketing authorisation, Safinamide (Xadago®) is not recommended for use within NHS Scotland’, June 2017.</p>
Local Guidance	None

<p>Evidence for use</p>	<p>NICE conducted an Evidence Review on 'Parkinson's disease with motor fluctuations: safinamide', published on 21 February 2017. Click here for the full evidence review.</p> <p>A summary of the main points from the review are outlined in table 1 below:-</p> <p>Table 1 Summary of the evidence on effectiveness, safety, patient factors and resource implications</p>
	<p>Effectiveness</p> <ul style="list-style-type: none"> • Safinamide was more effective than placebo at improving on time without troublesome dyskinesia by approximately 30 to 60 minutes daily (from a baseline of about 9 hours daily) at 24 weeks and 2 years follow-up. There were similar reductions in off time (3 RCTs: study 016, SETTLE study, study 018, total n=1,218). • Safinamide did not improve dyskinesia in the 3 RCTs (measured by DRS total score) compared with placebo. This was the primary outcome of study 018. • In study 016 and SETTLE, safinamide improved motor symptoms during on time (by about 2 points on UPDRS-III) compared with placebo at 24 weeks (from a baseline of 22 to 29 points). This improvement was still observed at 2 years only in the safinamide 100 mg daily group. • Safinamide 100 mg or 50–100 mg was more effective than placebo at improving health-related quality of life (measured by PDQ-39). There was no statistically significant difference between safinamide 50 mg and placebo (3 RCTs). • More people had improvement in clinical global impression (measured by CGI-C) with safinamide compared with placebo at 24 weeks; this was statistically significant. This difference was still observed at 2 years only in the safinamide 50 mg daily group. <p>Safety</p> <ul style="list-style-type: none"> • The SPC states that safinamide is contraindicated in severe hepatic impairment and should be used with caution in moderate hepatic impairment. • Safinamide is also contraindicated in people with albinism, retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy; and with other MAO inhibitors or pethidine.

	<ul style="list-style-type: none"> The SPC states that safinamide used as an adjunct to levodopa may potentiate the adverse effects of levodopa, and pre-existing dyskinesia may be exacerbated.
	<p>Patient factors</p> <ul style="list-style-type: none"> Common adverse effects reported in the SPC are dyskinesia, insomnia, nausea, somnolence, dizziness, headache, Parkinson's disease symptoms, cataracts, orthostatic hypotension and falls. Impulse control disorders have been seen with other MAO inhibitors, and patients and carers should be made aware of the behavioural symptoms of these. Safinamide can be used without any dietary tyramine restrictions. Safinamide has not been investigated in people with severe, disabling peak dose or biphasic dyskinesia with unpredictable or wide fluctuations; people with a history or presence of retinal disease; or people with psychiatric illness, bipolar disorder or severe depression.
	<p>Resource implications</p> <ul style="list-style-type: none"> The NHS list price for safinamide 50 mg or 100 mg is £69.00 for 30 tablets (Drug Tariff, February 2017; excluding VAT). The 30-day cost of other MAO-B inhibitors is £3.38 for rasagiline 1 mg daily and £9.67 for selegiline 10 mg daily (Drug Tariff, February 2017; excluding VAT).
	<p>A literature review, providing an update to the clinical evidence published after the NICE Evidence Review was published, identified no additional RCTs.</p> <p>Two Research Reports looked at the 'Effects of Safinamide on Pain in Fluctuating Parkinson's Disease Patients: A <i>Post-Hoc</i> Analysis'⁴ and 'Long-Term Effects of Safinamide on Mood Fluctuations in Parkinson's Disease'⁵ respectively. Both studies were pharmaceutical company sponsored and carried the major limitation that they were <i>post-hoc</i> analyses of the original trials which were not designed to investigate the outcomes of pain and mood fluctuations as primary outcomes. The findings of the trials should only be considered as exploratory and are subject to confirmation in larger clinical trials.</p> <p>A meta-analysis (abstract only reviewed) of monoamine oxidase type B inhibitors for Parkinson's Disease ⁶, concluded that all of the included MAO-B inhibitors (rasagiline, selegiline and safinamide) were effective when given as monotherapy. Combination therapy with MAO-B inhibitors and levodopa showed that all three</p>

	<p>MAO-B inhibitors were effective compared to placebo, but selegiline was the most effective drug.</p> <p>A Drug and Therapeutics Bulletin review entitled 'Which MAO-B inhibitor for Parkinson's Disease?' which reviewed the above meta-analysis, noted that 'given the absence of a significant major difference between the drugs, a sensible first-line choice would be the drug with the lowest acquisition cost.'⁷</p>
Safety*	<p>Side-effects</p> <p>Common or very common Cataract; dizziness; dyskinesia; drowsiness; headache; hypotension; injury; falls; nausea; sleep disorders; Parkinson's disease.</p> <p>Uncommon Anaemia; anxiety; appetite abnormal; arrhythmias; asthenia; cognitive disorder; confusion; constipation; cough; decreased leucocytes; depression; diarrhoea; dry mouth; dysarthria; dyslipidaemia; dyspnoea; emotional lability; eye disorders; eye inflammation; gastrointestinal discomfort; gastrointestinal disorders; glaucoma; hallucination; hyperglycaemia; hypertension; increased risk of infection; joint disorders; movement disorders; muscle complaints; muscle weakness; neoplasms; oral disorders; pain; palpitations; peripheral oedema; photosensitivity reaction; psychotic disorder; QT interval prolongation; red blood cell abnormality; rhinorrhoea; sensation abnormal; sensation of pressure; sexual dysfunction; skin reactions; sweat changes; syncope; temperature sensation altered; urinary disorders; varicose veins; vertigo; vision disorders; vomiting; weight changes</p> <p>Rare or very rare Alopecia; arterial spasm; atherosclerosis; benign prostatic hyperplasia; breast abnormalities; bronchospasm; cachexia; concentration impaired; delirium; diabetic retinopathy; dysphonia; eosinophilia; eye pain; fat embolism; fever; gambling; haemorrhage; hyperbilirubinaemia; hyperkalaemia; illusion; malaise; myocardial infarction; oropharyngeal complaints; osteoarthritis; paranoia; psychiatric disorders; pyuria; reflexes decreased; suicidal ideation; taste altered.^{2,3}</p>
Cautions*	<p>Hypertension (may raise blood pressure); may exacerbate pre-existing dyskinesia (requiring levodopa dose reduction); moderate hepatic impairment.</p> <p>Impulse control disorders (ICDs) 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.</p> <p>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^{2,3}</p>
Contra-indications*	<p>Active retinopathy; albinism; family history of hereditary retinal disease; retinal degeneration; severe progressive diabetic retinopathy; uveitis; severe hepatic impairment; concomitant treatment with other monoamine oxidase inhibitors; concomitant treatment with pethidine.^{2,3}</p>
Interactions*	<p>The following major drug interactions is listed in the summary of product characteristics for Safinamide (Xadago®)²:</p> <p>MAO inhibitors and pethidine Safinamide must not be administered along with other MAO inhibitors (including moclobemide) as there may be a risk of non-selective MAO inhibition that may lead to a hypertensive crisis.</p> <p>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.</p> <p>Sympathomimetic medicinal products There have been reports of medicinal product interactions with the concomitant use of MAO inhibitors and sympathomimetic medicinal products. In view of the MAO inhibitory activity of safinamide, concomitant administration of safinamide</p>

and sympathomimetics, such as those present in nasal and oral decongestants or cold medicinal products containing ephedrine or pseudoephedrine, requires caution.

Dextromethorphan

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

Antidepressants

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

Serious adverse reactions have been reported with the concomitant use of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic/tetracyclic antidepressants and MAO inhibitors. In view of the selective and reversible MAO-B inhibitory activity of safinamide, antidepressants may be administered but used at the lowest doses necessary.

Tyramine/safinamide interaction

Results of one intravenous and two short term oral tyramine challenge studies, as well as results of home monitoring of blood pressure after meals during chronic dosing in two therapeutic trials in PD patients, did not detect any clinically important increase in blood pressure. Three therapeutic studies performed in PD patients without any tyramine restriction, also did not detect any evidence of tyramine potentiation. **Safinamide can, therefore, be used safely without any dietary tyramine restrictions.**

[Click here](#) for the drug interaction information contained in the eBNF.³

The severe interactions are listed with the evidence for the interaction in brackets:- Adrenaline/epinephrine (anecdotal); Bambuterol (theoretical); Dexamfetamine (theoretical); Dobutamine (anecdotal); Dopamine (anecdotal); Ephedrine (anecdotal); Formoterol (theoretical); Indacaterol (theoretical); Isocarboxacid (theoretical); Isometheptene (anecdotal); Linezolid (theoretical); Metaraminol (anecdotal); **Mitodrine (anecdotal)**; Moclobemide (theoretical); Noradrenaline/norepinephrine (anecdotal); Olodaterol (theoretical); Pethidine (theoretical); Phenelzine (theoretical); Phenylephrine (anecdotal); Pseudoephedrine (anecdotal); Salbutamol (theoretical); Salmeterol (theoretical); Terbutaline (theoretical); Tranylcypromine (theoretical); Vilanterol (theoretical); Xylometazoline (anecdotal).

**Costs
Tariff status
Activity costs**

Drug & Dosage	30 day cost/per patient #	Annual Cost per patient
Safinamide (Xadago®) 50mg to 100mg per day.	£69.00	£828
Selegiline (Eldepryl®) 10mg daily	£9.67	£116.04
Selegiline (Eldepryl®) 5mg daily	£4.96	£59.52
Selegiline (Zelapar®) 1.25mg daily (Non-Formulary)	£43.16	£517.92

	Rasagiline (generic) 1mg daily. (Non- Formulary)	£3.38	£40.56
Cost effectiveness (if available)	<p>N.B. Doses are for general comparison and do not imply therapeutic equivalence</p> <p># Drug Tariff August 2019</p>		
Potential number of patients in Bedfordshire and Luton Impact per 100,000 population Affordability considerations	<p>The requesting specialist (from the Luton & Dunstable Hospital) has indicated that this drug may be useful in 20-30 patients per year which would result in an annual cost pressure of between £16,500 and £25,000.</p> <p>Any costs/usage associated with use of the drug at Bedford Hospital would be additional to these usage/cost estimates.</p>		

<p>Decisions from other bodies</p> <p>Comments sought from –</p>	<p>Hertfordshire CCGs: Thurrock CCG, Milton Keynes CCG, Bucks Healthcare NHS Trust – Not requested or reviewed.</p> <p>Regional joint formulary committee (North Central London; NCL) – Reviewed and not approved.</p> <p>North Essex CCG – Approved – Specialist initiation, GP to continue.</p>
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Evidence strengths and limitations

The following information reflects the strengths and weaknesses of the major evidence base for the use of safinamide i.e. the trials reviewed in the NICE Evidence Summary.

The efficacy and safety of safinamide has been investigated in 3 placebo-controlled RCTs, which included a total of 1,218 participants ([Borghain et al. 2014a](#) [study 016], [Borghain et al. 2014b](#) [study 018] and [Schapira et al. 2016](#) [SETTLE study]). The studies were [double-blind](#) and [allocation was concealed](#).

An [intention-to-treat analysis](#) was used for efficacy outcomes. The safety analyses included all participants who had received at least 1 dose of study medicine. Withdrawal rates were relatively low in the 24-week studies and were similar across all treatment and comparison groups (11.2% in study 016 and 11.5% in SETTLE). In study 018, 19.1% of participants who enrolled did not complete the study, but these rates were similar across all groups.

Safinamide has not been compared with an active comparator in a head-to-head study, for example, other MAO-B inhibitors, dopamine agonists or COMT inhibitors. Therefore, the size of the effect is difficult to determine ([EPAR: Xadago](#)). A post-hoc analysis of pooled data from study 016 and the SETTLE study presented results of several sub-group analyses ([Cattaneo et al. 2016](#)). This showed that very few participants were taking levodopa alone at baseline (89/971, 9.2%). At baseline, 61% of participants in study 016 and 74% of participants in the SETTLE study were taking a dopamine agonist. There was also relatively high usage of anticholinergics in study 016 (37%), which is not likely to reflect UK practice. In the NICE guideline on [Parkinson's disease](#), anticholinergics are not included as an option for adjuvant treatment in people with later Parkinson's disease.

The SETTLE study was conducted in North America and Europe and 68% of participants were Caucasian. However, studies 016 and 018 were predominantly conducted in India and the majority of participants (80%) were Asian. This is not reflective of the UK population and routine clinical practice is likely to be different from that in India.

Safinamide has not been investigated in people with:

- severe, disabling peak dose or biphasic dyskinesia with unpredictable or wide fluctuations
- history or presence of retinal disease
- psychiatric illness, bipolar disorder or severe depression ([EPAR: Xadago](#)).

In addition, there are no data on the long-term use (longer than 3 years) of safinamide, or use in people over the age of 75 years ([EPAR: Xadago](#)). The average age of participants recruited into the studies was 60 years in study 016 and 62 years in the SETTLE study. This may not be representative of people with mid- to late-stage Parkinson's disease who are experiencing motor fluctuations in real world practice. Participants also had to be able to adhere to strict daily requirements to keep a diary, and were excluded from the studies if they weren't able to do this.

Not all participants in study 016 continued into the 18-month extension study (study 018). People who had experienced clinically significant adverse events or had shown clinically significant deterioration in motor symptoms during study 016 were excluded from enrolling into study 18 ([Borghain et al. 2014b](#)). This may overestimate the benefits and underestimate the harms of safinamide at 2 years, compared with placebo.

In study 018, there was no significant difference between either safinamide 50 mg or safinamide 100 mg and placebo in the primary outcome ([DRS](#) total score during on time). Therefore, caution is needed when interpreting the observed treatment effects on secondary outcomes. Two post-hoc subgroup analyses have been published; 1 of pooled data from study 016 and the SETTLE study ([Cattaneo et al. 2016](#)) and 1 of data from study 018 ([Cattaneo et al. 2015](#)). However, these subgroups were not pre-specified in the original studies and the findings should be interpreted with caution.

An overview of the quality assessment of each included study can be found in [evidence tables](#).

** Consult Summary of Prescribing Characteristics for full prescribing detail.*

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

Appendix 1- Search Strategy

- 1. NICE Evidence Search – July 2019**
- 2. Embase Search (30/7/2019) by MI, the Luton & Dunstable Hospital**

Appendix 2 – References

1. Parkinson's disease with motor fluctuations: safinamide, NICE evidence summary 6, published 21st February 2017.
2. Summary of Product Characteristics for Safinamide (Xadago®), accessed July 2019. <https://www.medicines.org.uk/emc/product/2159/smpc>
3. eBNF, accessed July 2019.
4. Cattaneo, C et al, 'Effects of Safinamide on Pain in Fluctuating Parkinson's Disease Patients; A *Post-Hoc* Analysis', Journal of Parkinson's Disease 7 (2017); 95-101.
5. Cattaneo, C et al, 'Long-Term Effects of Safinamide on Mood Fluctuations in Parkinson's Disease', Journal of Parkinson's Disease 7 (2017): 629-634.
6. Binde C.D et al, A multiple treatment comparison meta-analysis of monoamine oxidase type B inhibitors for Parkinson's Disease, British Journal of Clinical Pharmacology, Sep 2018; 84 (9): 1917-1927. (abstract reviewed).
7. Which MAO-B inhibitor for Parkinson's disease?, Drug and Therapeutics Bulletin; Jan 2019: 57:8.
8. Summary of Product Characteristics for Selegiline (Eldepryl) tablets. <https://www.medicines.org.uk/emc/product/6627/smpc> (accessed 5/8/19).
9. Summary of Product Characteristics for Rasagiline tablets. <https://www.medicines.org.uk/emc/product/1968/smpc>

<p>Treatment assessed (Sept 2019): Safinamide for the Treatment of Parkinson's disease</p>
<p>JPC Recommendation A Formulary application for Safinamide for the treatment of Parkinson's Disease was considered at the September 2019 JPC meeting.</p> <p>Following discussion, the Committee decided not to support the Formulary application for safinamide. The main concerns were the lack of head to head trials with appropriate comparators, safety issues (e.g. retinopathy) and cost/cost-effectiveness.</p>
<p>1) Clinical Effectiveness See evidence review</p>
<p>2) Cost Effectiveness No cost-effectiveness analyses were identified from the literature. The requesting specialist (from the Luton & Dunstable Hospital) has indicated that this drug may be useful in 20-30 patients per year which would result in an annual cost pressure of between £16,500 and £25,000.</p> <p>Any costs/usage associated with use of the drug at Bedford Hospital would be additional to these usage/cost estimates.</p>
<p>3) Equity & Equality Impact Assessment* As Safinamide is used for the treatment of Parkinson's Disease and Parkinson's Disease is a protected characteristic under Equality and Diversity legislation, a negative or positive decision could potentially impact on this patient group in a disproportionate manner to the general population.</p>
<p>4) Needs of the community See above under Cost-Effectiveness.</p>
<p>5) Need for healthcare (incorporates patient choice and exceptional need) Alternative treatment options are available.</p>
<p>6) Policy drivers NICE Clinical Guideline 71 – Parkinson's disease in adults.</p>
<p>7) Disinvestment Some offsetting of costs as the alternative product, selegiline would not be used. However, safinamide is considerably more expensive than selegiline.</p>

The JPC agreed the following sections within the PCT Ethical and Commissioning Framework were not relevant to JPC discussions: Health Outcomes, Access, and Affordability.

***Equality Impact Assessment for BCCG only**

Where the implementation of the decision of the Bedfordshire and Luton Joint Prescribing Committee (JPC) may impact on one or more equality group differently to others, BCCG will require an equality impact assessment to be completed. The guidance on this can be found in the attached document. Please summarise the equality impact in the in the Equity & Equality Impact Assessment box above.

Protected Characteristics (under the Equality Act):-

Age; Disability; Gender reassignment; Marriage & Civil Partnership (in employment only); Pregnancy & Maternity; Race; Religion & Belief; Sex; Sexual orientation; carers; other identified groups.

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or *poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or <i>n</i> -of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, <i>n</i> -of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or <i>n</i> -of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

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