New Medicines Committee Briefing

Updated November 2017

Rasagiline for the treatment of Parkinson's Disease

Rasagiline is to be reviewed for use within:

Primary Care	✓
Secondary Care	✓

Summary:

- Rasagiline is a Monoamine Oxidase-B Inhibitor (MAOI) which is indicated for the treatment of idiopathic Parkinson's disease as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end of dose fluctuations.
- The recommended dose of rasagiline is 1 mg once daily, to be taken with or without levodopa.
- Rasagiline was previously reviewed in July 2011 and the Area Prescribing Committee (APC) concluded that there was insufficient evidence available to suggest that rasagiline was more effective than less expensive selegiline.
- Rasagiline is now available generically.
- There is no updated guidance available from NICE, SIGN, SMC, RDTC, MTRAC or Cochrane since July 2011. There are no new trials comparing rasagiline with other MAO-B inhibitors.

Formulary application

Dr Ellis has requested for safinamide to be considered for inclusion in the North Staffordshire Joint Formulary for treatment of Parkinson's disease (PD) where selegiline and rasagiline are inappropriate; however rasagiline is not currently on the formulary.

Rasagiline was previously reviewed in July 2011 and was not approved by the Area Prescribing Committee (APC) for inclusion within the North Staffordshire Joint Formulary as there was insufficient evidence available to suggest that rasagiline was more effective than less expensive selegiline. The economic case for rasagiline needs to be reviewed; rasagiline is now available generically.

Current formulary status

Monoamine-oxidase-B inhibitors			
Selegiline	2	Restriction: Initiation by specialist	
Rasagiline		Not approved for inclusion in the North Staffordshire Joint Formulary	Medicines Review Verdict Sheet

Patent Status

Available as Azilect® or generic.

Guidance and Evidence Summary

There is no updated guidance available from NICE, SIGN, SMC, RDTC, MTRAC or Cochrane since July 2011.

There are no new trials comparing rasagiline with other MAO-B inhibitors.

Cost Analysis

Comparative Costs and Expenditure of MAO-B inhibitors in Secondary Care (UHNM) July 2016 – June 2017:

MEDICINE DESCRIPTION	PACK SIZE	CURRENT PRICE UHNM (incl. VAT)	PRICE PER 28 DAYS (incl. VAT)	UHNM TOTAL QUANTITY	UHNM TOTAL EXPENDITURE (VAT applied as appropriate)
SAFINAMIDE 50mg TABLETS (XADAGO)	30				**£89.66**
SAFINAMIDE 100mg TABLETS (XADAGO)	30				**£44.90**
RASAGILINE 1mg TABLETS (AZILECT/GENERIC)	28				**£6,652.90**
SELEGILINE 1.25mg ORODISPERSIBLE TABLETS (ZELAPAR)	30				**£97.24**
SELEGILINE 5mg TABLETS	100				**£130.00**
SELEGILINE 10mg TABLETS	100				**£0.00**
TOTAL					**£7,014.70**

*Price of Azilect brand £84.86 July 2016 – May 2017; switched to generic from June 2017

Comparative Costs and Expenditure of MAO-B inhibitors in Primary Care July 2016 – June 2017:

MEDICINE DESCRIPTION	PACK SIZE	CURRENT PRICE	PRICE PER 28 DAYS	NORTH STAFFS CCGs TOTAL QUANTITY	NORTH STAFFS CCGs Sum of Total Nic
SAFINAMIDE 50mg TABLETS (XADAGO)	30	£69.00	£64.40	112	**£257.60**
SAFINAMIDE 100mg TABLETS (XADAGO)	30	£69.00	£64.40	0	**£0.00**
RASAGILINE 1mg TABLETS (GENERIC)	28	£1.59	£1.59	50,055	**£19,136.06**
RASAGILINE 1mg TABLETS (AZILECT)	28	£70.72	£70.72	11,158	**£28,181.92**
SELEGILINE 1.25mg ORODISPERSIBLE TABLETS (ZELAPAR)	30	£43.16	£40.28	880	**£1265.94**
SELEGILINE 5mg TABLETS (ELDEPRYL/GENERIC)	100	£16.52	£4.63	7918	**£1308.37**
SELEGILINE 10mg TABLETS (ELDEPRYL/GENERIC)	100	£32.23	£9.02	8646	**£2786.58**
TOTAL					**£52,936.47**

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New Medicines Committee Briefing
July 2011

Rasagiline (Azilect®) for the treatment of Parkinson's Disease

Rasagiline is to be reviewed for use within:

Primary Care	✓
Secondary Care	✓

Summary:

Rasagiline is a monoamine oxidase type B inhibitor used in the treatment of Parkinson's disease (PD)[1]

Rasagiline is licensed for the treatment of idiopathic Parkinson's disease as monotherapy (i.e. without levodopa) or as an adjunct therapy (with levodopa) in patients with end-of-dose fluctuations[1]

NICE recommends monoamine oxidase B inhibitors as a class as a first-choice option for initial therapy for early PD and as an adjuvant to levodopa in later PD[2]

SMC has rejected rasagiline for use within NHS Scotland[3,4]

SIGN recommends that monoamine oxidase B inhibitors may be considered for the treatment of early PD with motor symptoms and for the management of motor complications in patients with advanced PD[5]

In early PD rasagiline significantly improves UPDRS scores from baseline compared to placebo[6,7]

As an adjunct to levodopa in advanced PD rasagiline has been shown to reduce daily 'off' time compared to placebo[8,9]

Formulary application:

Consultant submitting application: Dr Jonathan Partridge (Consultant Neurologist)
Clinical Director supporting application: Dr Simon Ellis

Following a review of BNF section 4.9.1 of the formulary it was suggested by Dr Carl Mann (Consultant Neurologist) that rasagiline should be added to the formulary; Dr Jonathan Partridge agreed to support the application at the New Medicine Committee. Current treatment choice in Parkinson's disease is largely dependent on symptoms with the line of treatment being more general than specific ie a monoamine oxidase B (MAO-B) inhibitor, then a dopamine agonist, then levodopa, then a catechol-*O*-methyltransferase (COMT) inhibitor; rasagiline is currently prescribed in the treatment of early PD and also in the later stages of the condition.

Background:

Parkinson's disease is a neurodegenerative disorder characterised by loss of dopaminergic neurons in the substantia nigra. Classic presenting symptoms include hypokinesia, bradykinesia, rigidity and tremor at rest. Parkinson's disease affects about 120,000 people in the UK (about 200 per 100,000) with symptoms appearing usually in patients aged over 50 years[10].

Drug therapy does not prevent disease progression, but it improves most patients' quality of life. The symptoms of PD are not usually treated until they cause significant interruption of daily activities[11].

Levodopa (in combination with a dopa-decarboxylase inhibitor) is the most potent antiparkisonian drug and is the mainstay of treatment for the majority of the course of the disease in all patients. A complication of long-term levodopa treatment is motor complications including dyskinesias and response fluctuations, or 'on/off' episodes.

Dopamine-receptor agonists have a direct action on dopamine receptors and are used in early PD and also used as an adjunct to levodopa in more advanced disease. Non-ergot-derived dopamine-receptor agonists include pramipexole, ropinirole and rotigotine and ergot-derived dopamine-receptor agonists are bromocriptine, cabergoline and pergolide; ergot-derived dopamine-receptor agonists are associated with fibrotic reactions.

Monoamine oxidase B (MAO-B) inhibitors (rasagiline and selegiline) are used as monotherapy and as adjuncts to levodopa for the alleviation of end-of-dose fluctuations in patients with later disease.

Catechol-*O*-methyltransferase (COMT) inhibitors (entacapone and tolcapone) prevent the peripheral breakdown of levodopa and are used with co-beneldopa and co-careldopa for patients with PD who experience end-of-dose deterioration and cannot be stabilised on these combinations[11].

Current formulary status:

The North Staffordshire Joint Formulary currently lists the following agents:

4.9 DRUGS USED IN PARKINSONISM AND RELATED DISORDERS

Parkinson's disease: diagnosis and management in primary and secondary care

NICE Clinical Guideline CG35 (date 06/06)

4.9.1 Dopaminergic drugs used in Parkinson's disease			☑CSM
Amantadine	2	Restriction: Initiation by specialist	
Co-beneldopa (Madopar® preparations)	2	Restriction: Initiation by specialist	
Co-careldopa (Sinemet® preparations)	2	Restriction: Initiation by specialist	
Entacapone	2	Restriction: Initiation by specialist	☑MTRAC
Ropinirole	2	Restriction: Initiation and stabilisation by specialist	☑MTRAC
Rotigotine	2	Restriction: Patients that are NBM or have swallowing difficulties. Prescribing should be reviewed on discharge from secondary care	☑MTRAC
Selegiline	2	Restriction: Initiation by specialist	

Entacapone – MTRAC recommendation VS99/01 (date 01/99)

A COMT inhibitor for the treatment of Parkinson's Disease – RESTRICTED USE

Ropinirole – MTRAC recommendation VS00/01 (date 01/00)

A dopamine agonist for the treatment of Parkinson's Disease – RESTRICTED USE

Ropinirole – MTRAC recommendation VS07/01 (date 01/07)

For the treatment of restless leg syndrome

Q3, Category A – suitable for prescribing in primary care

Therapeutic class and mode of action:

Rasagiline is a monoamine oxidase type B inhibitor; it irreversibly inhibits the enzyme monoamine oxidase type B (MAO-B) in the brain that decreases the breakdown of dopamine,

leading to increased post-synaptic availability of dopamine and improved dopaminergic function[1].

Licensed indication:

Treatment of idiopathic Parkinson's disease as monotherapy (i.e. without levodopa) or as an adjunct therapy (with levodopa) in patients with end-of-dose fluctuations[1].

Dosage and administration:

Dose:	1mg daily with or without levodopa (no initial titration required)[1]
Administration:	With or after food; dietary tyramine restrictions are not required[1]
Hepatic impairment:	Avoid in moderate to severe impairment; use with caution in mild impairment[1,11]
Renal impairment:	No change in dosage required[1]

Presentation:

Blister packs of 28 x 1mg tablets[1]

Guidance:

NICE Guidance[2]:

NICE guidance published	Yes
Relevant guidance	NICE Clinical Guideline– Parkinson's disease: diagnosis and management in primary and secondary care (June 2006)

NICE guidance stated that it was not possible to identify a universal first-choice drug therapy for either early PD or as an adjuvant drug therapy for later PD; the guidance recommended the following first-choice treatment options:

- Initial therapy for early PD- levodopa, dopamine agonists and MAO-B inhibitors
- Adjunctive therapy for later PD to reduce motor complications and improve quality of life in patients taking levodopa- dopamine agonists, MAO-B inhibitors and COMT inhibitors

The guidance recommended that when choosing treatment clinical and lifestyle preferences and patient preference, after informing the patient of the short- and long-term benefits and drawbacks of drug classes, should be taken into account.

Scottish Medicines Consortium (SMC)[3,4]

SMC recommended use within NHS Scotland:	No

Treatment of idiopathic Parkinson's disease as monotherapy (without levodopa) (November 2006):

SMC not recommended: rasagiline provides a modest symptomatic improvement for patients with early Parkinson's disease; economic case not demonstrated[3]

Adjunct therapy (with levodopa) in patients with end-of-dose fluctuations (November 2006):
SMC not recommended: rasagiline reduces off-time in patients with Parkinson's disease and end-of-dose fluctuations on levodopa similar to reductions shown with the less effective of the 2 currently marketed COMT inhibitors (entacapone); economic case not demonstrated[4]

Cochrane Review[12,13]:

Monoamine oxidase B inhibitors versus other dopaminergic agents in early Parkinson's disease[12]:
Authors concluded that MAO-B inhibitors are one option for the early treatment of PD although they have weaker symptomatic effects than levodopa and dopamine agonists. They may reduce the rate of motor fluctuations compared with initial levodopa therapy and may have fewer significant adverse effects than the older agonists but data are too few to provide reliable conclusions.

Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson´s disease patients with motor complications[13]:
Authors concluded that compared to placebo, adjuvant therapy reduces off-time, levodopa dose, and improves UPDRS scores in PD patients who develop motor complications on levodopa therapy. However, this is at the expense of increased dyskinesia and numerous other side-effects. Indirect comparisons suggest that dopamine agonist therapy may be more effective than COMTI and MAOBI therapy, which have comparable efficacy. However, as indirect comparisons should be interpreted with caution, direct head-to-head randomised trials assessing the impact of these different drug classes on overall patient-rated quality of life are needed.

Scottish Intercollegiate Guidelines Network (SIGN)[5]:

SIGN guidelines published	Yes
Relevant guidelines	113- Diagnosis and pharmacological management of Parkinson's disease (January 2010)

SIGN recommends that monoamine oxidase B inhibitors may be considered for:

- Patients with early Parkinson's disease and motor symptoms
- Management of motor complications in patients with advanced Parkinson's disease

MTRAC[10]

MTRAC reviewed	Yes

MTRAC have recommended that Parkinson's disease should be diagnosed and managed in secondary care and that rasagiline is suitable for prescribing in primary care with the guidance of an ESCA, upon the advice of a specialist, which could include a specialist nurse in a neurology clinic or a GP with a specialist interest in neurology; the need for specialist involvement gave rasagiline a low place in therapy in primary care.

Efficacy:

Outcome measures used to evaluate efficacy of treatment of PD:
Unified Parkinson's Disease Rating Scale (UPDRS) is a standardised scale comprising 4 sections that are evaluated by interview and clinical assessment- the higher the UPDRS score, the more severe the disease and a positive change signifies a worsening of the disease.

Changes in time spent 'on' and 'off' can be used to evaluate drug efficacy in patients that have developed motor symptoms
'off' time refers to periods when treatment is not working and patient activity is impaired
'on' time refers to periods when treatment in working

Early Parkinson's Disease (as monotherapy)

Summary: Rasagiline significantly improves UPDRS scores from baseline compared to placebo[6,7]

TEMPO study[6]- a 26-week, double-blind placebo-controlled, parallel-group trial evaluating the efficacy and safety of monotherapy with rasagiline in patients with early PD (n=404).
Patients randomised to receive rasagiline 1mg od, rasagiline 2mg od (unlicensed dose) or placebo.
Primary outcome measure- change in UPDRS score from baseline at 26 weeks comparing each active treatment group with the placebo group- the difference between the mean change from baseline to week 26 was statistically significant for rasagiline 1mg compared to placebo (-4.2 $p<0.0001$) and for rasagiline 2mg compared to placebo (-3.6 $p<0.0001$).

A smaller 10-week double-blind, randomised, placebo- controlled trial also evaluated the safety, tolerability and efficacy of rasagiline (n=56)[7]- patients were randomised to rasagiline 1mg, 2mg, 4mg od or placebo. The authors reported significantly greater improvements in UPDRS score for the 2mg od group compared with placebo; for the 1mg and 4mg groups improvements in UPDRS score were seen but were not significant

Advanced Parkinson's Disease (with levodopa)

Summary: Rasagiline as adjunct therapy to levodopa has been shown to reduce daily 'off' time compared to placebo[8,9]

The effect of rasagiline on levodopa-treated PD patients with motor fluctuations was investigated in two double blind, placebo-controlled trials: PRESTO[9] and LARGO[8]; both of which assessed reduction in daily 'off' time as their primary endpoints.

PRESTO[9] study- 26-week randomised, double-blind, placebo-controlled trial (n=472). Patients were randomised to rasagiline 1mg od, rasagiline 0.5mg od (unlicensed dose) or placebo. Rasagiline 1mg od reduced the daily 'off' time from baseline by 1.85 hours (29%) compared with reductions of 1.41 hours (23%) in the rasagiline 0.5mg group and 0.91 hours (15%) in the placebo group. The mean difference in 'off' time for the rasagiline 1mg group compared to placebo was statistically significant ie -0.94 hours ($p<0.0001$).

LARGO[8] study- 18-week, randomised, double-blind, placebo-controlled trial (n=687). Patients were randomised to rasagiline 1mg od, entacapone 200mg with each levodopa dose (active-comparator) or placebo.
Rasagiline and entacapone reduced mean daily 'off' time (-1.18 hours rasagiline and –1.2 hours entacapone vs placebo 0.40 hours p=0.0001, p<0.001 respectively). The authors concluded that rasagiline reduces the daily off-time and improves symptoms of PD in levodopa-treated patients with motor fluctuations, an effect similar to that of entacapone.

Comparison with other MAO-B inhibitors

No trials available comparing rasagiline with selegiline.

Manufacturer states that compared to selegiline, rasagiline has the following advantages[14]-

- When selegiline is used in conjunction with levodopa, it may be possible to reduce the levodopa dosage by an average of 30%; no levodopa dose adjustment is required for rasagiline
- Selegiline in combination with levodopa is contra-indicated in patients with specific cardiac problems, including cardiovascular disease, tachycardia, arrhythmias, severe angina and arterial hypertension whereas rasagiline is not contra-indicated

Safety and adverse effects[1]:

Contraindications:	Severe hepatic impairment[1;] see also drug interactions
Adverse effects:	Commonly reported adverse effects Monotherapy- headache, nausea, pain, dizziness Adjunct to levodopa- dyskinesia, hallucinations, sleep disorder, dizziness, nausea

For additional information in adverse effects refer to the Summary of Product Characteristics[1].

Drug Interactions[1]:

Manufacturer advises to avoid concomitant use with the following[1]:

- Fluoxetine and fluvoxamine
- MAO inhibitors including medicinal and natural products without prescription eg St John's Wort
- Pethidine
- Dextromethophan or sympathomimetics eg ephedrine and pseudoephedrine

Manufacturer recommends that antidepressants should be administered with caution in patients taking rasagiline; serious adverse drug reactions have been reported with the concomitant use of SSRIs, SNRIs, tricyclic and tetracyclic antidepressants and MAO inhibitors[1].

For additional drug interactions refer to the Summary of Product Characteristics[1].

Cost analysis

Costs of in primary and secondary care:

Rasagiline	Pack size	Primary Care (exc. VAT) (Drug Tariff[15] price)	Secondary Care (inc. VAT)
1mg tablets	28	£70.72	

Expenditure in primary and secondary care for a 6-month period: (October 2010- March 2011):

Rasagiline	UHNS	Stoke-on-Trent PCT	North Staffordshire PCT
1mg tablets	£1186	£28890	£23221

Estimated cost:

Rasagiline is currently already in use- please refer above to expenditure data

Comparison with other therapy:

Early PD as monotherapy:

Class	Drug	Formulary status[#]	Usual daily dose*	Cost for 28 days treatment[$]
Dopamine agonists (non-ergot derived)	Rotigotine	F	2-8mg daily	£77.24-£142.79
	Ropinirole	F	9-16mg	£72-£135
	Pramipexole IR	A	0.264mg-3.15mg (as base)	£10.36-£160.44
	Pramipexole MR	A	0.26mg-3.15mg (as base)	£26.88-£320.88
Dopamine agonists (ergot derived)	Pergolide	F	2.1-2.5mg	£33.25-£41.47
Levodopa	Co-beneldopa	F	400-800mg (levodopa)	£6.60-£13.19
	Co-careldopa	F	300-800mg (levodopa)	£20.54-£30.54
MAO-B inhibitor	Selegeline	F	10mg daily	£6.87
	Rasagiline	**A**	**1mg**	**£70.72**

Advanced PD (in combination with L-dopa):

Class	Drug	Formulary status[#]	Usual daily dose*	Cost for 28 days treatment[$]
Dopamine agonists (non-ergot-derived)	Rotigotine	A	4-16mg	£117.71-£285.58
	Ropinirole	F	9-24mg	£72-£180
	Pramipexole IR	A	0.264mg-3.15mg (as base)	£10.36-£160.44
	Pramipexole MR	A	0.26mg-3.15mg (as base)	£26.88-£320.88
Dopamine agonists (ergot-derived)	Pergolide	F	Max. 3mg	£35.23
MAO-B inhibitor	Selegeline	F	10mg	£6.87
	Rasagiline	**A**	**1mg**	**70.72**
COMT inhibitor	Entacapone	F	600-2000mg	£48.33-£160.86

[#] F= formulary; NF=non-formulary; A= formulary application under consideration

*Doses are for general comparison and do not imply therapeutic equivalence

[$] Prices from BNF 61[11]

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