Commissioning Support: Safinamide (*Xadago®▼*)

Management of mid- to late-stage Parkinson's disease

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of safinamide:

- The available monoamine-oxidase – B (MAOB) inhibitors for the treatment of mid- to late-stage Parkinson's disease are rasagiline (Azilect or generic; 1 mg daily), selegiline (Eldepryl or generic 10 mg daily or Zelapar 1.25 mg daily) and safinamide (Xadago; 50-100 mg daily).
- Rasagiline and selegiline are both licensed for use as monotherapy and as adjunctive therapy to levodopa. Safinamide is licensed for adjunctive therapy only.
- Generic versions of rasagiline and selegiline are available.
- The cost of safinamide (50 or 100 mg daily) is £69 per 30 tablets, giving a yearly cost per patient of £839.50.
- The costs for existing treatments are £922 per year for rasagiline, and £115 per year with selegiline (generic).

Strength of the evidence for efficacy: relatively weak

Two randomised, placebo-controlled trials evaluated safinamide as adjunctive treatment to levodopa in people with mid-to-late-stage Parkinson's disease;and showed a significant and clinically relevant improvement in 'ON' time. One trial was fully published (Study 016) and details of the other (SETTLE) were available from abstracts and the European public assessment report for safinamide. There were no trials that compared safinamide with other MAOB-inhibitors for the treatment of mid-to-late-stage Parkinson's disease that would enable an estimate of place in therapy.

Description of technology

Safinamide is a highly selective and reversible MAO-B inhibitor that acts through both dopaminergic and non-dopaminergic pathways. It is licensed for the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of levodopa alone or in combination with other medicinal products for PD in mid-to late-stage fluctuating patients.[1]

Safinamide treatment should be started at 50 mg/day. The dose may be increased to 100 mg/day on the basis of individual clinical need. No change in dose is required for elderly patients.[1]

For full details, see the Summary of Product Characteristics.[1]

Background

Parkinson's disease is a progressive neurodegenerative condition characterised by tremor, rigidity (increased resistance during passive joint movement) and bradykinesia (slowed movement).[2] There are also non-motor complications associated with PD that can occur as early symptoms[3]; these are impaired olfaction, constipation, dementia (about 40% of individuals), depression, anxiety, psychosis, sleep disturbance, autonomic disturbances, falls, and pain.[2]

The prevalence of PD in industrialised countries is estimated at 0.1 to 0.2% of the general population (5,600 to 11,200 people in the West Midlands). The disease occurs in about 1% of people over 65, rising to 2% in people over 80.[2] The median age of onset of this disorder is age 60, and mean duration of the disease from diagnosis to death is 15 years.[4]

There are currently no disease-modifying therapies available for PD; only therapy for symptoms causing significant interruption of daily activities. In people with mid-to-late stage PD, once pharmacological therapy is needed, levodopa (in combination with the dopa-decarboxylase inhibitors benserazide or carbidopa) forms the mainstay of therapy. Eventually many people treated with levodopa experience end-of-dose fluctuations in the management of symptoms and need additional adjunctive therapy with dopamine receptor agonists (pramipexole, ropinirole or rotigotine; or more rarely bromocriptine, cabergoline, lisuride, and pergolide *[risk of cardiac fibrosis with ergot-derived dopamine receptor agonists*[5]*]*), MAO-B inhibitors: (selegiline or rasagiline), catechol-O-methyl transferase (COMT) inhibitors (entacapone or tolcapone *[risk of hepatoxicity]*), apomorphine, or amantadine.

The NICE clinical guideline on the diagnosis and management of Parkinson's disease in over 20s (CG35; 2006) advised that there is no single drug of choice in the pharmacotherapy of later PD. The choice of adjuvant therapy is dependent upon the patient's clinical and lifestyle characteristics, their preferences and their choices once they've been informed of the short- and long-term benefits and drawbacks of the drug classes.[6]

Clinical evidence for efficacy

Two trials evaluated safinamide as an add-on therapy to levodopa with or without concomitant AntiParkinson medication in people with mid-to-late stage PD; one (Study 016 and extension 018) published[7;8] and the second trial (SETTLE) available as an abstract[9]. Data were also included from the European assessment report (EPAR)[10].

Study 016 was a randomised, double-blind, placebo-controlled trial that evaluated safinamide 100 mg or

50 mg daily in 669 patients with mid-to-late-stage PD, who were experiencing motor fluctuations while receiving levodopa and other dopaminergic treatments. Eligible patients had a Hoehn and Yahr stage I-IV score (mild up to severe motor symptoms but still able to walk) during an OFF period (lack of mobility: bradykinesia or akinesia) and motor fluctuations of at least 1.5 hours' off time/day. Patients in Study 016 were eligible to continue in an 18-month placebo-controlled extension Study 018.

Information on the SETTLE trial was taken from the European assessment report for safinamide. The trial evaluated safinamide as an add-on treatment to levodopa in 549 patients and the inclusion criteria, and outcomes measured were similar to those described in Study 016. Unlike Study 016, the dosing of safinamide in the SETTLE trial was flexible within the range 50 to 100 mg/day.

The primary outcome in Study 016 and the SETTLE trial was the change in mean daily ON time (normal function for a particular individual) without troublesome dyskinesias over 18 hours. In Study 018 the primary outcome was the change in the dyskinesia rating scale from baseline (Study 016 week 0) to the end of Study 018 (week 78).

Other outcomes included the total daily OFF time, the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor) scores during ON, Clinical Global Impression-Change (CGI-C) scores, Dyskinesia Rating Scale (DRS) scores during ON time, UPDRS Part II (activities of daily living) scores during ON, and Clinical Global Impression-Severity (CGI-S) scores.

Results: In both Study 016 and the SETTLE trial the primary outcome measure, the mean total daily ON time without troublesome dyskinesias, increased significantly more with safinamide treatment than placebo. In Study 016, the difference *vs*. placebo was 0.51 hours (95% CI 0.07 to 0.94) for the safinamide 50 mg/day group ($p = 0.023$) and 0.55 (95% CI 0.12 to 0.99) hours for the safinamide 100 mg/day group, $p = 0.013$. In the SETTLE trial, the difference *vs.* placebo was 0.96 hours for the safinamide 50 to 100 mg/day group [$p < 0.001$].

Other outcomes: The OFF time decreased by 0.5 and 1.00 hour in Study 016 and the SETTLE study, respectively, compared with placebo; both changes were significantly greater than placebo ($p < 0.01$).

In Study 016, UPDRS scores relating to motor function were significantly better than placebo in both dose groups. The UPDRS score relating to activities of daily living was only significantly greater than placebo for the 100 mg/day dose.

In the SETTLE study, there were statistically significant improvements in health-related quality of life and functioning, as assessed by the PDQ-39 (Parkinson's disease questionnaire) and EQ-5D scales (quality of life outcome measure). Scores for dyskinesia (DRS) and depression (GRID-HAMD) were not significantly different than placebo.

Adverse events

Safinamide at doses of 50 and 100 mg per day was generally well tolerated in combined safety data from studies 016 and 018. Dyskinesia occurred more frequently in patients receiving safinamide 50 mg and 100 mg than in placebo-treated patients (31.2% and 27.8%, respectively, *vs*. 21.7% in the placebo group). Adverse events in more than 10% of patients were cataract, asthenia, pyrexia, fall, back pain, dyskinesia, worsening of PD, headache, and insomnia. In the 18-month extension (study 018), the incidence of new or worsening dyskinesia adverse events was similar to placebo. No treatment-related deaths occurred in either study.

The EMA risk management plan for safinamide included the increased incidence of dyskinesia, and the potential for development of impulse control disorders.

Considerations for cost impact

- The yearly cost of treatments for this stage of PD:
  - Rasagiline 1 mg daily (Azilect®/generic) £922
  - Safinamide 50 or 100 mg daily £839.50
  - Selegiline 10 mg daily (Eldepryl®) £118 to £121
  - Selegiline 1.25 mg daily (Zelapar®) £525

References

1. Xadago 100mg film-coated tablets. EMC 2016 www.medicines.org.uk/emc/medicine/31917
2. Parkinson's disease. NICE CKS 2016 http://cks.nice.org.uk/parkinsons-disease
3. Kalia LV, Lang AE. Parkinson's disease. *Lancet* 2015; 386(9996):896-912.
4. Lees AJ, Hardy J, Revesz T. Parkinson's disease. The Lancet [2009 374:[684] http://www.sciencedirect.com/science/article/pii/S014067360960492X
5. Drug safety update: Ergot-derived dopamine agonists: risk of fibrotic reactions. MHRA 2008 www.gov.uk/drug-safety-update/ergot-derived-dopamine-agonists-risk-of-fibrotic-reactions
6. Parkinson's disease in over 20s: diagnosis and management. NICE 2006 www.nice.org.uk/guidance/cg35
7. Borgohain R et al. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. *Mov Disord* 2014; 29(2):229-237.
8. Borgohain R et al. Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. *Mov Disord* 2014; 29(10):1273-1280.
9. Safinamide is associated with clinically important improvement in motor symptoms in fluctuating PD patients as add-on to levodopa (SETTLE). MDS 17th International Congress of Parkinson's Disease and Movement Disorders; 13 Jun 16; 2013.
10. Assessment report: Xadago. EMA 2014 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002396/WC500184967.pdf

Keele University Centre for Medicines Optimisation

School of Pharmacy, Keele University, Keele, Staffordshire ST5 5BG Tel: 01782 733831 Email: mtrac@keele.ac.uk Web: www.mtrac.co.uk