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NEUROLOGY
New medicinal product
October 2015

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

XADAGO (safinamide), antiparkinsonian

In combination with levodopa, no clinical benefit when compared with other antiparkinsonians in controlling motor fluctuations in mid- to late-stage patients

Main points

- XADAGO is a monoamine-oxidase B (MAOB) inhibitor which is indicated in combination with a stable dose of levodopa (L-dopa) alone or in combination with other antiparkinsonian medicines in adult patients with idiopathic, fluctuating Parkinson's disease in the mid- to late stage of the disease.
- Two randomised double-blind studies have demonstrated its efficacy versus placebo in terms of the improvement in the amount of time spent per day in the ON phase without dyskinesia or with non-troublesome dyskinesia. During the day, the effect observed was of low clinical relevance: safinamide increases from 30 to 60 minutes the period for which patients are in the ON phase, without dyskinesia or without troublesome dyskinesia.
- This is an additional treatment option in the management of patients with Parkinson's disease with motor fluctuations on a stable dose of L-dopa .

Therapeutic use

- After a phase in which the symptoms of the functional disorder were controlled with dopa therapy (L-dopa), the health of the Parkinson's patient deteriorated because of the occurrence of dopa-induced motor disorders (motor fluctuations and dyskinesia) and signs specific to the disease.
- Given the motor complications, a check should be made for medicines likely to aggravate the "off" periods and dyskinesia, then the dopa therapy should be optimised (by splitting the daily dose, adjusting administration schedules, or prescribing different pharmaceutical forms).
- Therapeutic management of these complications may also prompt the combination of one or more other medicines with levodopa:
  - In first-line treatment: dopamine receptor agonists (ergot- or non-ergot-derived), catechol-O-methyltransferase (COMT) inhibitors or MAOB inhibitors
  - In second-line treatment: anticholinergics for tremor control only in patients with no cognitive deterioration, amantadine, apomorphine (in separate subcutaneous injections or through a pump)
- Rehabilitation has an important place in the management of Parkinson's disease patients. Rehabilitation methods, even short-term ones, must be adjusted to the unforeseen complications and fluctuations of the disease.
- **Role of the medicinal product in the therapeutic strategy**
  XADAGO is an additional treatment option in the management of patients with mid- to late-stage Parkinson's disease with motor fluctuations on a stable dose of L-dopa alone or in combination (particularly with dopamine receptor agonists and COMT inhibitors).
  Its addition is not recommended in patients with severe, disabling or diphasic dyskinesia and/or unpredictable or variable fluctuations because of the exclusion of these patients from clinical trials.

Clinical data

- The evaluation of the efficacy and safety of safinamide 50 and 100 mg is based on two randomised, double-blind, placebo-controlled studies: study 016 (n=669) and the SETTLE study (n=549).

- The patients included had similar characteristics, i.e. mid- to late-stage Parkinson's disease that had been developing for 8-9 years with a disabling disease. On inclusion in the two studies, the mean time spent in the ON phase without dyskinesia or with non-troublesome dyskinesia was between 9.1 and 9.6 hours. All patients had motor fluctuations on L-dopa (dosage 600 to 800 mg according to the study) as monotherapy or in combination with dopamine receptor agonists in particular. Patients received a safinamide dose of 50 mg/day or 100 mg/day (study 016), or a dose ranging from 50 to 100 mg/day (SETTLE study) for 24 weeks.
- The primary efficacy endpoint was identical: it was the mean increase in the daily time in the ON phase without dyskinesia or with non-troubling dyskinesia at 24 weeks and by comparison with baseline, versus placebo, as reported in the patients' diaries.
- The results of the two studies showed the superiority of safinamide compared with placebo with increases in the daily time in the ON phase without dyskinesia or with non-troubling dyskinesia of: +0.5 hours (95% CI [0.1; 0.9], p=0.0054) with safinamide 50 mg and +0.7 hours (95% CI [0.3; 1], p=0.0002) with safinamide 100 mg [study 016] and +0.9 hours (95% CI [0.6; 1.2], p < 0.001) with safinamide 50-100 mg [SETTLE study].
- The main adverse events observed were dyskinesia (31.3% to 20.7%), psychiatric disorders (19.8% to 15.9%), gastrointestinal disorders, particularly constipation (8.2% to 6. %) and cardiovascular disorders with AHT (8.2% to 4.8%). Cataracts were observed in 6.3 to 14% of patients

- The Committee emphasised in particular:
  - methodological limitations linked to a comparison with placebo, whereas a study versus another MAO-B inhibitor, or even a COMT inhibitor, would have allowed an assessment to be made of the benefit of adding safinamide to L-dopa.
  - the low clinical relevance of the observed effect on the primary efficacy endpoint, since safinamide increases from 30 to 60 minutes the period during the day for which patients are in the ON phase, without dyskinesia or without troublesome dyskinesia.

Benefit of the medicinal product

- The actual benefit* of XADAGO is moderate, given:
  - the modest quantity of effect observed, particularly on the improvement of the daily time spent in the ON phase,
  - the low clinical relevance of these results given the comparative methodology versus placebo and the population included in these studies.
- XADAGO does not provide clinical added value** (CAV V) compared with the other antiparkinsonian medicines used in the management of motor fluctuations during mid- to late-stage Parkinson's disease, in combination with levodopa used alone or in combination.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 07 October 2015 (CT-14371) and is available at **www.has-sante.fr**

[i] * The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".