HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

1 October 2008

Assessment to re-evaluate actual benefit of the MAO B inhibitors class of therapies, with reference to article R 163-21 of the French social security code.

AZILECT 1 mg, tablet
Box of 30 tablets (CIP: 365 783-5)

AZILECT 1 mg, tablet
Box of 100 tablets (CIP: 566 199-9)

Applicant: LUNDBECK SA

rasagiline (mesilate)

List I

ATC Code: N04BD02

Date of Marketing Authorisation: 21 February 2005

Reason for request: re-evaluation of actual clinical benefit of the MAO B inhibitors class of therapies in the indication "motor fluctuations on levodopa".

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Rasagiline

1.2. Indications

"Treatment of idiopathic Parkinson's disease (PD) as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end of dose fluctuations."

1.3. Dosage

1 mg once daily.

2 SUMMARY OF COMMITTEE OPINIONS AND CONDITIONS FOR INCLUSION

Opinion dated 1 March 2006

"In patients with motor fluctuations on levodopa, this product can be considered to have a high actual clinical benefit, given the lack of available medical resources, particularly for elderly patients with Parkinson's disease."
"AZILECT does not offer an improvement in actual clinical benefit (IACB/ASMR level V) in comparison with current symptomatic treatments for Parkinson's disease. The Committee notes that there is a lack of efficacy studies lasting more than 12 months and a lack of comparative data involving selegiline or dopamine agonists. "

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2008)

N Nervous system
04 Anti-parkinson drugs
B Dopaminergic agents
D Monoamine oxidase B inhibitors
02 Rasagiline

3.2. Medicines in the same therapeutic category

Other medicinal products in the MAO B inhibitors class contain selegiline:

DEPRENYL 10 mg, scored tablet and generics
DEPRENYL 5 mg, scored tablet and generics
OTRASEL 1.25 mg, oral lyophilisate

3.3. Medicines with a similar therapeutic aim

Other antiparkinson therapies indicated for reduction of motor fluctuations in combination with levodopa:

- Dopamine agonists (bromocriptine, lisuride, piribedil, pramipexole, ropinirole, pergolide, apomorphine)
- COMT inhibitors: entacapone, tolcapone (in patients who do not respond to or who are intolerant to other COMT inhibitors)

4 UPDATE ON DATA MADE AVAILABLE SINCE PREVIOUS OPINION

- **Summary of studies on the motor fluctuation stage on levodopa that have previously been examined by the committee as part of the inclusion application dossier.**

Two randomised placebo-controlled studies involving patients on levodopa were presented in the inclusion application dossier:

- the PRESTO study
- the LARGO study, including a group of patients treated with entacapone

The committee's conclusions in its opinion of 1 March 2006 were as follows:

The PRESTO study compared the efficacy of rasagiline (0.5 mg/day and 1 mg/day) with placebo for a period of 26 weeks in patients with Parkinson's disease with motor fluctuations on levodopa combined in most cases with other anti-Parkinson drugs (dopamine agonists in 70% of cases).
Analysis of data showed that duration of ″off″ periods was reduced on rasagiline 1 mg/day by 0.94h compared with placebo in these patients. UPDRS motor and UPDRS ADL subscores were improved on rasagiline: the differences observed could be considered as moderate (-2.9 and -1.3 points respectively) compared with placebo.

The LARGO study compared the efficacy of rasagiline 1 mg/day with placebo for a period of 18 weeks in patients with Parkinson's disease with end-of-dose motor fluctuations on levodopa. In nearly 60% of patients, a dopamine agonist was combined with levodopa therapy. One group of patients was treated with entacapone.
Analysis of data showed that duration of ″off″ periods reduced on rasagiline 1 mg/day by 0.78h compared with placebo. UPDRS motor and UPDRS ADL subscores improved on rasagiline: the differences observed were moderate (-2.9 and -1.7 points respectively) compared with placebo.
Changes from baseline in ″off″ time (-0.8 h) and in UPDRS subscores recorded for entacapone 200 mg combined with each dose of levodopa also differed from those recorded for placebo and were similar to those recorded with rasagiline.

- **New efficacy data**

Quality of life analysis of rasagiline as monotherapy, in the TEMPO study (Biglan[1])
This is an analysis of one of the secondary endpoints of the TEMPO study: change in PD-QUALIF score[2]. To summarise, mean adjusted changes in PD-QUALIF score observed for rasagiline (1 and 2 mg/day) differed from those observed for placebo (-2.91 on 1 mg/day and -2.74 points on 2 mg/day).

Observational efficacy study: the LEGATO study
This was a 12-week open-label observational study that was carried out in the United States and which included 272 patients treated with AZILECT for Parkinson's disease, either as a monotherapy or in combination with levodopa or a dopamine agonist. The primary objective was to determine the time taken for rasagiline to act, using as criteria the change in UPDRS bradykinesia score and overall clinical improvement as evaluated by the investigator.
The results showed an improvement from the first week, increasing by the end of the second week, and then reaching a plateau until the end of the 12th week.

1 Biglan *et al*. Rasagiline Improves Quality of Life in Patients With Early Parkinson's Disease. Movement Disorders 2006, 21, 5: 616-623

2 Welsh M, McDermott MP, Holloway RG, et al; Parkinson Study Group. Development and testing of the Parkinson's Disease Quality of Life scale. Mov. Disord. 2003;18:637-645.

4.1. Safety

- New safety data

Carrying out the TEMPO and PRESTO (rasagiline) studies in elderly patients (Goetz [3])
This was an age-based analysis of adverse effects that occurred in patients receiving AZILECT in these two studies.
The age threshold was set at 70, in order to achieve a sufficiently large number of elderly patients (69 patients in the TEMPO study and 68 in the PRESTO study).
The adverse effects attributed to rasagiline were not more frequently observed in the group of patients aged over 70 than in younger patients.
This study is of limited use, as it was carried out on small numbers of patients.

Impact of rasagiline on cognitive and behavioural symptoms (Elmer[4])
This study compared adverse effects of rasagiline in patients included in the TEMPO study (early stage Parkinson's disease) and PRESTO study (motor fluctuations on levodopa) who had received either rasagiline 1 mg or placebo.
Results showed no difference between the rasagiline and placebo groups in terms of cognitive and behavioural adverse effects. The main effects were: sleep disorders, depression and hallucinations.

- Summary of SPC

SPC for AZILECT (rasagiline)
"For AZILECT given as monotherapy, the most common adverse effects were headache, flu syndrome, malaise, neck pain, fever, dyspepsia, arthralgia, depression, vertigo, rhinitis, conjunctivitis. When given as an adjunct therapy with levodopa, the following were the most commonly reported adverse effects: dyskinesia, postural hypotension, digestive problems, falls and abnormal dreams.

Cases of melanoma were reported during studies. "

In 2007, the SPC for AZILECT was amended with the addition of the following paragraph:
"Parkinson's disease is associated with symptoms of hallucinations and confusion. In post marketing experience these symptoms have also been observed in Parkinson's disease patients treated with rasagiline. "

Comparison of the SPCs of selegiline and rasagiline shows that they have similar safety profiles. The main difference is a passage that appears in the selegiline SPC but does not in the SPC for rasagiline, which indicates the risk of increased adverse effects of levodopa when the two products are given in combination, requiring special monitoring when starting treatment.

- Conclusion

No new efficacy data that would lead the committee to amend its 2006 opinion concerning AZILECT have been provided. In particular, no comparative studies of rasagiline and selegiline have been provided.

3 Goetz *et al*. Safety of rasagiline in elderly patients with Parkinson disease. Neurology 2006;66:1427-1429

4 Elmer *et al*. Rasagiline-associated motor improvement in PD occurs without worsening of cognitive and behavioral symptoms. Journal of the Neurological Sciences 248 (2006) 78 – 83

5 DATA RELATING TO USE OF MEDICINAL PRODUCT

AZILECT is not currently marketed.

6 TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Re-assessment of actual benefit

In patients with motor fluctuations on levodopa, the actual benefit of this product still remains high, given the lack of available medical resources, particularly for elderly patients with Parkinson's.

6.2. Improvement in actual benefit

AZILECT provides no improvement in actual benefit (IAB V) in comparison with current symptomatic treatments for Parkinson's disease.
The Committee considers that AZILECT is an additional therapy that is useful in the advanced stages of Parkinson's disease compared to current therapeutic strategies.

6.3. Therapeutic use[5,6,7]

Age of onset and level of functional impairment are the two factors that guide treatment choices in the initial phase of the disease:

- if there are no motor symptoms, drug therapy is not essential;
- if there is minimal functional impairment, a dopamine agonist, an MAOB I or an anticholinergic drug may be prescribed. The choice depends on the predominant symptoms and the patient's age;
- if the patient has significant functional impairment, treatment depends on the patient's age:
    - in young patients, dopamine agonists should preferably be used for as long as possible. Levodopa therapy can be started if the patient is intolerant to these or if the therapeutic response is inadequate. The dose of levodopa should be as small as possible.
    - In elderly patients, levodopa can be used as a first-line therapy. If cognitive decline is observed, the minimal effective dose should be used.

After an initial phase of good symptom control on treatment ("honeymoon" period), the patient's health will deteriorate when levodopa-induced motor problems arise (motor fluctuations and dyskinesia) and because of the specific signs of the disease (dysautonomic cognitive disorders, psychological and behavioural disorders) which are most often resistant to levodopa therapy.

In case of motor complications of levodopa treatment, it is necessary to find the therapies that are likely to worsen the "off" periods and dyskinesia, and then to optimise levodopa therapy (dividing the daily dose, changing dosage schedule, prescribing different pharmaceutical forms).

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5 National Collaborating Centre for Chronic Conditions. Parkinson's Disease: national clinical guideline for diagnosis and management in primary and secondary care. London, Royal College of Physicians, 2006

6 Pahwa *et al*. Treatment of Parkinson Disease with motor fluctuations in dyskinesia (an evidence-based review) : report of the quality standards subcommittee of the American Academy of Neurology. Neurology 2006 ; 66 : 983-995.

7 La Maladie de Parkinson : critères diagnostiques et thérapeutiques [Parkinson's disease: diagnostic criteria and therapies]. ANAES Consensus conference - 3 March 2000

Therapeutic management of these complications can also require a combination of one or several other drugs in association with levodopa:

- Dopamine agonist
- COMT inhibitor
- MAO B inhibitor (selegiline, rasagiline)

Rehabilitation therapy has an important role to play in the management of patients with Parkinson's disease. Rehabilitation methods must be tailored, even over the short term, to the changes and fluctuations of the disease.

Stereotactic surgery is an effective remedy for severe motor problems in advanced Parkinson’s disease and for intractable tremor.