TRANSPARENCY COMMITTEE

OPINION

1 October 2008

Examination within the framework of the reassessment of the actual benefit of the MAO-B inhibitor class, pursuant to article R 163-21 of the Social Security Code.

**OTRASEL 1.25 mg, oral lyophilisate**

Pack of 30 freeze-dried tablets (CIP: 352 317-0)

Applicant: CEPHALON FRANCE

selegiline

List I

Marketing authorisation (MA) date: 20 June 2000

Reason for request: reassessment of the actual benefit of the MAO-B inhibitor class in the indication “motor fluctuations in combination with levodopa”,

Medical and Economic Evaluation and Public Health Division
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Selegiline

1.2. Indications
Adjunctive therapy in combination with levodopa (with a peripheral decarboxylase inhibitor) in the treatment of Parkinson's disease. Selegiline in combination with maximal levodopa therapy is indicated particularly in patients who experience fluctuations in their condition such as 'end-dose' type fluctuations, 'on-off' symptoms or other dyskinesias.

Selegiline may be used alone in early Parkinson's disease for symptomatic relief and/or to delay the need for levodopa.

1.3. Dosage

When prescribed as monotherapy for the first time in the early stage of Parkinson's disease or as an adjuvant to levodopa, the dose of Otrasel is one 1.25 mg oral lyophilisate placed on the tongue in the morning, at least five minutes before breakfast and allowed to dissolve.

2 REMINDER OF THE COMMITTEE'S OPINION AND LISTING CONDITIONS

9 May 2007
The actual benefit remains high in the MA indications.

30 May 2001
OTRASEL provides a level IV Improvement in Actual Benefit (IAB) in terms of ease of use and dose reduction compared to the currently available tablet forms of selegiline.

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2008)
N Nervous system
04 Antiparkinson drugs
B Dopaminergics
D Monoamine oxidase-B inhibitors
01 Selegiline

3.2. Medicines in the same therapeutic category
The other medicinal products in the MAO-B inhibitor class are:
Rasagiline: AZILECT 1 mg, tablet
Selegiline: DEPRENYL 10 mg, scored tablet and generics
DEPRENYL 5 mg, scored tablet and generics
3.3. Medicines with a similar therapeutic aim
These are the other antiparkinson drugs indicated in the reduction of motor fluctuations in combination with levodopa:
- Dopamine agonists (bromocriptine, lisuride, piribedil, pramipexole, ropinirole, pergolide, apomorphine)
- COMTI: entacapone, tolcapone (in patients not responding or who are intolerant to other COMT inhibitors)

4 UPDATING WITH DATA OBTAINED SINCE THE PREVIOUS OPINION

4.1. Efficacy
The laboratory presented 1 randomised double-blind study in Parkinson's disease patients receiving L-dopa therapy at the motor fluctuation stage which compared selegiline with placebo on 150 patients, during 12 weeks. This did not show a significant difference between the two groups for the duration of the “off” periods.

4.2. Safety
Continuation of two studies over 12 months
This comprised the 12-month open-label extension of two safety studies of selegiline versus placebo. This analysis which was carried out in the United States, included 254 patients treated by selegiline at the dose of 2.5 mg; 95.7% of patients presented an adverse effect. The most frequent adverse events were: depression (4.3%), vertigo (3.1%), hallucinations (2%), falls (3.9%), chest pain (3.1%).

SPC
The “undesirable effects” section of the proprietary medicine OTRASEL has been unchanged since 2006.

The comparison of the SPC of selegiline and rasagiline shows a similar safety profile. The main difference lies in the wording in the selegiline SPC that does not appear in the SPC for rasagiline, concerning the risk of an increase in the undesirable effects of levodopa after combination of these 2 products and the need for specific monitoring after institution of treatment.

4.3. Conclusion
The data provided are not sufficient to modify the conclusions of the previous opinion of the French Transparency Committee.

5 DRUG USAGE DATA

According to data from the IMS/Dorema database (CMA Feb. 08), 15,000 prescriptions of DEPRENYL are made per year.

6.1. Reassessment of actual benefit
The actual benefit of this proprietary medicine remains substantial in Parkinson's disease, in the case of motor fluctuations in combination with levodopa.

6.2. Therapeutic use\textsuperscript{3, 4, 5}

The age of onset and degree of functional impairment are the two factors which determine the choice of therapy during the initial stage of the disease:

- In the absence of motor repercussions, antiparkinson medication is not indispensable;
- The following agents may be prescribed even when there is only minor functional impairment: a dopamine agonist, MAO B inhibitor or an anticholinergic. The choice depends on the predominant symptom and the patient's age;
- When there is a more severe functional impairment, treatment depends on the patient's age:
  - In young subjects, dopamine agonists should be preferred for as long as possible. The use of L-dopa therapy is justified in the event of adverse effects or an insufficient therapeutic response. The dose of levodopa must remain as low as possible.
  - L-dopa may be used as first-line treatment in the elderly subject. The minimum effective dose should be used if the patient develops cognitive impairment.

After a "honeymoon" phase with good symptom control by treatment, the patient's health status worsens with the onset of dopa-induced motor disorders (motor fluctuations and dyskinesia) and the specific signs of the disease (dysautonomic cognitive impairment, psycho-behavioural signs) which are generally dopa-resistant.

Because of these motor complications caused by dopaminergic treatment, drugs should be sought that worsen the "off" periods and dyskinesias and L-dopa therapy should then be optimized (splitting of daily dose, adjustment of the dosing schedule, prescription of different pharmaceutical forms).

The therapeutic management of these complications may also justify the combination of other medicinal products with levodopa:
  - Dopamine agonist
  - COMT inhibitor
  - MAO-B inhibitor (selegiline, rasagiline)

Rehabilitation plays a major role in the management of Parkinson's disease patients. Rehabilitation procedures must be adjusted, even in the short term, according to the unpredictable fluctuations of the disease.

Stereotactic surgery is an effective method of treatment of severe motor disorders in advanced Parkinson's disease and intractable tremor.

\textsuperscript{3} 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


\textsuperscript{5} Parkinson's disease: diagnostic and therapeutic criteria. ANAES Consensus conference - 3 March 2000