HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

1 March 2006

Zyprexa Velotab 5 mg, orodispersible tablet
Aluminium blister strip(s) 28 tablets: 354 542-1

Zyprexa Velotab 10 mg, orodispersible tablet
Aluminium blister strip(s) 28 tablets: 354 543-8

Applicant: Lilly France

olanzapine

List I

Date of European Marketing Authorization (AMM) and amendments: 03 February 2000, 08 October 2003, 13 July 2004, 04 November 2004, 09 February 2005, 31 August 2005.

Reason for application: Inclusion on the list of drugs reimbursed by National Insurance in the indications “treatment of schizophrenia” and “prevention of recurrence in patients with a bipolar disorder, whose manic episode has responded to treatment with olanzapine”.

Inclusion on the list of medicinal products reimbursed by National Insurance in the indication “treatment of moderate to severe manic episodes” was approved on 18 December 2002.

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCTS

1.1. Indications

Olanzapine is indicated in the treatment of schizophrenia.

In patients who have initially responded to treatment, olanzapine has been shown to be effective in maintaining this clinical improvement in the long term.

Olanzapine is indicated in the treatment of moderate to severe manic episodes.

Olanzapine is indicated in preventing recurrence of bipolar disorder in patients whose manic episode has responded to treatment with olanzapine.

1.2. Dosage

Schizophrenia: recommended starting dose of Olanzapine is 10 mg.

Manic episode: recommended starting dose is 15 mg/day in a single dose in monotherapy or 10 mg/day in combination therapy.

Preventing recurrence in bipolar disorder: recommended starting dose of Olanzapine is 10 mg/day.

In patients previously treated with olanzapine during a manic episode, treatment should be maintained at the same dose to prevent recurrence. If a new episode occurs (manic, mixed bipolar or depressive episode) olanzapine should be continued at the optimal dose. Mood-modifying drugs should be added to olanzapine, depending on the clinical expression of the episode.

In all indications, the daily dose of Olanzapine may be adjusted between 5 and 20 mg/day according to the patient's clinical state. The dose should only be increased after clinical re-assessment, with an interval of at least 24 hours between increases. Food consumption has no affect on absorption and olanzapine may be given without regard to meals. Olanzapine should be withdrawn by a gradual reduction in the dose.

Children: Olanzapine has not been studied in patients under 18 years.

Elderly patients: A lower starting dose (5 mg/day) is not routinely indicated but should be considered in patients aged 65 years and over when clinical factors warrant.

Renal and/or hepatic/impairment: the starting dose should be lower in patients with renal and/or hepatic impairment (5 mg/day). In the case of moderate hepatic impairment (cirrhosis, Child-Pugh class A or B), the starting dose should be 5 mg and be increased with caution.

When there is more than one factor which might cause slower metabolism (female, elderly patient, non-smoker) the starting dose may need to be reduced. Any dose increase indicated should be made with caution in these patients.

2. SIMILAR MEDICINAL PRODUCTS

The medicinal products Zyprexa Velotab 5 mg and 10 mg, orodispersible tablets are additions to the range of the Zyprexa medicinal products, 5 mg and 10 mg coated tablets.

3. ANALYSIS OF AVAILABLE DATA

The company has submitted three studies:

The VELOBS prospective study is an observational study of hospital prescriptions of Zyprexa Velotab for 6 weeks in patients presenting with an acute psychotic episode. 150 psychiatrists participated in this study of 515 patients (average age = 35). 70% had been diagnosed as schizophrenic. 343 patients were followed up for 6 weeks. 27.5% of patients had taken an antipsychotic (cyamemazine 37%, risperidone 20%, loxapine 20%, haloperidol 16%) for the current episode before starting treatment with olanzapine. The total mean PANSS[1] score at inclusion was 107.

47% of patients took Zyprexa Velotab as monotherapy; 21% combined olanzapine with an antipsychotic (cyamemazine in 46% of cases); and 32% of patients combined olanzapine with another psychotropic (benzodiazepine in 45% of cases).

Zyprexa Velotab was stopped before week 6 of treatment in 306 patients: 76.8% changed over to another treatment because they were discharged from hospital, 6.9% refused treatment, 6.5% on the psychiatrist's decision, 5.6% because of lack of efficacy, 2.9% because of undesirable effects.

Of the 277 patients who changed antipsychotic drugs, 223 patients (80.5%) were given Zyprexa (coated tablet) as a replacement for the orodispersible form.

Zyprexa prescriptions over one year were the subject of a retrospective study of 923 included patients between January and May 2005.
Data on 798 patients who received at least two prescriptions during the period of retrospective follow-up were analysed:

- The dose was increased in 152 patients,
- The dose was reduced in 127 patients,
- The dose remained unchanged in 519 patients.

The most common doses for the last prescription were: 5 mg/day (36%), 7.5 mg/day (17%), 10 mg/day (26%), 15 mg/day (11%), 20 mg/day (8%).

Prescriptions over two years were monitored in 14 694 outpatients newly treated with Zyprexa between January and September 2003. Data for 6967 patients treated during the last 6 months have been analysed.

In the two years following start of treatment:

- 60% of patients were still being treated with Zyprexa,
- 14% of patients had changed treatment,
- 26% were no longer receiving treatment.

1 PANSS: Positive And Negative Syndrome Scale (score from 30 to 210).Three sub-scales: subscale of positive symptoms (7 items), subscale of negative symptoms (7 items), and subscale of general psychopathology (16 items). Severity of each symptom is scored from 1 to 7.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The actual benefit for these orodispersible medicinal products is substantial.
The absence of a 7.5 mg unit dose makes it impossible to adjust the daily dose in 2.5 mg steps, which can be done with 5 mg, 7.5 mg and 10 mg coated tablets. The availability of only 5 mg and 10 mg doses of orodispersible forms is not therefore appropriate for all the prescription requirements for olanzapine.

4.2. Improvement in actual benefit

Zyprexa Velotab orodispersible tablets are additions to the range and do not contribute any improvement in actual benefit (IAB V1) compared with Zyprexa, coated tablets in outpatient management of patients treated with olanzapine.

4.3. Transparency Committee Recommendations

The committee recommended inclusion on the list of medicinal products reimbursed by National Insurance in the indications "treatment of schizophrenia" and “prevention of recurrence in patients with a bipolar disorder, whose manic episode has previously responded to treatment with olanzapine”.

The Committee regretted that there is no 7.5 mg dose, which would allow dose adjustment and/or continuity of treatment with Zyprexa Velotab in patients requiring daily doses of 7.5 mg, 12.5 mg or 17.5 mg, particularly during long-term outpatient treatment.

4.3.1 **Packaging:** Suitable for the conditions of the prescription.

4.3.2 **Reimbursement rate:** 65%

1 ASMR in French