European Medicines Agency
*Pre-Authorisation Evaluation of Medicines for Human Use*

London, 25 September 2008
Doc.Ref. EMEA/CHMP/342542/2008

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE**
**SUMMARY OF POSITIVE OPINION***
**for**
**ZYPADHERA**

International Nonproprietary Name (INN): ***olanzapine***

On 25 September 2008 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion,** recommending to grant a marketing authorisation for the medicinal product Zypadhera, 210 mg, 300 mg, 405 mg powder for suspension for injection intended for treatment of schizophrenia. The applicant for this medicinal product is Eli Lilly Nederland B.V.

The active substance of Zypadhera is olanzapine (as pamoate monohydrate), an antipsychotic medicinal product (ATC code: N05AH03) with a broad binding and pharmacological profile. In vitro, olanzapine showed medium-to-high affinity (Ki <100 nM) for dopamine $D_1$, $D_2$, $D_3$, $D_{4.2}$, $D_5$, serotonin 5-$HT_{2A}$, 5-$HT_{2C}$, 5-$HT_3$, 5-$HT_6$, $\alpha_1$-adrenergic, histamine $H_1$, and 5 muscarinic receptor subtypes. Olanzapine had lower affinity for $\alpha_2$-adrenergic receptors and relatively low affinity for 5-HT1 subtypes, $GABA_A$, β-adrenergic, and benzodiazepine binding sites. Overall, the binding profile of olanzapine is very similar to that produced by clozapine, although the affinity of olanzapine is somewhat higher at dopamine receptors and lower at $\alpha_2$-adrenergic receptors.

The benefits with Zypadhera are,

- its superiority over placebo in the treatment of schizophrenia as demonstrated in a 8-week randomized placebo controlled superiority study that showed that mean decreases in Positive and Negative Syndrome Scale (PANSS) total scores compared to placebo arm from baseline to endpoint (week 8) were as follows: Zypadhera 300 mg/2 weeks: 17.81 points ($p<0.001$), Zypadhera 405 mg/4 weeks: 14.06 points ($p<0.001$), Zypadhera 210 mg/2 weeks: 13.98 points ($p<0.001$). All Zypadhera treatments were superior to placebo from week 1 visit on and continued to be more effective through-out the study period. None of the Zypadhera treatments were superior to any one of two other Zypadhera treatments over 8 weeks.

- non inferior efficacy as compared to oral olanzapine in terms of exacerbation rates after 24 weeks, and superior efficacy of 300 mg/ 2weeks, 405 mg/4 weeks, and 15 mg/2weeks as compared to 45 mg/2 weeks (low dose close to placebo) in terms of time to exacerbation of symptoms of schizophrenia. Analysis of the first primary variable showed that Zypadhera in the pooled 2-week group analysis was no inferior to oral olanzapine (10-20 mg).

The most common side effects are comparable to the ones observed with oral olanzapine, i.e., weight gain, somnolence, elevated plasma prolactin levels, elevated cholesterol, glucose and triglycerides levels, glucosuria, increased appetite, dizziness, akathisia, parkinsonism, dyskinesia, orthostatic hypotension, mild, transient anticholinergic effects including constipation and dry mouth, transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment, rash, asthenia, fatigue, oedema.

However, specific aspects related to the different formulation were identified. In particular, post injection syndrome events caused by inadvertent intravenous administration, presented with signs and

* Summaries of positive opinion are published without prejudice to the Commission Decision, which will normally be issued within 67 days from adoption of the Opinion.

** Applicants may request a re-examination of any CHMP opinion, provided they notify the EMEA in writing of their intention to request a re-examination within 15 days of receipt of the opinion.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

symptoms consistent with olanzapine overdose. These events occurred in 0.7% of injections and approximately 1.4% of patients. Most of these patients have developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension or possible convulsion. In most cases, initial signs and symptoms related to this event have appeared within 1 hour following injection, and in all cases full recovery was reported to have occurred within 24 – 72 hours after injection.

Another aspect specific for Zypadhera was represented by the treatment-emergent injection-site-related adverse events. The analysis of all these events demonstrated that injection-site pain is the most common event (5.5% in the Overall Integrated Database) and that most patients reported it as “mild” in severity.

A pharmacovigilance plan for Zypadhera, as for all medicinal products, will be implemented as part of the marketing authorisation.

The approved indication is: “Maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine”.

Detailed recommendations for the use of this product will be described in the Summary of Product Characteristics (SPC) which will be published in the European Public Assessment Report (EPAR) and will be available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers that there is a favourable benefit to risk balance for Zypadhera and therefore recommends the granting of the marketing authorisation.