London, 25 April 2014
EMA/384213/2014
Committee for Medicinal Products for Human Use (CHMP)

Zypadhera

olanzapine

Procedure No. EMEA/H/C/000890/II/0022

Marketing authorisation holder: Eli Lilly Nederland B.V.

Assessment report for paediatric use studies submitted according to Article 46 of Regulation (EC) No 1901/2006

Assessment report as adopted by the CHMP with all commercially confidential information deleted

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 5 February 2014 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Zypadhera	olanzapine	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

The MAH has proposed an update of sections 4.4 and 5.1 of the SmPC in order to reflect the level of data available in adolescents with bipolar I disorder (manic or mixed episodes) or schizophrenia following the completion of a long-term safety study, in fulfilment of the requirement laid down in Article 46 of the paediatric regulation.

In addition, administrative updates to the reconstitution instructions in the SmPC and PL to align with information provided by the manufacture of the kit needles and syringes are proposed. Finally, a correction to the pharmacotherapeutic group in line with the WHO ATC index and a correction to a listed excipient of the Zypadhera solvent are proposed.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

Rapporteur: Janne Komi

1.2. Steps taken for the assessment

Submission date:	5 February 2014
Start of procedure:	24 February 2014
Rapporteur's variation assessment report circulated on:	25 March 2014
CHMP opinion:	25 April 2014

2. Scientific discussion

2.1. Introduction

Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems. Olanzapine exhibits a range of receptor affinities for serotonin $5HT_{2A/2C}$, $5HT_3$, $5HT_6$; dopamine D_1- D_5; cholinergic muscarinic receptors M_1-M_5; α_1 adrenergic receptors; and histamine H_1 receptors.

Zyprexa (olanzapine coated tablets and powder for solution for injection (rapid-acting, RAIM)) was first authorised in European Union on 27th September 1996. Oral and RAIM formulations are marketed in 121 countries. Zypadhera (powder and solvent for prolonged release suspension for

injection) was authorised in Europe on 19th November 2008. It is marketed in 106 countries worldwide. Zypadhera is indicated in maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine. The effectiveness of Zypadhera in the treatment and maintenance treatment of schizophrenia is consistent with the established effectiveness of the oral formulation of olanzapine. In the EU, olanzapine is indicated in adult patients only.

2.2. Quality aspects

This variation includes a correction to the list of excipient of Zypadhera solvent. Module 3.2.P.3.2 states that the solvent contains carmellose sodium. In the current package information croscarmellose sodium is listed as an excipient of Zypadhera solvent and this information will be now corrected (SmPC, PL, labelling). The error has been in place since the initial MA approval in November 2008. The variation also updates the reconstitution instructions in the SmPC and PL to align with information provided by Smiths Medical, the manufacturer of the kit needles and syringes.

2.3. Clinical Safety aspects

This variation results from previous assessment according to Art. 46 of the paediatric regulation and is related to ongoing worksharing process for Zyprexa and Zyprexa Velotab (EMEA/H/C/XXX/WS/485). Relevant data submitted for the issue has been assessed thoroughly within process EMEA/H/C/XXX/WS/485. This is a parallel process to stay in line with Zyprexa and Zyprexa Velotab. The changes proposed in the SmPC sections 4.4 and 5.1 of Zypadhera are exactly the same as proposed and assessed as approvable in the SmPC sections 4.4 and 5.1 of Zyprexa (excluding RAIM) and Zyprexa Velotab in worksharing process EMEA/H/C/XXX/WS/485.

2.4. Discussion

The results of study HGMX provide additional data on the long-term safety of olanzapine treatment in adolescents. Previous long-term data in adolescents have extended to 32 weeks of treatment (McCormack 2010) but were open-label and uncontrolled. Results of study HGMX extend the data in adolescents to 52 weeks and support the findings from the previous studies of up to 32 week's duration. The data of olanzapine from study HGMX were also open-label and uncontrolled. Therefore, these findings should be interpreted with caution.

The findings from study HGMX do not change the overall benefit-risk profile of olanzapine in adolescents. However, evaluating the relevant sections of the SmPC in light of the newly available data, the MAH proposes modifications to SmPC sections 4.4 and 5.1 to remove or correct statements regarding the availability of long-term data in the paediatric population. Sections 4.2 and 4.8 of the SmPC contain paediatric information that the MAH does not propose to change.

2.5. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), in the SmPC of Zypadhera (deleted as ~~strikethroughs~~ and additions as <u>underlined</u>) to which the CHMP agreed:

4.4 Special warnings and precautions for use

Paediatric population

Olanzapine is not indicated for use in the treatment of children and adolescents. Studies in patients aged 13-17 years showed various adverse reactions, including weight gain, changes in metabolic parameters and increases in prolactin levels~~. Long-term outcomes associated with these events have not been studied and remain unknown~~ (see sections 4.8 and 5.1).

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, ~~and~~ thiazepines and oxepines, ATC code N05A H03.

...

Paediatric population

ZYPADHERA has not been studied in the paediatric population. Controlled efficacy data ~~The experience~~ in adolescents (ages 13 to 17 years) ~~is~~ are limited to short term oral olanzapine studies ~~efficacy data~~ in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents.

Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin (see sections 4.4 and 4.8) were greater in adolescents than in adults. There are no controlled data on maintenance of effect or ~~and limited data on~~ long term safety (see sections 4.4 and 4.8). Information on long term safety is primarily limited to open-label, uncontrolled data.

6.1 List of excipients

...

C~~rosc~~armellose sodium

...

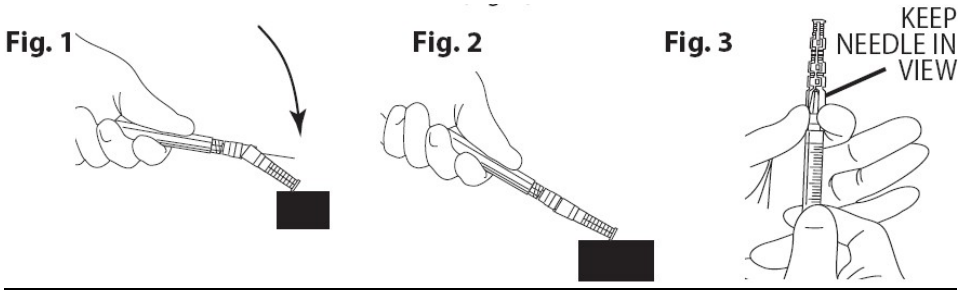
In addition the following similar changes are proposed into section 6.6 and Instructions for Health Care Professionals:

6.6 Special precautions for disposal and other handling

...STEP 3: Reconstituting ZYPADHERA

1. Loosen the powder by lightly tapping the vial.
2. Open the pre-packaged Hypodermic syringe and needle with needle protection device. Peel blister pouch and remove device. Attach a syringe (if not already attached) to the Luer connection of ~~Insure needle is firmly seated on~~ the device with an easy twisting motion. Seat the needle firmly on the device with a push and a clockwise twist, then pull the needle cap straight away from the needle. Failure to follow these instructions may result in a needlestick injury.
3. Withdraw the pre-determined solvent volume (Step 2) into the syringe.
4. Inject the solvent volume into the powder vial.
5. Withdraw air to equalize the pressure in the vial.
6. Remove the needle, holding the vial upright to prevent any loss of solvent.
7. Engage the needle safety device. Press the needle into the sheath using a one-handed technique. Perform a one-handed technique by GENTLY pressing the sheath against a flat surface. AS THE SHEATH IS PRESSED (Fig. 1), THE NEEDLE IS FIRMLY ENGAGED INTO THE SHEATH (Fig~~ure 1 and~~ 2)

8. Visually confirm that the needle is fully engaged into the needle protection sheath. (Figure 3) Only remove the device with the engaged needle from the syringe when required by a specific medical procedure. Remove by grasping the Luer hub of the needle protection device with thumb and forefinger, keeping the free fingers clear of the end of the device containing the needle point (Fig. 3).



…

Administration
STEP 1: Injecting ZYPADHERA
… 7. Engage the needle safety device. (Fig~~ure~~ 1 and 2) …

The CHMP considered that the proposed changes are approvable. The proposed changes in the PL, instructions for the HCPs and labelling are in line with those proposed in the SmPC sections 6.1 and 6.6.

3. Overall conclusion and impact on the benefit / risk balance

This is a parallel procedure with ongoing worksharing process for Zyprexa and Zyprexa Velotab to fulfill the requirements of Article 46 of the paediatric regulation following the completion of the study HGMX (F1D-MC-HGMX), 'A Long-Term, Open-Label, Safety Study of Oral Olanzapine in Adolescents with Bipolar I Disorder (Manic or Mixed Episodes) or Schizophrenia', and to update the SmPC in order to reflect the level of safety data now available in this patient population, and to be in line with Zyprexa and Zyprexa Velotab.

Relevant data submitted for the issue has been assessed thoroughly within parallel process EMEA/H/C/xxxx/WS/0485. The changes proposed in the SmPC sections 4.4 and 5.1 of Zypadhera are exactly the same as proposed and assessed as approvable in the SmPC sections 4.4 and 5.1 of Zyprexa (excluding RAIM) and Zyprexa Velotab in the worksharing process EMEA/H/C/xxxx/WS/0485.

In principle, the proposed clinical amendments to the Product Information provide updated information from current knowledge gathered from results from uncontrolled study among children and adolescents of 13 to 17 years, and that no controlled long-term data on maintenance of effect or safety exists. In EU, olanzapine is not indicated in the treatment of adolescents. The proposed clinical changes in the Product Information sections 4.4 and 5.1 are approvable.

This variation also includes corrections to the pharmacotherapeutic group in line with the WHO ATC index and to the list of excipient of Zypadhera solvent, and updates the reconstitution instructions in the SmPC and PL to align with information provided by the manufacturer of the kit needles and syringes. These changes are also approvable.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Update of sections 4.4 and 5.1 of the SmPC in order to reflect the level of data available in adolescents with bipolar I disorder (manic or mixed episodes) or schizophrenia following the completion of a long-term safety study, in fulfilment of the requirement laid down in Article 46 of the paediatric regulation.

In addition, administrative updates to the reconstitution instructions in the SmPC and PL to align with information provided by the manufacture of the kit needles and syringes were proposed.

The MAH took also the opportunity to implement editorial changes with this variation.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

Conditions and requirements of the marketing authorisation

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

An education program to the health care professionals (HCP) (doctors-nurses-pharmacist) shall address,

1) Description of post injection syndrome
- Education about the 2 intramuscular formulations of olanzapine, including packaging differences
- Description of reconstitution and proper administration technique
- Recommendation for a 3-hour on-site observation period post injection
- Recommendation that, immediately prior to a patient leaving the health care facility, it should be confirmed that the patient is alert, oriented, and absent of any signs or symptoms of overdose
- Recommendation that the 3-hour observation period should be extended as clinically appropriate for patients who exhibit any signs or symptoms consistent with olanzapine overdose
- Recommendation for informing patients that for the remainder of the day of the injection, they should not drive or operate machinery, should be vigilant for signs and symptoms of a post injection syndrome event, and should be able to obtain assistance if needed
- Description of the most common symptoms reported with olanzapine overdose that represent the clinical manifestation in post injection syndrome events
- Recommendation for appropriate monitoring until the event resolves if an event should occur

2) Recommendations for monitoring of patients for glucose, lipids, and weight
- Promote awareness of appropriate metabolic monitoring by distributing utilized published antipsychotic guidelines

A patient card shall be distributed to all patients, including:

- Description of post injection syndrome
- Recommendation for a 3-hour on-site observation period post injection
- Recommendation for informing patients that for the remainder of the day of the injection, they should not drive or operate machinery, should be vigilant for signs and symptoms of a post injection syndrome event, and should be able to obtain assistance if needed
- Description of the most common symptoms reported with olanzapine overdose that represent the clinical manifestation in post injection syndrome events
- Recommendation for appropriate monitoring until the event resolves if an event should occur