London, 25 April 2014
EMA/334375/2014
Committee for Medicinal Products for Human Use (CHMP)

Zyprexa / Zyprexa Velotab

(olanzapine)

Procedure No. EMEA/H/C/xxxx/WS/0485

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

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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 6 November 2013 an application for a variation, following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

This application concerns the following medicinal products:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Zyprexa	olanzapine	See Annex A
Zyprexa Velotab	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 to update the 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.

The MAH has also taken the opportunity to align the Product Information with the Quality Review of Documents (QRD) template (Version 9) and to update the list of local representatives in the Package Leaflet.

In addition, the MAH has corrected a mistake in the ATC code (section 5.1 of the SmPC) since the addition of “oxepines” to the pharmacotherapeutic group description was needed to comply with the WHO ATC index.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Appointed Rapporteur for the WS procedure: Janne Komi

1.2. Steps taken for the assessment

Submission date:	6 November 2013
Start of procedure:	24 November 2013
Rapporteur's preliminary assessment report circulated on:	20 December 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	23 January 2014
MAH's responses submitted to the CHMP on:	5 March 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	21 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. Zyprexa Velotab (orodispersible tablets) was authorised in Europe on 3rd February 2000. Oral and RAIM formulations are marketed in 121 countries.

In the EU, Zyprexa and Zyprexa Velotab are indicated in adults for the treatment of schizophrenia (including maintenance treatment), for the treatment of moderate to severe manic episode and in prevention of recurrence in patients with bipolar disorder whose manic episode has responded to olanzapine. Zyprexa RAIM is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or manic episode, short-termly when oral therapy is not appropriate.

In the US, olanzapine was approved in 2009 for the treatment of schizophrenia or manic or mixed episodes associated with bipolar I disorder in patients 13 to 17 years of age. In the EU, olanzapine is indicated in adult patients only.

2.2 Background

The MAH conducted a phase IV study HGMX as a condition to the US adolescent approval and to fulfill the EU planned pharmacovigilance action to evaluate the long-term safety of olanzapine in adolescents,

In 2007 the MAH submitted type II variations for Zyprexa and Zyprexa Velotab that included data from 2 randomised, double-blind, placebo-controlled studies of oral olanzapine in patients 13 to 17 years of age. Study F1D-MC-HGIN (HGIN), evaluated efficacy of oral olanzapine for the treatment of adolescent patients suffering from schizophrenia; study F1D-MC-HGIU (HGIU), evaluated efficacy of oral olanzapine for the treatment of adolescent patients suffering from bipolar mania.

- Study HGIN was a multicenter, randomised, double-blind, placebo-controlled, parallel study comparing the efficacy of once-daily oral olanzapine with placebo in adolescent patients (aged 13-17) with schizophrenia. The study included a 6-week, acute treatment period followed by a 26-week, open-label period (i.e. up to 32 week).
- Study HGIU was a multicenter, randomised, double-blind, placebo-controlled, parallel study comparing the efficacy of once-daily oral olanzapine 2.5 to 20 mg/day with placebo in adolescent patients (aged 13-17) with bipolar I disorder. In study HGIU a 3-week acute period was followed by a 26-week open-label period (i.e. up to 29 week).

Placebo-controlled database in studies HGIN and HGIU included 268 patients (olanzapine n=179, placebo n=89).

In addition to these, the dossier included pharmacokinetic and safety data from 2 supportive studies (F1D-MC-HGMF (HGMF) and F1D-MC-LOAY (LOAY).

- Study HGMF was a 4-week, open-label pharmacokinetic study of adolescents aged 13-17 years with schizophrenia or bipolar I disorder.
- Study LOAY was an open-label safety and efficacy study which included adolescents aged 12-21 years with schizophrenia, schizoaffective disorder or schizophreniform disorder. The study included a 6-week, open-label treatment phase followed by an 18-week, open-label extension phase for patients who responded to treatment at week 6 (i.e. up to 24 week). Only patients 13-17 years of age were included into pooled olanzapine adolescent database.

The pooled adolescent olanzapine exposure database was constituted of these studies HGIN, HGIU, HGMF and LOAY, and includes information on 454 adolescent patients (13-17 years) exposed to olanzapine up to 32 weeks. This database was previously used in the making of the adverse reaction table for paediatric population in SmPC section 4.8 and as a reference when analysing the safety data from the HGMX study. Also, slightly larger adolescent metabolic database (FDA Metabolic Response December 2007, submitted to EMA on 04 August 2008) was used, which, in addition to the subjects in the pooled olanzapine adolescent database, included 35 additional adolescent patients pulled from olanzapine studies for indications other than bipolar disorder or schizophrenia.

2.3. Clinical Efficacy aspects

2.3.1. Methods – analysis of data submitted

Study HGMX was a global, multicenter (total of 29 centers in Germany, Poland, USA, Puerto Rico and Russia), open-label, uncontrolled single-drug-arm, 52-week study to evaluate the long-term safety and effectiveness of olanzapine in the treatment of adolescent patients (aged 13-17) with schizophrenia or manic or mixed episodes associated with bipolar I disorder.

The study was conducted in accordance with GCP, Declaration of Helsinki and ethical guidelines. First patient was enrolled on 30th September 2009 and the last patient completed on 7th May 2013. HGMX clinical study report, approved on 5th November 2013.

The primary objectives of study HGMX were to assess in adolescent patients with bipolar I disorder manic or mixed episode) or schizophrenia:

1) whether an intense behavioral weight intervention program was superior to a standard behavioral weight intervention program in mitigation of weight gain (efficacy) as assessed by overall mean change from baseline body mass index (BMI), and

2) the overall safety of olanzapine for up to approximately 52 weeks of treatment.

The secondary objectives of this study were:

- to assess the mean change in BMI of 2 intervention programs for patients with at least 6 months of data.
- to assess the time to event for 7%, 15%, and 25% weight gain between patients randomized to either an intense or standard behavioral weight intervention program.
- to assess the mean change from baseline in waist circumference for all patients.
- to assess the efficacy of oral olanzapine treatment in adolescents, as measured using psychiatric assessments including rating scales that assess symptoms of bipolar I disorder (Young Mania Rating Scale, YMRS) or schizophrenia (Brief Psychiatric Rating Scale for Children, BPRS-C) and clinical global evaluations (Clinical Global Impression of Improvement/Severity, CGI-I/CGI-S).

Patients recruited in screening period (period I, duration of 2-14 days) were inpatients or outpatients who met DSM-IV-TR criteria for schizophrenia or bipolar I disorder with acute current manic or mixed episode. Diagnosis was confirmed with the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime (K-SADS-PL). Patients with schizophrenia had to have a BPRS-C total score >30 at baseline (i.e. at visits 1 and 2), with an item score ≥3 for hallucinations, delusions or peculiar fantasies. Patients with bipolar disorder were required to have a YMRS total score of ≥15 at baseline. These cutoff scores reflect standard thresholds to ensure a homogenous population with acute symptoms.

Concomitant use of other antipsychotics or medicinal products for mood stabilization used for the bipolar I disorder or schizophrenia was prohibited. Such medications needed to be discontinued at least 2 days prior to visit 2 (i.e. when olanzapine was to be initiated). Concomitant medications for the purpose of control or reduction of weight were not allowed during the study. Psychostimulants and other agents with potential weight effects were allowed if the patient had been on a stable dose for at least 2 weeks before visit 1. If a need for initiating any of these agents was required during the study, continued participation or discontinuation was to be evaluated with the sponsor prior to this occurring. Use of benzodiazepines was allowed.

Eligible patients were to begin treatment with open-label olanzapine (period II from visit 2 onwards), flexible doses between 2.5 and 20 mg once a day. A flexible dosing regimen was used to facilitate the chance for optimal dosing and to minimise potential adverse events (AEs). Patient visits occurred twice in the first week, weekly for the next 3 weeks, every second week for the next 4 weeks and then every 4 weeks for the remaining 44 weeks of the year-long trial.

The standard intervention (negative control) consisted of a single counseling session (visit 2 only) with basic information on healthy eating and exercise habits at the time of randomisation for the patient and the parent or caregiver. This standard program was designed to approximate a typical practice situation. The intense intervention (active control) consisted of a counseling session at each study visit for both the patient and the parent or caregiver. In addition to basic information, patients in the intense intervention group received a pedometer and daily lifestyle log for recording their diet and physical activity, which was reviewed at each session. Patients in the intense intervention who met criteria for obesity (tier 2) also received a bathroom scale for home use and additional information and guidance with an emphasis on calorie reduction and weight loss.

Mean baseline weight and BMI were above average toward overweight. 57% of all patients were in the healthy range and 24% of all patients met criteria for obesity at baseline. Patients in the bipolar subset had a mean baseline BMI about 3 kg/m^2 higher, weighted over 5 kg more and had mean waist circumference over 8 cm wider than the schizophrenia subset at baseline. In standard group a mean weight was over 5 kg more ($p=0.042$) and waist circumference over 5 cm wider ($p=0.016$) at baseline than that of the intense group. Baseline BMI did not differ significantly between intervention groups.

A total of 261 patients were screened. 205 patients were randomised in a 1:1 ratio to a standard or intense behavioural weight intervention group at visit 2 (in the beginning of period II). In randomization, region, BMI group (obese or non-obese) and disease group were taken account. Two patients were not included in the final analyses: One patient (an orphan) was removed from the database due to improper consent and a second patient was mis-entered in the system but never had data collected.

Final analyses are based on 203 patients (52 % males; 81 % white; mean age 15.8 years) treated with olanzapine. 102 subjects were randomised into standard weight intervention group and 101 into intense weight intervention group. Of 87 (43 % of all) patients with schizophrenia 44 were randomised into standard and 43 in intense group. 116 (57 % of all) patients with bipolar I disorder were randomised equally in both groups (58 each).

The patients diagnosed with schizophrenia were more likely to be male (63%) and from outside the US (82%), predominantly from Russia (61%), with a relatively lower proportion of non-white patients (9%). Patients diagnosed with bipolar disorder were more likely to be female (56%) and from the USA (96%), with a relatively higher proportion of non-white patients (27%).

The primary analysis was an assessment of the efficacy evaluated by overall mean change from baseline in BMI in standard behavioral weight intervention program compared with intense behavioral weight intervention program using mixed-effects model repeated measures (MMRM) methodology.

Safety measures included collecting vital signs, weight, height, waist circumference, AEs, serious adverse events (SAEs), concomitant medications, laboratory measurements, electrocardiograms (ECGs), and ratings on the Barnes Akathisia Rating Scale, Abnormal Involuntary Movements Scale (AIMS), Simpson-Angus Rating Scale and Columbia Suicide Severity Rating Scale (C-SSRS).

In addition, efficacy of olanzapine to the disease state was assessed by using psychiatric assessments including rating scales (CGI-S and CGI-I for all patients, BPRS-C for patients with schizophrenia, and YMRS for patients with bipolar disorder).

In addition to BMI, MMRM analyses were performed for the all continuous variables with multiple measurements. The primary variable BMI was also evaluated using last-observation-carried-forward (LOCF) methodology using analysis of covariance (ANCOVA) to verify the robustness of the results. For baseline characteristics, analysis of variance (ANOVA) was used. For categorical variables, Fisher's exact test was used with no stratifying variables, and the Cochran-Mantel-Haenszel (CMH) test was used with stratified analyses. The intent-to-treat (ITT) population was used in all analyses performed. All tests of intervention effects were conducted at a 2-sided alpha level of 0.05, unless otherwise stated.

Post hoc analyses were conducted to explore possible differences between Tier 1 (non-obese at baseline) and Tier 2 (obese at baseline) of the intense intervention with respect to efficacy of the weight intervention. Results were not provided in the dossier but are available upon request.

2.3.2. Results

Efficacy of the weight intervention

Of 203 subjects 82 (40 %) completed the study HGMX. Of them 45 belonged to standard and 37 to intense behavioural weight intervention group. 43 (49%) patients with schizophrenia and 39 (34%) patients with bipolar I disorder completed the 52-week study. The average daily dose of olanzapine during the study was 10.75 mg and mean duration of exposure was 215 days.

Estimated 6-month discontinuation rate was 47.1% for the standard and 45.5% for the intense group. Estimated 1-year discontinuation rate was 54.9% for the standard and 63.4% for the intense group. Median time for discontinuation was 238 days for standard and 211 days for intense group. The most frequent reason for discontinuation from the study was AE (19% in the standard and 15% in the intense group). The most frequent AE leading to discontinuation was weight gain (8% standard, 6% intense). There were no statistically significant differences between intervention groups for completion rate or any of the reasons for discontinuation.

The study did not achieve its primary objective of demonstrating the superiority of the intense weight intervention over the standard weight intervention: There was no statistically significant difference between the interventions in overall mean change from baseline in BMI (p=0.134).

From baseline to 52 weeks

- mean change in BMI was +3.64 kg/m2 for the standard group and +2.83 kg/m2 for the intense group (p=0.150), and
- mean change in weight was +12.05 kg for the standard group and +9.63 kg for the intense group (p=0.148).

None of the secondary measures achieved statistical significance between interventions either.

Baseline-to-LOCF-endpoint evaluation of mean changes in patients treated for at least 6 months (n=109) revealed numeric but not statistically significant differences favouring the intense intervention:

- in increases in BMI (3.36 kg/m2 standard, 2.99 kg/m2 intense, p=0.520) and
- weight (+10.97 kg standard, +9.82 kg intense, p=0.495).

There were no statistically significant differences between intervention groups in the percentages of patients who gained clinically significant amounts of weight at any time or at endpoint.

- more patients in the standard group gained ≥15% of their baseline bodyweight compared to the intense group at endpoint (40% standard vs. 31% intense, p=0.187)

- more patients in the standard group ended the study in the obese BMI category (36%) than did those in the intense group (27%).

49% of all patients were in the healthy range at endpoint (at baseline 57%). 32% of all patients met criteria for obesity at endpoint (at baseline 24%). Evaluation of the highest BMI category indicated that for the standard group, 25.5% were in the obese category at baseline and 36.3% at endpoint, whereas for the intense group, 22.8% were in the obese category at baseline and 26.7% at endpoint, suggesting that the intense intervention may have prevented the shift into the most extreme category for at least some patients.

There was no statistically significant difference in mean change in waist circumference, which increased by approximately 7 cm in each group from baseline to week 52. No statistically significant differences between intervention groups on BMI and weight were found across all of the demographic subgroups evaluated (gender, race, region and disease state).

Efficacy of olanzapine

Across all patients, mean CGI-S score at baseline was 4.5, indicating a moderately to markedly ill population. For the total group of patients, mean change from baseline to 52 weeks on the CGI-S was -2.15, indicating a substantial reduction in severity from moderately/markedly ill at baseline to borderline ill at 52 weeks. CGI-I, with a mean score of 1.78 at 52 weeks, indicated an improvement rating between much improved and very much improved.

For the patients with schizophrenia, baseline BPRS-C total score was 45.4 (range from 31 to 74), indicating an acutely psychotic population. Baseline BPRS score in HGMX was lower than in study HGIN (approximately 50 points). For the patients with schizophrenia, mean change on the BPRS-C from baseline to 52 weeks was -32.51, indicating a change from acutely psychotic at baseline to mildly or very mildly symptomatic at 52 weeks. These results were roughly comparable to those from the acute and open-label extension phases of a previous study of olanzapine in adolescents with schizophrenia (F1D-MC-HGIN; Kryzhanovskaya et al 2009a; McCormack 2010). There was no statistically significant difference between the weight intervention groups with respect to schizophrenia disease state efficacy.

For the patients with bipolar disorder, baseline YMRS total score was 23.2 (range from 13 to 40), indicating an acutely manic population. Baseline YMRS score in HGMX was lower than in study HGIU (approximately 33 points). For the patients with bipolar disorder, mean change on the YMRS from baseline to 52 weeks was -16.74, indicating a change from acute mania at baseline to a remission of mania at 52 weeks. These results were roughly comparable to those from the acute and open-label extension phases of a previous study of olanzapine in adolescents with bipolar mania (F1D-MC-HGIU; Tohen et al 2007; McCormack 2010).

There was a statistically significant difference between the weight intervention groups with respect to bipolar disease state efficacy. Bipolar patients in the intense group showed statistically significantly less improvement than in the standard group on both the YMRS (overall p=0.018) and the CGI-S (overall p=0.016). YMRS mean change from baseline at 52 weeks was -17.66 for the standard group and -12.05 for the intense group (p=0.008), and CGI-S mean change from baseline at 52 weeks was -2.20 for the standard group and -1.44 for the intense group (p=0.015).

2.3.3. Discussion

The MAH concluded that study HGMX did not demonstrate superiority of the intense weight intervention. There was no statistically significant difference between the standard and intense intervention groups on the primary measure of BMI or on any of the secondary measures of weight-related outcomes. However, the consistent direction of modest numeric differences between

groups on BMI and weight suggest that some individual patients may have gained clinically meaningful benefit from the intense intervention.

Results of weight mitigation programs are typically modest at best, particularly when the intervention is of a counseling or educational type nature and does not require actual dieting or exercise but only counsels toward it. Systematic reviews of childhood obesity prevention programs found that none of the home-based programs resulted in change in weight-related outcomes (Showell et al. 2013), and few of the community-based programs resulted in such changes (Bleich et al. 2013). Programs that were more successful were for younger aged children and included a school-based component (Bleich et al 2013). Somewhat similar to the intervention program in study HGMX, Daumit et al. (2013) conducted a behavioral weight intervention versus a negative control intervention in mentally ill adults (predominantly patients with schizophrenia and bipolar disorder). That study found that the differences between intervention groups in body weight at 6, 12, and 18 months were 1.5 kg, 2.5 kg, and 3.2 kg, respectively. The magnitude of 1-year difference in that adult study is thus similar to the magnitude of difference in the present adolescent study. Daumit et al. considered the observed weight differences to be modest but clinically relevant.

Although study HGMX was an open-label, uncontrolled study, results are supportive of the effectiveness of olanzapine in the acute and long-term treatment of patients 13 to 17 years of age with bipolar I manic or mixed episodes or schizophrenia.

These results were roughly comparable to those from the acute and open-label extension phases of previous studies of olanzapine in adolescents with schizophrenia (F1D-MC-HGIN; Kryzhanovskaya et al 2009a; McCormack 2010) and with bipolar mania (F1D-MC-HGIU; Tohen et al 2007; McCormack 2010). There was no statistically significant difference between the weight intervention groups with respect to schizophrenia disease state efficacy.

Bipolar patients in the intense group showed statistically significantly less improvement than the standard group on both the YMRS (overall p=0.018) and CGI-S (overall p=0.016). Although there is no clear explanation for this finding, several hypotheses exist. One possibility is that the intense intervention, and particularly Tier 2 of the intense intervention, may be considered aversive or stressful for a myriad of reasons: pressure to change behaviors that are hard to change, pressure to produce "homework" that may or may not have been completed (daily lifestyle log), and focus on weight which may be embarrassing and may impact self-esteem. Patients with a mood disorder and depressive tendencies may be at higher risk for susceptibility to and negative impact from such stressors, and such stressors could theoretically trigger a bipolar exacerbation. A second hypothesis might be that weight gain is a greater risk and also more of a social concern for patients with bipolar disorder relative to patients with schizophrenia, and having been made to feel more conscious of and concerned about this weight gain during the intense intervention, patients with bipolar disorder in the intense group may have been more likely to stop taking their medication periodically in an attempt to mitigate weight gain, which would place these patients at greater risk for relapse. A third but less likely hypothesis would be that weight gain and efficacy are interrelated and that attempts to mitigate weight gain might result in some reduction in efficacy.

Overall, results were comparable to those of previous studies of olanzapine in this patient population.

In conclusion, the CHMP considered that the study HGMX did not demonstrate the superiority of the intense weight intervention. On the measures of BMI or weight-related outcomes no statistically significant differences were found between the standard and intense intervention groups. Patients in both weight intervention groups demonstrated clinically remarkable mean increases in weight and body mass very commonly throughout the study. More patients in the standard group gained at least 15% or even excessively, over 25% of their baseline bodyweight

compared to the intense group. Mean changes in BMI and weight favored numerically but not statistically significantly patients treated in the intense intervention group from the most substantial weight gain. Some individual patients may have gained clinically meaningful benefit from the intense intervention.

Some benefits were noted in adolescent schizophrenia and bipolar I patients receiving olanzapine treatment during the study HGMX, but due to uncontrolled and open label design of this study, no strong conclusions can be drawn of efficacy. Surprisingly, bipolar patients in the intense group improved statistically significantly less than patients in the standard group, assessed by YMRS and CGI-S. In EU, there are no indications for use of olanzapine in children or adolescents.

2.4. Clinical Safety aspects

2.4.1 Methods – analysis of data submitted

Adverse events

The primary safety objective of study HGMX was to assess in adolescent patients with bipolar I disorder manic or mixed episode) or schizophrenia the overall safety of olanzapine for up to approximately 52 weeks of treatment.

No deaths occurred in the study HGMX. A total of 162 experienced at least one treatment-emergent AEs (TEAE) (79.8%), with 140 of these having a AE that was rated by the investigator as possibly related to study drug.

The most common reason for discontinuation (n=34, 16.7%) was due to AE. In study HGMX, 19% of the patients in the standard group discontinued and 15% in the intense group. The most common AE leading to discontinuation was weight increased (n=14, 7%). Weight gain led to discontinuation in study HGMX among 8% in standard and 6% in intense group. Other reasons for discontinuation were: Increased TG, increased BMI, abnormal liver test, schizophrenia and pregnancy (two of each); and neuroleptic malignant syndrome (NMS), suicide attempt, agranulosytosis, neutropenia, leukopenia, pneumothorax, increased insulin, dysphoria, fall and gastroduodenitis (one of each). There were no statistically significant differences between intervention groups for completion rate or any of the reasons for discontinuation (p=0.445).

Among all patients, the most common ADRs (>10%) were weight increased (25,6%), somnolence (21,2%), headache (19,2%), increased appetite (14,3%) and nasopharyngitis (12,3%). In addition, blood insulin increased (8.4%), fatigue (7.4%), blood creatine phosphokinase increased (5.9%), sedation (5.4%) and vomiting (5.4%) were reported commonly in study patients. Blood insulin has not been collected or analysed in previous clinical trials. All the other events have been reported previously in adults and adolescents treated with olanzapine.

Review of AE terms identified several terms of potential clinical significance. Patients with those TEAEs are described briefly here:

- Patient had a SAE of NMS leading to study discontinuation at week 16. Patient was receiving 17.5 mg/day olanzapine and was hospitalized with hallucinations, agitation, disorganized behavior and stereotypy, and subsequently developed fever and high CPK as well as elevated liver enzymes. Study drug was discontinued, and the patient recovered from the event of NMS 3 days later. Laboratory values had returned to the normal range 3 weeks later.
- Patient had 2 episodes of convulsions, 1 of mild severity at week 4, and 1 of moderate severity (“petit mal seizures”) at week 16. Patient had a pre-existing condition of

bronchospasm. Patient was receiving multiple concomitant medications, but no treatment was reported for the seizures although patient later received treatment for headache and migraine. Patient discontinued at week 44 due to treatment noncompliance.

- Patient had 2 episodes of convulsions, 1 of mild severity at week 8 lasting 15-20 seconds, and one of moderate severity 19 days later lasting 2-3 minutes. No preexisting conditions which might predispose to convulsion were reported. Patient was treated with lorazepam. Patient was discontinued from the study 6 days later due to caregiver decision. No further information was available.
- Patient had a TEAE of agranulocytosis which led to study discontinuation. Patient was diagnosed with sickle cell trait and had an abnormally low neutrophil count at baseline. White blood cell count was normal at baseline and lymphocytes were abnormally high at baseline and throughout the trial. An AE agranulocytosis was reported at week 3 due to absolute neutrophil count of 0.08 GI/L. Patient had been receiving olanzapine 2.5 mg/day. Study drug was discontinued, and patient was retested 2 days later, at which time neutrophil count was 2.42 GI/L, consistent with patient's Visit 2 baseline. Patient was also diagnosed with mild lymphadenopathy at that follow-up visit.

A total of 5 patients were reported to have overdose or intentional overdose. All patients recovered from the events. Those cases were as follows:

- One patient was hospitalized for an intentional severe overdose of study drug and was subsequently discontinued from the study.
- One patient took an intentional mild overdose of Tylenol PM (1 day) and completed the study.
- One patient was hospitalized for a suicide attempt involving an intentional overdose of study drug and was subsequently discontinued from the study.
- Two patients had repeated mild AEs described as "parent increased patient's dose."

A total of 33 patients (16%) in study HGMX experienced 43 serious adverse events (SAEs); those which occurred in 2 or more patients were related to the schizophrenia or bipolar disease state or suicidal ideation (n=5) or suicide attempt (n=2). Patients in the HGMX intense group had more SAE bipolar exacerbations (n=6) than did patients in the HGMX standard (n=0) group (p=0.014). 10 of the SAEs were for a single patient with bipolar disorder in the intense group who fell or jumped from a 4 story building.

Incidence of extrapyramidal symptoms (EPS) was low at baseline and throughout the study. Incidences of treatment-emergent akathisia, parkinsonism and dyskinesia were 9%, 6% and 1%, respectively, at any time, and 3%, 3% and 1%, respectively, at endpoint. Incidence of dyskinesia at any time in the pooled adolescent database (1%) was similar to that of study HGMX, but rates of akathisia and parkinsonism at any time were somewhat lower in the pooled database (6% and 2%, respectively) compared with study HGMX.

Suicidality

Rates of suicidal ideation and behavior were relatively low throughout the study, particularly given the disease states and the length of the study. Based on the C-SSRS, 13% of patients (n=27) displayed suicidal ideation during the study and 3% (n=6) displayed suicidal behavior. There were no completed suicides. The pooled database did not collect C-SSRS data. Comparison of rates indicated that 2.5% of patients in study HGMX had suicidal ideation, which was similar to the rate in the pooled database (2.4%). A total of 2.5% of patients in study HGMX had a SAE of suicide attempt, which was higher than the rate of 0.4% in the pooled database.

Weight and BMI

In study HGMX mean change from baseline to LOCF-endpoint (anytime) in BMI was +2.53 kg/m^2. Increase in BMI was +2.68 kg/m^2 in the standard group and +2.31 kg/m^2 in the intense group. In the pooled database a mean baseline-to-LOCF endpoint change in BMI was +2.31 kg/m^2.

In study HGMX among all patients mean change from baseline to LOCF-endpoint (anytime) in weight was +8.12 kg (8.56 kg in the standard group and 7.40 kg for the intense group, p=.293), slightly greater than that reported in the pooled database (+7.35 kg).

Mean weight gain in patients in study HGMX and treated for at least 6 months was +10.49 kg, slightly lower than seen in pooled database (+11.2 kg). The MAH suggests that rate of weight gain in adolescent patients treated with olanzapine starts to plateau as patients' duration of treatment with olanzapine increases from 6 months to 1 year. Intense weight intervention appeared to result in an earlier plateauing of weight gain.

There was a numeric but not statistically significant difference in incidence of the AE of weight increased (30% standard, 21% intense, p=0.148), although this finding reached significance within female patients (female in standard group 46%, female in intense group 21%; p-value for gender interaction=0.028).

During study HGMX, a total of 68% of patients gained ≥7% of their baseline body weight at any time. 40% of patients gained ≥15%, and 21% of patients gained ≥25%, of their baseline body weight at any time during study HGMX. There was no statistically significant difference between intervention groups. These results are comparable to the findings from the pooled adolescent metabolic database, which reported that among all patients, 64% gained ≥ 7% of their baseline bodyweight, 32% gained ≥ 15%, and 14% gained ≥ 25%. Again, the percentages in study HGMX were somewhat higher, as would be expected due to the longer study duration.

Laboratory measurements

Mean baseline-to-endpoint changes in laboratory values in study HGMX were mostly small and not clinically significant, and to the same direction as to those observed in the previous pooled database.

Changes in lipids were common in study HGMX, especially in HDL and triglycerides. The percentage of patients changing from normal to high for total cholesterol was 11% at any time and 0% at endpoint, and for LDL cholesterol was 10% at any time and 1% at endpoint. The percentage of patients changing from normal to high for triglycerides was 47% at any time and 14% at endpoint. Change from normal/borderline at baseline to low for high density lipoprotein (HDL) cholesterol was 26% at any time and 10% at endpoint. Change from normal to low for HDL cholesterol was 5% at any time and 0% at endpoint. Patients in the intense group had more categorical changes to low HDL cholesterol at endpoint compared to the standard group (normal/borderline to low: 16% intense vs. 5% standard, p=0.023).

Mean increases in total and LDL cholesterol were lower in study HGMX despite the longer study duration, whereas mean changes in HDL cholesterol and particularly for triglycerides were slightly greater than in the pooled adolescent database combined from earlier studies. Incidences for these potentially clinically significant changes in lipids at any time in the adolescent metabolic database were generally similar: normal to high total cholesterol, LDL cholesterol and triglycerides in 9%, 9% and 32%, respectively, and normal to low HDL cholesterol in 0%.

A total of 4% of patients had fasting glucose change from normal to high at any time, but 0% met this criterion at endpoint. Incidence of change from normal to high fasting glucose in the previous pooled adolescent database was 1% at any time and 0% at endpoint. 60.5% of subjects had treatment-emergent above normal insulin levels at any time. 20% had treatment-emergent above

normal insulin levels at endpoint. Also decreases in insulin were noticed. With regard to insulin, insulin sensitivity can be strongly affected by changes at puberty (Amiel et al. 1986; Caprio et al. 1989); also, fasting status may be less reliable in adolescents, making the findings difficult to interpret. No patients developed above normal hemoglobin A1c at any time, and there were no AEs indicative of associated diabetic symptomatology.

Rates of treatment-emergent abnormal high hepatic enzyme values were higher at any time than at endpoint, as also observed in the pooled database, consistent with the transient nature of the hepatic increases typically observed in patients treated with olanzapine. In study HGMX, hepatic analytes showed a transient peak at 3 weeks, similar to the peak observed in the pooled database. Incidence of potentially clinically significant increases in hepatic enzymes were relatively low (5% of study HGMX patients changed from normal to >3x ULN at any time versus 9% in the pooled database). Only 1 patient in study HGMX developed treatment-emergent ALT >5x ULN, which resolved and remained in the normal range thereafter. Hepatic changes were generally small and transient, with few patients experiencing potentially clinically significant increases.

Changes in prolactin were common but generally small in study HGMX and also often resolved over the course of the study, with very few changes associated with any symptomatology. Abnormal elevations in prolactin occurred in 27% at any time and 12% at endpoint, and no patients developed potentially clinically significant elevations. No patients developed prolactin elevations above value 200 µg/l. In study HGMX, mean changes in prolactin were generally small and transient, with patients showing a mean decrease at endpoint (-1.17 µg/l). In the pooled database mean prolactin at endpoint increased from baseline (+4.74 µg/l). In the pooled database incidence of high prolactin was 56%. The overall mean changes in prolactin appeared consistent with the pattern observed in the pooled adolescent database. In both study HGMX and the pooled database, prolactin levels peaked at week 6 and then decreased thereafter, although in the present study, they continued to decrease below baseline levels on average.

Very few patients had values of thyroid function above or below the normal range: There was no evidence of clinically significant change in thyroid function. Means at baseline and endpoint indicated that patients were, on average, in the normal range at both time points. Mean change in TSH of +0.26 mU/l was statistically significant (p=0.016) but was not considered clinically meaningful. Mean changes in T4 and free T4 were not statistically significant. A total of 1% of patients had treatment-emergent above-normal TSH, but no patients with above-normal T4 or free T4. A total of 2% had below-normal TSH, and 1% had below-normal T4 or free T4. TSH was also measured in some patients in the pooled integrated database, but mean change to endpoint in that database indicated a small mean decrease in TSH.

Vital signs and ECG

Mean changes in vital signs and ECG parameters were small and not clinically significant. No patients developed corrected QT interval (Fridericia method [QTcF]) ≥450 msec or had a change ≥60 msec. Results were consistent with those of the pooled adolescent database.

Small mean changes in heart rate were observed in study HGMX, consistent with the known profile of olanzapine. Patients in the standard group had a greater mean increase in heart rate from baseline to 52 weeks (+8.79 bpm relative to +1.06 bpm for the intense group; p<.001). Heart rate in patients in the intense weight intervention group showed relatively little mean change, and the mean increase observed in the total group was driven primarily by the increase in heart rate of the patients in the standard group. This group difference would appear to be consistent with greater adoption of the healthier lifestyle recommended by the behavioral weight intervention in the intense group.

Patients in the standard group had small mean increases in blood pressure compared to the intense group patients, who demonstrated little to no mean change in blood pressure from baseline.

2.4.2 Results

Overall the safety profile for olanzapine was found to be generally consistent with the profile observed in previous studies of olanzapine in the treatment of adolescent patients. The most notable exception was that changes in prolactin were smaller and much less frequent than those observed in previous studies of olanzapine in adolescents, with patients in the present study demonstrating a mean decrease in prolactin compared to previous studies which found mean increases. Mean increases in total and low-density lipoprotein (LDL) cholesterol were smaller in the present study as well.

The CHMP considered that the results in rates and nature of adverse events, suicidality, weight-related parameters, laboratory measurements and vital signs from the study HGMX are generally in line with earlier results among adolescents.

Increases in weight-related issues were very common and significant in nature, as noted in earlier studies among adolescents (and adults). In study HGMX versus overall pooled adolescent exposure database, the most common AEs were weight increased (26% vs. 32%), somnolence (21% vs. 20 %), increased appetite (14% vs. 17%) and sedation (5% vs. 14%). Also, the most common reason for discontinuation was weight increased (7% in HGMX vs. 4% in pooled database). In addition, approximately 2/3 of adolescent subjects gained more than 7% weight from their baseline, more than 1/3 gained more than 15% weight, and 1/5 gained excessively, more than 25% weight.

In overall pooled adolescent exposure database 7.7% (vs 16% in HGMX) of olanzapine treated adolescents experienced 1 or more SAE (worsening of bipolar disorder (n=4), worsening of bipolar I disorder (n=8), worsening of schizophrenia (n=6) and aggression (n=3)). In overall pooled adolescent exposure database 13 subjects experienced suicidal ideation (2.9% vs. 2.5% in HGMX), 6 subjects behaved self-injuriously (1.3%), 2 subjects made preparatory acts toward committing suicide (0.4%) and 2 subjects attempted suicide (0.4% vs. 2.5% in HGMX).

Changes in prolactin during study HGMX appeared less than in earlier studies. It seems that there were statistically significant but not clinically relevant changes in several laboratory measurements, such as increases in insulin, uric acid, TG, TSH and ALT, and decreases in HDL, fructosamine and bilirubin. Insulin has not been detected in previous adolescent studies.

The existing pediatric data in the Product Information has been gathered from earlier adolescent studies in patients treated up to 32 weeks. Only AEs which have occurred more frequently among adolescents than among adults have been included into PI. The PI does not however describe specifically AE or safety profile among adolescents. This is not crucial, as in EU, olanzapine is not indicated in the treatment of adolescents.

The MAH proposed no safety information changes into PI. The CHMP was also of the opinion that safety issues reported in the study HGMX were already reflected adequately in the PI of olanzapine.

2.4.3. Discussion

The MAH's conclusions on the study HGMX was that overall safety findings for the total group of patients were generally consistent with the known profile of olanzapine in adolescent patients 13 to 17 years of age with schizophrenia or bipolar disorder, with increases in BMI and weight similar to what has been observed in previous studies of olanzapine in adolescents.

The 40% study completion rate for study HGMX was as expected based on the length of the study, the patient population, and the known completion rate observed in previous shorter studies (55% in the 32-week Kryzhanovskaya pooled database). In both HGMX and the previous pooled database, the most common reason for discontinuation was due to AE (17% in HGMX, 11% in

pooled database), and the most common AE leading to discontinuation was weight increased (7% in HGMX, 4% in pooled database).

Consistent with the known profile of olanzapine in adolescents, changes in BMI were quite notable. Based on the WHO growth charts, typical growth in an adolescent over 1 year's time equates to an annual expected increase of approximately half a unit of BMI (0.5 kg/m^2). In study HGMX, mean baseline-to-LOCF endpoint change in BMI was +2.53 kg/m2 (+2.68 kg/m^2 for the standard and +2.31 kg/m^2 for the intense group), representing a substantial increase beyond normal expected growth.

Changes in weight were also substantial in study HGMX. Results were similar to those of the previous pooled database, which reported a mean baseline-to-LOCF endpoint change in weight of +7.35 kg, with results from the HGMX intense group again appearing nearly the same as those of the shorter pooled database. Thus, while mean weight gain across all patients in study HGMX was somewhat higher than observed in the shorter term databases, as would be expected based on study duration, mean weight gain in those patients treated for at least 6 months was actually lower than seen in the previous studies, despite the longer duration of study HGMX. This suggests that rate of weight gain in adolescent patients treated with olanzapine slows and may start to plateau as patients' time on olanzapine increases from 6 months to 1 year. Examination of the visitwise HGMX weight intervention data suggests that the intense weight intervention also contributed to this lower long-term weight change and appeared to result in an earlier plateauing of the weight gain.

Evaluation of potentially clinically significant changes in weight found that across all patients in study HGMX are comparable to the findings from the pooled adolescent metabolic database. The percentages in study HGMX were somewhat higher, as would be expected due to the longer study duration.

Rates of suicidal ideation and behavior were relatively low throughout the study. Comparison of rates of TEAEs indicated that 2.5% of patients in study HGMX had suicidal ideation, which was similar to the rate in the pooled database (2.4%). A total of 2.5% of patients in study HGMX had a SAE of suicide attempt, which was higher than the rate of 0.4% in the pooled database. To put these rates into context, a 2011 survey of US high school students as part of the Youth Risk Behavior Surveillance System (YRBSS) found that almost 8% of students had attempted suicide in the 30 days prior to the survey (CDC 2012). Among young patients with diagnoses of bipolar disorder or schizophrenia, rates of suicide attempt are even higher, with a recent study indicating a 2-year prevalence of 12.4% among first-episode patients with psychosis 9 to 17 years of age (Sanchez-Gistau et al. 2013) and another indicating a 5-year prevalence of 18% among patients with bipolar disorder 7 to 17 years of age (Goldstein et al. 2012).

In conclusion, the safety of olanzapine for up to 52 weeks in patients 13 to 17 years of age diagnosed with schizophrenia or bipolar disorder was generally similar to that observed previously in adolescent patients treated for up to 32 weeks with olanzapine. The most notable difference was that patients in study HGMX showed an overall mean decrease in prolactin from baseline, with fewer patients developing treatment-emergent abnormal high prolactin compared with previous adolescent olanzapine studies. Mean changes in hepatic enzymes and total and LDL cholesterol were slightly smaller despite the longer study duration, while mean changes in some lipids such as HDL cholesterol and triglycerides were slightly higher.

Although not an explicit *a priori* hypothesis of the study, it might have been hoped that the intense intervention would yield greater health benefits than the standard intervention. However, the study was unable to demonstrate such benefits. Although there were some mild but statistically significant differences between groups in heart rate and blood pressure in the expected direction,

changes to the lipid profile appeared somewhat contradictory, with apparent worsening in some aspects of the lipid profile in the intense group.

Demographic subgroup findings with respect to the weight interventions might bear further exploration. The finding with regard to the greater number of SAEs of bipolar exacerbation in the intense group is consistent with the findings on the disease state efficacy scales. The MAH's hypotheses around possible reasons for this difference have been discussed previously in this AR (discussion on efficacy). Another subgroup finding of interest, however, was with respect to differences between males and females in the reporting of AEs of "weight increased" in each of the weight intervention groups. Males in the intense group were more likely to have this AE reported than those in the standard group, whereas females in the standard group were more likely to have this AE reported than those in the intense group. Because of some confounding of demographic and disease state variables in this patient sample, further study would be needed to clarify possible gender differences in outcomes. In any case, the reasons for both these demographic subgroup findings are not clear, and multiple hypotheses should be considered. One question which might be raised is whether there are differential psychological impacts of the weight counselling interventions on the genders and the patient subpopulations.

There are a number of limitations to the present study. With regard to the disease state efficacy, the open-label uncontrolled design limits the ability to draw strong conclusions about efficacy. Nevertheless, this more naturalistic design is appropriate for the long-term evaluation of a medication and provides results which may be more generalizable to standard clinical practice.

With regard to the behavioral weight intervention, it is important to acknowledge that the interventions were office-based counseling programs which did not require actual changes in patients' diet and exercise behaviors. Although patients were to keep track of their nutritional intake and physical activity in daily logs, these data were not formally collected for data analysis, and no information was collected from parents or caregivers to attempt to quantify patients' actual level of adherence to the recommendations from the counseling sessions. Thus, the only conclusion that can be drawn with regard to the efficacy of the behavioral weight interventions was regarding the degree to which exposure to each intervention resulted in differences in weight-related outcomes, as opposed to the degree to which each program successfully changed diet and exercise habits or the degree to which such behavioral changes resulted in changes in weight-related outcomes.

Other limitations which should be mentioned are the baseline differences between the disease state populations and the possible confounding of disease state and geographical region. The patients with bipolar disorder were heavier at baseline and more likely to have a family history of obesity and metabolic disorders. At the same time, there was significant overlap between disease state and region as most of the bipolar patients were from the US. Thus, it is difficult to determine whether differences between the disease state groups can be attributed to the disease state or to cultural differences between regions. Although this confound does not affect the overall results of the study, it does make interpretation of some of the demographic subgroup analyses more difficult.

2.5. Risk management plan

2.5.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

No changes to safety specification, pharmacovigilance plan or risk minimisation measures are proposed.

The RMP is acceptable with minor editorial changes required with the next update (see attached PRAC Advice).

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Table SVIII.1. Summary of Safety Concerns (Important Identified Risks, Important Potential Risks, and Important Missing Information)

Summary of Safety Concerns: Olanzapine	
Important Identified Risks	• Weight gain • Glucose dysregulation • Dyslipidaemia
Important Potential Risks	• Increased risk of cardiac death (presumed sudden cardiac death)
Important Missing Information	• N/A
Summary of Safety Concerns: Paediatric-Specific Olanzapine	
Important Identified Risks	• Sedation • Hepatic-related events • Hyperprolactinaemia
Important Potential Risks	• N/A
Important Missing Information	• Potential long-term effects of hyperprolactinaemia on growth
Summary of Safety Concerns: RAIM-Specific Olanzapine	
Important Identified Risks	• N/A
Important Potential Risks	• Risk of mortality
Important Missing Information	• N/A

Abbreviations: N/A = not applicable; RAIM = rapid-acting intramuscular.

Pharmacovigilance plans

Table III.16. Completed Studies from the Postmarketing Pharmacovigilance Development Plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Completed)	Date of Submission of Final Report
Non-interventional PASS, F1D-MC-B042: Risk of Cardiac Mortality (including Sudden Cardiac Death) in Atypical Antipsychotic Users, Category 3	1. To assess and compare the incidence and risk of cardiac mortality (including SCD) among antipsychotic users 2a. To assess and compare the incidence and risk of cardiac mortality (including SCD) among antipsychotic users (atypical, typical, and specific antipsychotic agent) to a non-user psychiatric population by age, duration of use, and dose 2b. Secondary outcomes assessed for each antipsychotic cohort as compared to a non-user psychiatric population: a. Sudden cardiac death (assessing three definitions) by age and dose for the primary definition, b. All-cause mortality (excluding suicide-related death) c. Coronary heart disease (AMI and/or cardiac procedures) by age and duration of use d. Life-threatening ventricular arrhythmias	Risk of cardiac mortality (including sudden cardiac death) among patients treated with olanzapine	Completed. Final study report submitted.	Final study report submitted 25 November 2011 and accepted by CHMP.
Clinical trial, 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, Category 3	To assess the overall safety of olanzapine for up to approximately 52 weeks of treatment, and to assess whether an intense behavioral weight intervention program was superior to a standard behavioral weight intervention program in mitigation of weight gain. The behavioral interventions were assessed based on overall mean change from baseline BMI.	Weight gain, glucose dysregulation, dyslipidaemia, sedation, hepatic-related events, hyperprolactinaemia among adolescents (aged 13-17) treated with olanzapine	Completed. Final study report submitted.	Final study report submitted 06 November 2013.

Abbreviations: AMI = acute myocardial infarction; BMI = body mass index; CHMP = Committee for Medicinal Products for Human Use; PASS = post-authorisation safety study; SCD = sudden cardiac death.

Risk minimisation measures

Table V.12. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures[a]	Additional Risk Minimisation Measures
Olanzapine safety concerns: Weight gain Glucose dysregulation Dyslipidaemia Potential increased risk of cardiac death (presumed sudden cardiac death)	Appropriate labeling. Metabolic guidelines have been distributed in all European countries where olanzapine is approved. Survey results indicate that a high proportion of prescribers are conducting appropriate monitoring with respect to these parameters. At the request of CHMP following assessment of RMP Revision 3, a variation was submitted in March 2011 to add metabolic monitoring frequency examples to the special warnings and precautions Section 4.4 of the SmPC. This variation was approved in November 2011. The potential increased risk of cardiac death has not yet been confirmed; implementation of risk minimisation activities may not be appropriate since the definite mechanism of action for this risk is not known. This risk will be subject to continued monitoring and additional risk minimisation activities will be put into place as appropriate.	Not applicable.
Paediatric-specific safety concerns: Sedation Hepatic-related adverse events Hyperprolactinaemia	Appropriate labeling. Appropriate labeling is sufficient for the EU since olanzapine is not approved for paediatric use in the EU, and hence these risks are linked to the potential for off-label use.	Not applicable.
RAIM-specific safety concern: Potential risk of mortality	Appropriate labeling. Previous activities (letter, scientific dissemination of potential risk) have resulted in mitigation of this risk as evidenced by the decrease in number of reported deaths associated with the use of RAIM. Updated labeling was implemented to strengthen the recommendation not to concomitantly administer benzodiazepines and RAIM.	Not applicable.

Abbreviations: CHMP = Committee for Medicinal Products for Human Use; RAIM = rapid-acting intramuscular; RMP = risk management plan; SmPC = summary of product characteristics.

[a] Routine risk minimisation includes product information, labeling, and packaging. Non-routine risk minimisation includes educational or training programs or restricted access programs.

The CHMP endorsed this advice without changes.

2.6. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI) of Zyprexa (excluding rapid-acting, RAIM) and Zyprexa velotab (deleted as ~~strikethroughs~~ and additions as underlined), 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

Paediatric population

Controlled efficacy data ~~The experience~~ in adolescents (ages 13 to 17 years) ~~is~~ are limited to short term 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.

Moreover, the MAH has corrected a mistake in the ATC code as the addition of “oxepines “ to the pharmacotherapeutic group description was needed to comply with the WHO ATC index:

The section 5.1 of the SmPC was therefore amended as follows:

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

Changes were also made to the PI of Zyprexa and Zyprexa Velotab to bring it in line with the current QRD (version 9) template, which were reviewed and accepted by the CHMP.

In addition the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

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

This variation is a worksharing procedure 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’. The primary objectives of study HGMX were to assess the overall safety of olanzapine for up to 52 weeks of treatment in adolescent patients with schizophrenia or manic or mixed episodes associated with bipolar disorder and to determine whether an intense behavioral weight intervention was superior to a standard intervention in the mitigation of weight gain as assessed by overall mean change in BMI from baseline.

Firstly, the study HGMX did not demonstrate the superiority of the intense weight intervention. On the measures of BMI or weight-related outcomes no statistically significant differences were found between the standard and intense intervention groups. Patients in both weight intervention groups demonstrated clinically remarkable mean increases in weight and body mass very commonly throughout the study. More patients in the standard group gained at least 15% or even excessively, over 25% of their baseline bodyweight compared to the intense group. Mean changes in BMI and weight favored numerically but not statistically significantly patients treated in the intense intervention group from the most substantial weight gain. Some individual patients may have gained clinically meaningful benefit from the intense intervention.

The safety findings in overall were in line with the known profile of olanzapine in adolescents that are already included into the Product Information of Zyprexa and Zyprexa Velotab. Weight gain as a very common adverse reaction is in line with results found in earlier olanzapine studies among adolescents and adults.

Mean changes in laboratory analytes in study HGMX were generally similar to those observed in the previous pooled database. In the study HGMX mean changes in HDL and triglycerides were slightly greater than in the previous adolescent studies described in the pooled adolescent olanzapine exposure database. Elevations in lipids (total and LDL cholesterol and triglycerides) are included into the SmPC sections 4.4 and 4.8 as common adverse reaction among adults. The overall mean changes in prolactin appeared consistent with those observed in the pooled adolescent database. Mean changes in vital signs and ECG parameters were small and not clinically significant. No patients developed QTcF ≥ 450 msec or had a change ≥ 60 msec. Insulin has not been measured in previous studies. A change from baseline in insulin in total group was toward increase. No cases with symptomatic diabetes were observed during this 52 week study. In the SmPC sections 4.4 and 4.8, development or exacerbation of diabetes is included as a common adverse event among adults. The other reported changes in some laboratory values were not clinically relevant.

The existing pediatric information in the Product Information sections has been gathered from earlier adolescent studies and data. Only AEs which have occurred more frequently among adolescents than among adults have been included into SmPC section 4.8 by comparing adolescent and adult databases that contained treatment up to 32 weeks. The PI does not however describe specifically AEs or safety profile among adolescents. This is not crucial, as in EU, olanzapine is not indicated in the treatment of adolescents. Findings from this study HGMX revealed no new safety findings.

Secondary objectives also included assessment of the efficacy of olanzapine in the treatment of schizophrenia or bipolar mania. Some benefits were noted in adolescent schizophrenia and bipolar patients receiving olanzapine treatment during the study, but due to open label design of this study, no strong conclusions can be drawn of efficacy. Surprisingly, bipolar patients in the intense group improved statistically significantly less than patients in the standard group, assessed by YMRS (p=0.018) and CGI-S (p=0.016). The same limitations concerning design of this study as described earlier apply to this finding. Moreover, treatment of adolescents aged 13-17 with olanzapine is not an approved indication in EU, assessment of the efficacy is beyond the scope of this application.

In conclusion, the proposed 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. Therefore the CHMP considered that the proposed changes in the Product Information are approvable. The CHMP requested an updated RMP, which was submitted by the MAH and consecutively reviewed by PRAC during this procedure (as detailed earlier in this AR).

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation worksharing procedure acceptable and therefore recommends the variation(s) 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.

The MAH took also the opportunity to align the Product Information with the Quality Review of Documents (QRD) template (Version 9), to update the list of local representatives in the Package Leaflet and to correct an editorial mistake concerning the ATC code.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II 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.