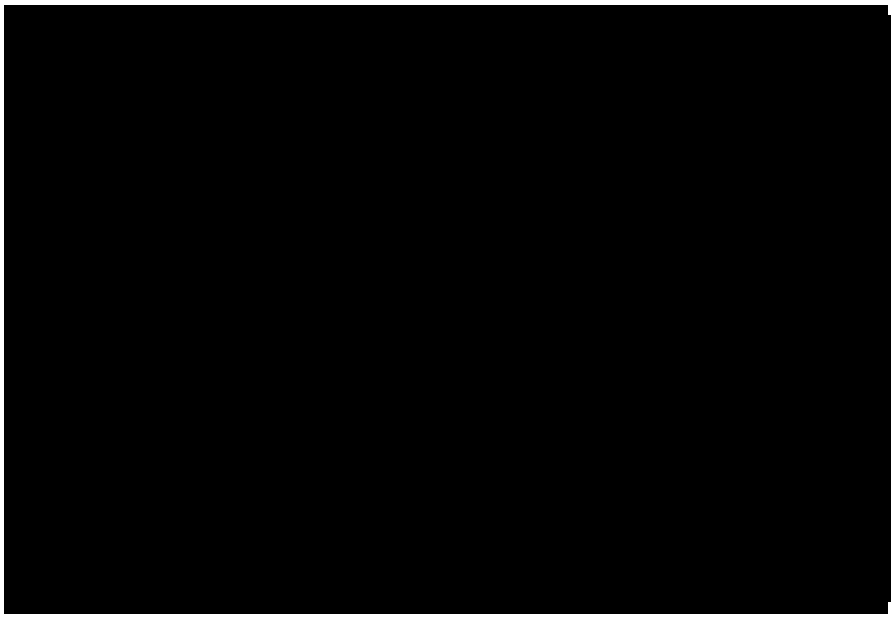

EU Risk Management Plan (Version 12)

Global Patient Safety
Signatory information is available on request.
Initial EU Risk Management Plan (Oral and RAIM Formulations) Electronically Approved by Lilly: 17 April 2008
Revised Risk Management Plan (Version 2, Oral and RAIM Formulations) approved by Lilly: 21 May 2009
Revised Risk Management Plan (Version 3, Oral and RAIM Formulations) approved by Lilly: 26 May 2010
Revised Risk Management Plan (Version 4, Oral and RAIM Formulations) approved by Lilly: 23 May 2011
Revised Risk Management Plan (Version 5, Oral and RAIM Formulations) approved by Lilly: 13 December 2013
Revised Risk Management Plan (Version 10.1, Olanzapine LAI formulation) approved by Lilly: 08 February 2013
Risk Management Plan (Version 11, Oral, Rapid-Acting Intramuscular, and Long-Acting Injection Formulations) approved by Lilly: 03 June 2014
Risk Management Plan (Version 12, Oral, Rapid-Acting Intramuscular, and Long-Acting Injection Formulations) Electronically Approved by Lilly on date provided below.

Approval Date: 13-Sep-2016 GMT

Active Substance(s) (INN or common name):	Olanzapine
Pharmacotherapeutic group (ATC Code):	Atypical antipsychotic
Name of Marketing Authorisation Holder or Applicant:	Eli Lilly and Company
Number of medicinal products to which this RMP refers:	4
Product(s) concerned (brand name[s]):	ZYPREXA Film-Coated Tablets: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg Olanzapine Lilly Film-Coated Tablets: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg ZYPREXA/VELOTAB Orodispersible Tablets: 5 mg, 10 mg, 15 mg, 20 mg Olanzapine Lilly Orodispersible Tablets: 5 mg, 10 mg, 15 mg, 20 mg Zyprexa 10 mg powder for solution for injection: Olanzapine powder is reconstituted with sterile water for injection prior to its use. The reconstituted solution is intended for intramuscular injection only. Each vial provides 10 mg olanzapine. ZYPREXA, ZYPADHERA: intramuscular injection suspension vial 210, 300, and 405 mg of olanzapine base.

Data lock point for this RMP	Data in this document are through 30 SEP 2013 unless otherwise noted. Results of Study B034 (Clinical Study Report approval date 29 JUN 2016) were added.
Version number:	12
Date of final sign off:	Approval date on page 1

Part I. Product(s) Overview

Administrative Information on the RMP

Part	Module/Annex	Date Last Updated for Submission (Sign-off Date)	Version Number of RMP When Last Submitted/or Not Applicable
Part II Safety Specification	**SI** Epidemiology of the Indication(s) and Target Population	03 JUN 2014	11
	SII Nonclinical Part of the Safety Specification	03 JUN 2014	11
	SIII Clinical Trial Exposure	03 JUN 2014	11
	SIV Populations Not Studied in Clinical Trials	See date on cover page	12
	SV Post-Authorisation Experience	See date on cover page	12
	SVI Additional EU Requirements for the Safety Specification	03 JUN 2014	11
	SVII Important Identified and Potential Risks	See date on cover page	12
	SVIII Summary of the Safety Concerns	03 JUN 2014	11
Part III Pharmacovigilance Plan		See date on cover page	12
Part IV Plans for Post-Authorisation Efficacy Studies		03 JUN 2014	11
Part V EU Risk Minimisation Measures		03 JUN 2014	11
Part VI Summary of Activities in the RMP by Product		See date on cover page	12
Part VII Annexes		03 JUN 2014	11
	Annex 1 EudraVigilance Interface	03 JUN 2014	11
	Annex 2 SmPC and Package Leaflet	03 JUN 2014	11
	Annex 3 Worldwide Marketing Status by Country	03 JUN 2014	11
	Annex 4 Synopsis of Ongoing and Completed EU Clinical Trial Programme	03 JUN 2014	11
	Annex 5 Synopsis of Ongoing and Completed Pharmacoepidemiological Study Programme	See date on cover page	12
	Annex 6 Protocols for Proposed and Ongoing Studies in Categories 1-3 of the Section "Summary Table of Additional Pharmacovigilance Activities" in RMP Part III	03 JUN 2014	11
	Annex 7 Specific Adverse Event Follow-Up Forms	03 JUN 2014	11

Part	Module/Annex	Date Last Updated for Submission (Sign-off Date)	Version Number of RMP When Last Submitted/or Not Applicable
	Annex 8 Protocols for Proposed and Ongoing Studies in RMP Part IV	03 JUN 2014	11
	Annex 9 Newly available study reports for RMP Parts III - IV	See date on cover page	12
	Annex 10 Details of Proposed Additional Risk Minimisation Measures (if applicable)	03 JUN 2014	11
	Annex 11 Mock-up of Proposed Additional EU Risk Minimisation Measures (if applicable)	03 JUN 2014	11
	Annex 12 Other Supporting Data (including Referenced Material)	See date on cover page	12

Abbreviations: EU = European Union; SmPC = Summary of Medicinal Product Characteristics; RMP = risk management plan.

QPPV name:	**Name on file.**
QPPV signature:	**Signature on file.**
Contact person for this RMP:	**Please refer to the cover letter accompanying this RMP for Contact Information.**
Email address or telephone number of contact person:	

Overview of Versions

Version number of last agreed-upon RMP:	11
Version number	12
Agreed within	Centrally Authorized Procedure/Mutual Recognition Procedure in the European Union (EU)

Current RMP Versions under Evaluation

None

Invented name(s) in the European Economic Area (EEA)	Zyprexa Zyprexa Velotab ZypAdhera Olanzapine Lilly
Authorisation procedure	Centrally Authorized/Mutual Recognition Procedure in the EU
Brief description of the product • Chemical class	 Thienobenzodiazepine
• Summary of mode of action	*Mode of Action:* Olanzapine is a selective monoaminergic antagonist with a high affinity binding to the following receptors: serotonin, dopamine, muscarinic, histamine, and adrenergic α_1 receptors. Olanzapine binds weakly to $GABA_{A2}$ BZD, and β adrenergic receptors. Mechanism of action with schizophrenia is unknown. It is proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism. The mechanism of action of olanzapine in the treatment of acute manic episodes associated with bipolar I disorder is unknown. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic $M_{1\text{-}5}$ receptors may explain its anticholinergic effects. Olanzapine's antagonism of histamine H1 receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.
• Important information about its composition (eg, origin of active substance biological, relevant adjuvants or residues for vaccines)	**Olanzapine Capsules:** The drug product is composed of olanzapine and the inactive ingredients of pregelatinised starch and dimethicone. Each capsule contains olanzapine equivalent to 2.5, 5, and 10 mg. **Olanzapine Tablets:** Each tablet contains olanzapine equivalent to 2.5, 5, 7.5, 10, 15, and 20 mg. It also contains lactose, hydroxypropyl cellulose, crospovidone, microcrystalline cellulose, magnesium stearate, hydroxypropyl methylcellulose, and other inactive ingredients. **Olanzapine Rapidly Disintegrating Tablets:** This drug product contains olanzapine and the inactive ingredients of gelatine, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben. Each tablet contains olanzapine equivalent to 5, 10, 15, or 20 mg. **Olanzapine 10 mg powder for solution for injection (Rapid-Acting Intramuscular Olanzapine [RAIM]):** Olanzapine is available as a powder for injection, intended for intramuscular (IM) use only. This drug product contains olanzapine and the inactive ingredients lactose monohydrate and tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH. The drug product is to be reconstituted in sterile water for injection prior to IM injection. Each vial is filled to provide olanzapine 10 mg on delivery. The unreconstituted drug product is stable at room temperature and must be used within 60 minutes after reconstitution in sterile water for injection. **Olanzapine Long-Acting Injection (LAI):** Olanzapine LAI is intended for deep intramuscular injection. The sterile drug product consists of the drug substance, olanzapine pamoate monohydrate, with no additional excipients. The sterile vehicle consists of sterile water for

	injection, carboxymethylcellulose sodium, mannitol, and polysorbate 80. Sodium hydroxide and/or hydrochloric acid may be added to adjust the pH during manufacture of the vehicle. The vehicle, when combined with the drug product immediately prior to administration, forms a suspension for IM injection.
Indications in the EEA Current	**Oral:** schizophrenia; bipolar disorder, manic or mixed episodes **RAIM:** agitation associated with schizophrenia or bipolar mania **Olanzapine LAI:** maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine
Proposed (if applicable)	Not applicable
Posology and route of administration in the EEA Current	**Oral:** Schizophrenia in Adults: Once a day without regard to meals. Target dose of 10 mg/day. Dose range of 5 mg/day to 20 mg/day. Special Populations: A lower starting dose of 5 mg/day may be considered for geriatric patients or when other clinical factors warrant. A 5-mg starting dose also may be considered for patients with severe renal or moderate hepatic impairment. A lower starting dose may be considered in patients who exhibit a combination of factors (female gender, geriatric age, nonsmoking status) which may slow the metabolism of olanzapine. Bipolar Disorder (acute and maintenance): Once a day without regard to meals. Dose range of 5 mg/day to 20 mg/day. Schizophrenia and/or Bipolar Disorder in Adolescents (United States only): Once a day without regard to meals. Dose range of 2.5 mg/day to 20 mg/day. **RAIM:** Adults: Recommended dose is 10 mg, administered as a single injection. Based on clinical evaluation, a second injection (up to 10 mg) may be administered as early as 2 hours after the first injection and a third injection, up to 10 mg, may be administered as early as 4 hours after the second injection. In the EU SmPC, the maximum daily dose is limited to 20 mg. Elderly: The recommended starting dose in elderly patients (>60 years) is 2.5 to 5 mg. Depending on the patient's clinical status, a second injection, 2.5 to 5 mg, may be administered 2 hours after the first injection. In the EU SmPC, the maximum daily dose of 20 mg (all formulations) should not be exceeded. **Olanzapine LAI:** Adults: 150 mg to 300 mg every 2 weeks or 300 mg to 405 mg every 4 weeks, administered by deep intramuscular gluteal injection by a healthcare professional. Patients should be treated initially with oral olanzapine before administering olanzapine LAI to establish tolerability and response.
Proposed (if applicable)	Not applicable

Pharmaceutical form(s) and strengths Current	Olanzapine Film-Coated Tablets: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg Olanzapine Orodispersible Tablets: 5 mg, 10 mg, 15 mg, 20 mg Olanzapine 10 mg powder for solution for injection (RAIM): Olanzapine powder is reconstituted with sterile water for injection prior to its use. The reconstituted solution is intended for IM injection only. Each vial provides 10 mg olanzapine. Olanzapine LAI Intramuscular injection suspension vial: 210 mg, 300 mg, and 405 mg
Proposed (if applicable)	Not applicable

Country and date of first authorisation worldwide	EU	27 SEP 1996
Country and date of first launch worldwide	UK	27 SEP 1996
Country and date of first authorisation in the EEA	UK	27 SEP 1996
Is the product subject to additional monitoring in the EU?	No	

Part II. Safety Specification

Module SI. Epidemiology of the Indications and Target Population

SI.1. Olanzapine for the Treatment of Patients with Schizophrenia

SI.1.1. Epidemiology of the Disease

SI.1.1.1. Incidence and Prevalence of the Target Indication

Worldwide, schizophrenia exhibits wide variation in incidence, with rates ranging from 0.5 to 5.0 per 10 000 or approximately 1% of the general population (American Psychiatric Association [APA] 2000; McGrath et al. 2004; Kirkbride et al. 2012). Incidence rates vary greatly in Europe. In Ireland the overall rate for ages ≥15 years was 6.4/100 000; 9.6 males/3.2 females (Owoeye et al. 2013). Scotland showed similar rates, with male verses female incidence per 100 000 ranging from 10.1 vs 5.2 for ages 15 to 19 years to 3.2 vs 3.3 for ages 55 to 59 years (Takei et al. 1996). Rates were much higher in Spain, Denmark, and Finland. A 2010 study by Bouza found the overall incidence in Spain for ages ≥15 years to be 46.23/100 000 and Pedersen et al. (2012) found the Danish incidence to be 49.36/100 000 person-years (PYs) for the same age group. In Finland, incidence ranged from 37.2 to 48.9/100 000 for ages 15 to 24 years, peaked at 45.3 to 62.4/100 000 for ages 25 to 34 years and then decreased to 22.3 to 32.5/100 000 for ages 45 to 64 years. Rates differed depending on diagnostic classification (Salokangas et al. 2011). Early onset schizophrenia is considered rare, with a Denmark study reporting a rate of 3.17/100 000 PYs for ages 0 to 18 years and 9.10/100 000 PYs for ages 12 to 18 years (Okkels et al. 2013).

Worldwide prevalence of schizophrenia also exhibits wide variation, ranging from 1.8 to 11.6/1000 (10% and 90% quantiles) with a median of 4.0/1000 (Saha et al. 2005). In the 1980s, the accumulated prevalence for ages 13 to 19 years was 0.23% in Sweden (Gillberg 2001). During a similar time frame, a study in Scotland found the point prevalence of schizophrenia to be 2.38/1000 in the general population, and this increased to 3.59/1000 by 2006 (Shivashankar et al. 2013). In 2011, a collaborative literature review of 27 European Union (EU) countries found the 12-month prevalence of psychotic disorders to be 1.2%, affecting approximately 5 million people (Wittchen et al. 2011).

SI.1.1.2. Demographics of the Target Population

Schizophrenia is extremely rare (approximately 3/100 000) during the first decade of life, increasing approximately 4-fold between ages 10 to 14 years to 13/100 000 (Okkels et al. 2013; Sikich 2013). Rates peak during the young adult years between ages 20 to 29 and are highest in males with male/female rate ratios ranging from 1.4:1 in a global meta-analysis study to 2.8:1 in Ireland (Takei et al. 1996; Aleman et al. 2003; Bouza et al. 2010; Owoeye et al. 2013). It is estimated that 39% of men with schizophrenia and 23% of the women experience disease onset before 19 years of age (Loranger 1984).

SI.1.1.3. Risk Factors for the Disease

Schizophrenia is a chronic and disabling brain disorder without a clear aetiology but is likely the result of an interaction between genetic risk and environmental exposures (Gilmore 2010). Genetic risk factors include having a parent with schizophrenia, gestational exposure to infections, and older age of parents at conception (Brown 2006; Gilmore 2010; Petersen et al. 2011). Environmental risk factors include maternal depression during pregnancy, childhood trauma, cannabis use during adolescence, prenatal viral insult, exposure to neurotoxins, birth complications (such as caesarean section, or hypoxia), prenatal maternal stress, perinatal insult (such as ventral hippocampal lesions), prenatal stress, and postnatal maternal and/or social deprivation (Henquet et al. 2005; Morgan and Fisher 2007; Powell 2010). The most established of the known risk factors for schizophrenia is the presence of an affected relative (McGrath and Murray 2007).

SI.1.1.4. Main Treatment Options

Adult Patients

Antipsychotic medicines remain the primary treatment for schizophrenia. No single medication is effective for all patients with schizophrenia; approximately 20% to 45% of patients fail to show a satisfactory response to antipsychotic medications (Conley and Kelly 2001; Kane 2006; Lambert 2006).

Nonpharmacological treatments are generally used in conjunction with pharmacotherapy. Psychological treatments including family intervention, supported employment, assertive community treatment, skills training, and cognitive-behavioural therapy (CBT) can prevent relapse and enable recovery during the stable phase of treatment (APA Practice Guidelines [2009]). While pharmacotherapy focuses on symptom diminution, psychosocial interventions may provide emotional support and address particular deficits associated with schizophrenia.

Adolescent Patients

The American Academy of Child and Adolescent Psychiatry (AACAP) guidelines (2013) for the treatment of schizophrenia recommends treatment with antipsychotics. In addition, psychoeducational therapy for the patient and for the family is recommended. Specialised educational programs and/or vocational training programs may be indicated for some children or adolescents to address the cognitive and functional deficits associated with the illness. Some individuals will require more intensive community support services, including day programs. Aripiprazole is the only atypical antipsychotic approved by the European Medicines Agency for use in patients with schizophrenia 15 years and older.

SI.1.1.5. Mortality and Morbidity

In adults, schizophrenia is characterised by the presence of positive symptoms such as hallucinations and delusions as well as negative symptoms such as anhedonia and avolition, as well as impairment in cognitive function. The course is typically characterised by periods of acute psychosis followed by periods of stabilisation but generally not recovery (APA 2000).

Similar to adult-onset schizophrenia, schizophrenia in adolescents is characterised by hallucinations (primarily auditory), delusions, thought disorder, and negative symptoms

(Werry et al. 1991; Russell 1994); however, the symptoms are overall less complex (Russell 1994). In addition, onset during childhood or early adolescence is frequently associated with a more severe course with more pronounced neurological abnormalities and poorer prognosis (Kumra et al. 2001; Remschmidt and Thiesen 2012).

Patients diagnosed with schizophrenia have increased mortality compared with the general population, with males having higher rates than females. Mortality increases with age and mortality rate ratios (MRRs) are higher in the younger age groups than in the older groups (Laursen et al. 2007; Tiihonen et al. 2009; Laursen et al. 2011b; Nielsen et al. 2013). Life expectancy in the EU for people with schizophrenia compared to controls was reduced by 14.6 to 18.7 years for males and by 9.8 to 16.3 years for females (Chang CK et al. 2011; Laursen et al. 2011b; Crump et al. 2013b). All-cause mortality rates for the EU schizophrenia population range from 12.5/1000 for males and 16.2/1000 for females in the United Kingdom (UK) to 31.3/1000 for males and 37.1/1000 for females in Finland (Tiihonen et al. 2009; Høye et al. 2011; Dutta et al. 2012; Crump et al. 2013b). When compared to the general EU population, people with schizophrenia have 2 to 3 times higher mortality, with all-cause standardized mortality ratios (SMRs) ranging from 1.7 to 3.9 for females to 2.1 to 3.5 for males (Brown et al. 2010; Høye et al. 2011; Dutta et al. 2012; Laursen et al. 2013; Nordentoft et al. 2013).

SI.2. Concomitant Medication(s) in the Target Population

Concomitant nonpsychiatric medication at baseline in a German population (N = 642) included statins (1.88%), other hypolipidaemic drugs (1.25%), beta-blockers (9.69%), diuretics (3.75%), Ca-antagonists (1.56%), ACE inhibitors (5.00%), angiotensin II antagonists (0.31%), other antihypertensive drugs (3.44%), insulins (1.41%), oral antidiabetic drugs (3.59%), oral corticosteroids (0.16%), and corticosteroid inhalants (0.47%) (Kraemer et al. 2011). Among children and adolescents receiving psychopharmacotherapy, medications included antidepressants (52%), stimulants (42%), antipsychotics (23%), antimanic agents (22%), other medications (13%), and anti-anxiety medications (8%). It was reported that 70.3% of those diagnosed with schizophrenia had concomitant pharmacotherapy (Duffy et al. 2005).

SI.3. Important Comorbidities Found in the Target Population

Adult Patients

Important comorbidities within the adult schizophrenic population include depression/suicide, substance use disorders, metabolic syndrome, violence/aggression, cardiovascular disease/hypertension, seizures, and pulmonary (chronic obstructive pulmonary disease [COPD]).

Depression/Suicide: At least 5% of people with a schizophrenia disorder will die by suicide (Palmer et al. 2005). Incidence rates per 1000 PYs for suicide in a Swedish national schizophrenia cohort were 5.3 (7.1%) for males, 3.7 (5%) for females, and 4.7 (6.3%) for all patients. Suicide was more common in men and the modal age group for suicide was 30 to 39 years (41.6% of schizophrenia deaths) followed by ages 20 to 29 years (37.3% of schizophrenia deaths) (Webb et al. 2011). Prevalence of depression ranges from 7% to 65%

worldwide, depending on the phase of schizophrenia (Hausmann and Fleischhacker 2000; Lako et al. 2012; Majadas et al. 2012). Worldwide, approximately 50% to 63.1% of patients with schizophrenia attempt suicide, while 5% to 13% are at risk for completing suicide (Nyman and Jonsson 1986; Meltzer and Fatemi 1995; Green et al. 2003; Meltzer et al. 2003; Palmer et al. 2005).

Substance Abuse Disorder/Smoking: Incidence is not well documented in the literature. Prevalence rates of substance use disorders (SUDs), including nicotine, are higher in patients with schizophrenia compared to the general population (Dekker et al. 2013), with reports of lifetime SUD of 70% to 80% (Westermeyer 2006). Nicotine use in the EU schizophrenia population ranged from 15% to 74.2% depending on country and type of study (Bouza et al. 2010; Falissard et al. 2011; Papageorgiou et al. 2011; Dekker et al. 2013; Mitchell et al. 2013). Alcohol abuse ranges from 2.8% in Greece to 23.2% in Spain (Bouza et al. 2010; Papageorgiou et al. 2011; Carra et al. 2012; Schoepf et al. 2012). Illicit drug abuse ranges from 4.7% in Greece to 26.1% in Spain (Bouza et al. 2010; Papageorgiou et al. 2011; Carra et al. 2012). Prevalence of cannabis use/hard drug use in the EU is 19.9%/5.8% for current users and 38.3%/17.8% for lifetime users; current use per lab screening of tetrahydrocannabinol (THC) is 16.9%; cocaine is 1.3%; and amphetamine is 0.9% (Dekker et al. 2013). Mortality for smoking in the schizophrenia population is higher than the general population with a SMR of 2.75 (Brown et al. 2010).

Metabolic Syndrome[1]**:** Incidence of metabolic syndrome among patients with schizophrenia was found to be 13% in during a 1-year follow-up study conducted in the Netherlands (Schorr et al. 2009[1]). In a 2013 review by Papanastasiou[3], prevalence rates of metabolic syndrome varied largely across studies and increased with age in the schizophrenia population. Country-specific studies found that the prevalence of metabolic syndrome, among patients treated with antipsychotics in the EU ranged from 19% in Spain and Finland to 35% in the Netherlands and 39% in Germany (Heiskanen et al. 2003[1]; Saari et al. 2005[1]; Sicras-Mainar et al. 2008[1]; Bernardo et al. 2009[1]; Koponen et al. 2010[1]; Arango et al. 2011[1]; Kraemer et al. 2011[1]). A 12-country (primarily EU) study found the prevalence to be 34% in the schizophrenia population (Falissard et al. 2011[1]). A meta-analysis by Mitchell (2013)[1,2] further found that metabolic syndrome prevalence increased with severity of schizophrenia disease.

Violence/Aggression: Incidence of hostility in the EU population with schizophrenia was 14.0% after 3 years and is more frequent in males (30.4% vs 24.4%) (Ochoa et al. 2013).

---

[1] Metabolic syndrome is defined using National Cholesterol Education Program Adult Treatment Panel III criteria. Three of the following five criteria were required: 1) abdominal obesity (waist circumference >102 cm or 40 inches in men; >88 cm or 35 inches in women; 2) fasting hypertriglyceridaemia ≥1.69 mmol/L or 150 mg/dL; 3) low fasting HDL <1.04 mmol/L or 40 mg/dL in men; <1.29 mmol/L or 50 mg/dL in women; 4) high blood pressure; ≥130/85 mm Hg or current treatment with antihypertensive medication; and 5) high fasting glucose ≥6.1 mmol/L or 110+ mg/dL or current treatment with antidiabetic medication.
[2] Using International Diabetes Federation (IDF) 2005 criteria.
[3] WHO (1998), EGIR (1999), NCEP-ATP-III (2001) and IDF (2006).
[4] Severe mental illness is defined as all forms of schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder, and their synonyms, and all other nonorganic psychoses.

Incidence of committing a violent crime is 5% to 6% in a smaller Danish schizophrenia population (Stevens et al. 2013). Prevalence of mild to very severe over-activity and aggression ranges from 18.9% to 25.2% depending on schizophrenia definition in the United Kingdom (UK), and prevalence of hostility in a 10-country EU study was 27.9% (Hayes et al. 2012; Ochoa et al. 2013). Mortality in the schizophrenia population with mild to very severe over-activity and aggression is 3.2% to 3.9% depending on schizophrenia definition, representing 17.95% of all cause deaths in the schizophrenia population and 29.63% of all-cause deaths in the schizophrenia disorder population (Hayes et al. 2012).

Cardiovascular/Hypertension: Incidence per 1000 PYs for chronic cardiovascular disorders in a Danish schizophrenia population was higher when compared to controls: 0.52 versus 0.31 for peripheral vascular disease (PVD), 0.58 versus 0.25 for myocardial infarction (MI) and 0.72 versus 0.13 for congestive heart failure (CHF) (Laursen et al. 2011a). However, in a Swedish national cohort study, schizophrenia patients had no elevated risk of diagnoses of cardiovascular disease (CVD), ischemic heart disease (IHD), or hypertension, and men showed only a slight elevated risk for stroke, with an adjusted hazard ratio (HR) of 1.19 when compared to the general population. Male/female incidence of cardiovascular disease in this schizophrenia population compared to controls (C) was 20.3%/21.9% (C: 25.0/24.4), ischemic heart disease was 5.6%/5.2% (C: 8.5/6.0), stroke was 2.9%/3.2% (C: 3.8/3.5), and hypertension was 6.8%/7.4% (C: 11.3/11.9) (Crump et al. 2013b). Prevalence of cardiovascular (CV) events among patients with schizophrenia in the EU ranges from 1.5% to 7.2% (3.1% male, 11.3% female) for CV disease, 1.5% to 2.1% for cardiac failure, 2.0% to 4.9% for ischemic heart disease, 1.6% for angina, 1.0% for MI, and 3.4% for PVD (Bouza et al. 2010; Oreski et al. 2012; Schoepf et al. 2012). Prevalence of hypertension ranges from 8.8% in the UK to 60.6% in Norway (Arango et al. 2011; Papageorgiou et al. 2011; Schoepf et al. 2012). Mortality from CV diseases is higher in the schizophrenia population, with SMRs in the EU ranging from 2.25 to 3.0 (Osby et al. 2000; Brown et al. 2010; Hoye 2011).

Seizures/Epilepsy: Incidence is not well documented in the EU. The incidence of seizures among those on placebo in Phase II and III clinical trials for antipsychotics between 1985 and 2004 (per 100 000 PY) was 784.3 (Alper et al. 2007). Prevalence: There is a strong association between schizophrenia and epilepsy, with this population being up to 6 times more likely to develop epilepsy compared to the general population, with no consistent difference in risk between genders (Chang YT et al. 2011). In the EU, prevalence of epilepsy in the schizophrenia population ranged from 3.5% (2.0% controls) to 4.5% (0.4% controls), with rate ratios ranging from 1.8 to 3.0 and an odds ratio of 11.1 (Makikyro et al. 1998; Oreski et al. 2012; Schoepf et al. 2012; Wotton and Goldacre 2012).

Mortality: The SMR for epilepsy in a small schizophrenia population in the UK was 2613 (Brown et al. 2000).

Chronic Obstructive Pulmonary Disease (COPD): Incidence of COPD in a Swedish schizophrenia population after 7 years of follow-up was 3.9% for men and 6.5% for females compared to 2.3% and 2.2%, respectively, in the general population (adjusted HR: males, 2.12, females, 2.58) (Crump et al. 2013b). Prevalence of COPD appeared equally frequent in both the

schizophrenia and general populations, with a prevalence ranging from 3.7% (2.6% controls) in Sweden to 5.5% in Spain, and was higher in males (6.4%) than in females (3.8%) (Bouza et al. 2010; Schoepf et al. 2012). Mortality from COPD in both men and women with schizophrenia was elevated compared to the general population, with 7.5% male schizophrenia deaths vs 3.0% (HR 6.28) and 4.8% female schizophrenia deaths vs 2.7% (HR 3.31) (Crump et al. 2013b).

Adolescent Patients

Attention Deficit Hyperactivity Disorder: Incidence and mortality are not well documented in the literature. Prevalence of childhood ADHD in an adult schizophrenia population in Spain is 17% (with the male/female ratio 4:1) compared to 5% in the general population (Peralta et al. 2011). In the US, prevalence of ADHD in children with schizophrenia aged 4 to 17 years range from 21% to 84%; (Ross et al. 2006; Nugent et al. 2012).

Depression: Incidence and mortality are not well documented in the literature. Prevalence of depression in a US population aged 4 to 15 years is 30%; 35% in females and 28% in males (Ross et al. 2006).

Substance Use Disorders (SUDs): Incidence and mortality are not well documented in the literature. Prevalence of SUDs in US young adults aged 12 to 35 years (median age 18) with schizophrenia is 52% (Caton et al. 1989). An Israeli study of 12- to 23-year-olds found the prevalence to be 28.2% (Shoval et al. 2006).

Obsessive-Compulsive Disorder (OCD): Incidence of obsessive compulsive symptoms (OCS) and OCD at different assessments varied between 22.7% to 30.6% and 7.3% to 11.8%, respectively, during follow-up of 6 weeks to 5 years in a Netherlands schizophrenia population aged 15 to 28 years and 82% male. Prevalence at baseline was 31.2% for OCS and 11.8% for OCD (de Haan et al. 2013). Prevalence of OCD in the US among children aged 4 to 17 years ranges from 5% to 20% (Ross et al. 2006; Nugent et al. 2012).

Anxiety: Incidence and mortality are not well documented in the literature. Prevalence of anxiety in the US population aged 4 to 17 years ranges from 4.0% to 55% (Ross et al. 2006; Nugent et al. 2012).

SI.4. Olanzapine for the Treatment of Patients with Bipolar Disorder

SI.4.1. Epidemiology of the Disease

SI.4.1.1 Incidence and Prevalence of Target Indication

Adult Patients

The incidence of bipolar I disorder for females in England ranges from 2.26 per 100 000 person-years among patients ≥76 to 12.06 per 100 000 person-years among patients 16 to 25. The range is similar for males, with the incidence of 2.50 per 100 000 person-years among patients ≥76 to 13.81 per 100 000 person-years among patients 16 to 25 (Kennedy et al. 2005). In the Netherlands, the incidence of bipolar disorder is 0.69 per 10 000 person-years and the

prevalence is 0.16% (Kroon et al. 2013). In a national cohort of Swedish adults, 0.12% of women and 0.08% of men were diagnosed with bipolar disorder (Crump et al. 2013a). The lifetime prevalence of bipolar disorder in the UK, Germany and Italy is approximately 1% (Fajutrao et al. 2009).

Adolescent Patients

In a UK study of 3586 children (aged less than 18 years), the prevalence of bipolar disorder was 1.0% (Chan et al. 2011). In Germany, national inpatient admission rates for bipolar disorder were 1.91 per 100 000 for the year 2007 in those aged 0 to 19 years (0.09 in those under 15 and 6.33 in those 15 to 19 years) (Holtmann et al. 2010).

SI.4.1.2. Demographics of the Target Population

Adult Patients

Bipolar I disorder affects men and women with equal frequencies and bipolar II appears to be more common in women (Bauer and Pfennig 2005). Women are more likely to experience rapid cycling, mixed states, and depressive episodes than men (Ketter 2010). In a global study of 1665 type-I bipolar subjects, 52.3% were women and median interquartile range (IQR) onset age was 23.0 (13.0) years (Baldessarini et al. 2012).

Adolescent Patients

In a cohort of bipolar patients in the UK, 51.4% were male and mean age was 14.26 years (Chan et al. 2011). In Italian children and adolescents with bipolar disorder, 49.2% were male, mean age (SD) was 14.7 (2.6) years and mean age at onset (SD) was 11.1 (2.9) years (Masi et al. 2006).

SI.4.1.3. Risk Factors for the Disease

A Danish study found that having a father, mother, or sibling with bipolar disease significantly increased the risk of bipolar disease, with odds ratios ranging from 6.12 [95% confidence interval (CI): 4.10-9.139] to 31.09 [95% CI: 12.19-83.46]. Also found to be a significant risk was gender, with female sex having an odds ratio of 1.40 [95% CI: 1.25-1.56] (Helenius et al. 2013).

SI.4.1.4 Main Treatment Options:

Adult Patients

There are multiple treatments for acute mania and maintenance of bipolar disorder. The Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder (Yatham et al. 2013) recommendations for first-line pharmacotherapy for acute manic episodes include monotherapy treatment with lithium, divalproex, divalproex ER, olanzapine, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, asenapine, and paliperidone ER, and adjunctive therapy treatment with lithium or divalproex: risperidone, quetiapine, olanzapine, aripiprazole, asenapine. The first-line recommendation for monotherapy maintenance therapy is lithium, lamotrigine (limited efficacy

in preventing mania), divalproex, olanzapine, quetiapine, risperidone long-acting injection, and aripiprazole; for adjunctive maintenance therapy, the recommendation is treatment with lithium or divalproex: quetiapine, risperidone long-acting injection, aripiprazole, and ziprasidone. Generally, it is suggested that the treatment that works in the acute phase should be continued as a maintenance treatment. Only aripiprazole is approved in the EU for treatment of adolescent patients with bipolar disorder (13 years and older). Data have supported the benefits of adjunctive psychoeducation, cognitive behavioural therapy (CBT), family therapy, and interpersonal and social rhythm therapy (IPSRT) in reducing recurrences and improving symptoms in patients with bipolar disorder.

Adolescent Patients

AACAP Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder (2007) states that the standard therapy, based on the adult literature, typically includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (McClellan et al. 2007). The choice of medication(s) should be made based on evidence of efficacy, the phase of illness, the presence of confounding presentations (eg, rapid cycling mood swings, psychotic symptoms), the agent's side effect spectrum and safety, the patient's history of medication response, and the preferences of the patient and his or her family. A history of treatment response in parents may predict response in offspring. Lithium is approved beginning at age 12 years for acute mania and maintenance therapy. Aripiprazole, valproate, olanzapine, risperidone, quetiapine, and ziprasidone are approved for acute mania in adolescents. Chlorpromazine is also approved for acute mania in adolescents, but it is generally not used as a first-line agent. Clozapine is reserved for treatment refractory cases. While there are no recommendations for alternative treatments of acute mania or mixed episodes of bipolar disorder, psychotherapeutic interventions (psychoeducational therapy, individual psychotherapy, social and family functioning, academic and occupational functioning, and community consultation) are recommended during the maintenance treatment of the disorder.

SI.4.1.5 Mortality and Morbidity in Target Indication

Adult Patients

A study conducted in the UK among patients with bipolar affective disorder found that the life expectancy for females (n=2592) was 70.4 years and males (n=4426) was 67.3 years. Compared with the UK general population, males had 10.1 years reduced life expectancy and females a reduction of 11.2 years (Chang CK et al. 2011).

Persons diagnosed with bipolar disorder may have significant problems with work and supporting themselves, and also may have decreased levels of functioning (Hirschfeld et al. 2003). They have high rates of disability compared with individuals without bipolar disorder, resulting in decreased productivity and excess unemployment (Ketter 2010).

Adolescent Patients

Childhood onset of bipolar disorder is associated with greater severity of illness (for example, psychosis, mixed mania, high rates of self-injury, and drug abuse) and more functional impairment (McClellan et al. 1993; Strober et al. 1995; Wozniak et al. 1995).

SI.5. Concomitant Medication(s) in the Target Population

Adult Patients

Concomitant medication use among patients with bipolar or schizoaffective disorder in the Netherlands was reported as follows: lithium, 81.5%; carbamazepine, 13.2%; valproic acid, 13.9%; antidepressive medication (tricyclic, selective serotonin reuptake inhibitor [SSRI], other), 30.5%; antipsychotic medication (typical and atypical and typical depot), 36.4% (Klumpers et al. 2004).

Among 194 adult patients with bipolar disorder under maintenance treatment at 13 Spanish centres, a total of 91.1% were receiving at least one mood stabiliser, 65.8% were receiving at least one antipsychotic, 28.8% were receiving at least one antidepressant, and 57.8% were receiving at least one benzodiazepine (Garcia-Portilla et al. 2010).

Adolescent Patients

Treatment of bipolar disorder in children and adolescents most often involves a multidisciplinary approach targeting the psychological, biological, and social aspects of the disease (Pfeifer et al. 2010). In a study of 61 paediatric (aged 8 to 18 years) bipolar patients, 55.7% were treated with SSRIs, 86.9% with mood stabilisers, and 55.7% with atypical antipsychotics (Masi et al. 2006).

SI.6. Important Comorbidities Found in the Target Population

Adult Patients

Patients with bipolar disorder have increased odds for diabetes (SDECG 2004) and drug abuse or dependence, including alcohol, nicotine, and illicit substances (Carney and Jones 2006). Studies in populations with bipolar disorder have shown a prevalence of elevated blood glucose levels 2 to 4 times higher than in the general population (Mukherjee et al. 1996; Dixon et al. 2000; Sernyak et al. 2002; Cohn et al. 2004).

Patients with bipolar disorder have increased odds for various medical conditions including cardiovascular, metabolic, neurological, pulmonary, and endocrine conditions (Carney and Jones 2006). Additionally, bipolar disorder is highly comorbid with substance abuse and anxiety (Hirschfeld et al. 2003).

Depression/Suicide

Seventy-one percent of patients with Bipolar I (n=1548) had at least one lifetime depressive episode (Perron et al. 2009).

In an EU study of 2219 patients with bipolar disease, 29.9% had at least one suicide attempt (Bellivier et al. 2011). In Finland, prevalence of attempted suicide is 51% and prevalence of suicidal ideation is 77% (Valtonen et al. 2005).

Substance Use Disorders

An EU study of bipolar disease found that the lifetime alcohol abuse (n=2189) was prevalent in 20.8% of those without a history of suicidal behaviour and 34.5% of those with suicidal behaviour; lifetime cannabis abuse (n=2174) was prevalent in 10.7% of those without suicidal behaviour and 17.3% of those with suicidal behaviour; lifetime abuse of other substances (n=2208) was 4.8% in those without suicidal behaviour and 11.5% in those with suicidal behaviour (Bellivier et al. 2011).

Based on data from the 2007 National Health Interview Survey on 23 393 non-institutionalized US adults, among those with bipolar disorder (n=387), 69.8% had ever smoked, 23.4% were former smokers, 46.4% were current smokers, and 30.2% never smoked (McClave et al. 2010).

Metabolic syndrome

Among 128 Spanish patients with bipolar disorder, the prevalence of metabolic syndrome (NCEP-AT III) was 25.8% (Sicras-Mainar et al. 2008). In Turkey, among outpatients with bipolar I, the total prevalence of metabolic syndrome was 32% (36.2% for females and 29.5% for males) (Yumru et al. 2007). In Croatia, prevalence of metabolic syndrome (NCEP ATP III) was 31% (Vuksan-Cusa et al. 2010).

Violence/Aggression

In the UK, the prevalence of aggression at first contact with services among those with first episode mania was 21.6% (Dean et al. 2007). In a Swedish study the prevalence of violent crime among bipolar patients (n= 3743) was 8.4% compared to 3.5% of the general population (n=37 429). The risk of violence was mostly confined to patients with substance abuse comorbidity (adjusted OR: 6.4, 95% CI: 5.1 to 8.1) (Fazel et al. 2009).

Cardiovascular Disease/Hypertension

Among Swedish patients with bipolar disease (n=6618), prevalence of cardiovascular disease was 31.0% in women and 31.5% in men; this included prevalence of 11.6% and 11.4% for hypertension in women and men, respectively (Crump et al. 2013a). In a study of 194 patients with bipolar disorder under maintenance treatment at 13 Spanish centres, prevalence of hypertension was 10.5%, prevalence of dyslipidaemia was 16.5%, and 8.3% of patients had an elevated risk of coronary heart disease (Garcia-Portilla et al. 2010).

Pulmonary (COPD)

In Sweden, the prevalence of COPD in bipolar patients (n=6618) was 5.9% in women and 4.4% in men (Crump et al. 2013a). In the US, the prevalence of pulmonary comorbidities ranges from 10.6% to 12.9% (Kilbourne 2005; Carney and Jones 2006).

Seizures

In US patients with epilepsy, 47.9% reported prior formal diagnosis of bipolar disorder (Ettinger et al. 2005).

Adolescent Patients

Attention Deficit Hyperactivity Disorder (ADHD)

In a Spanish cohort of 38 children with bipolar disease, 21.1% had a diagnosis of ADHD prior to their bipolar diagnosis (Soutullo et al. 2009). Among 98 Italian children with bipolar disorder, 37.8% had a lifetime diagnosis of comorbid ADHD (Masi et al. 2006).

Depression

In a UK cohort of children and adolescents with bipolar disease (n=35), prevalence of morbid depression, sadness, unhappiness, or tearfulness was 77.8% among those aged under 13 years and 50.0% in those aged 13 to 18 years (Chan et al. 2011). In Spain, the prevalence of depression (present before bipolar diagnosis) was 18.4% among 38 children with bipolar disease (Soutullo et al. 2009).

Substance Use Disorders

In a UK cohort of children and adolescents with bipolar disorder (n=35), the prevalence of drug use was 19.2% in those aged 13 to 18 years, and the prevalence of alcohol and solvent misuse was 11.1% in those aged under 13 years and 7.7% in those aged 13 to 18 years (Chan et al. 2011). Among 38 Spanish children with bipolar disorder, 18.4% had prevalent substance abuse disorder prior to their bipolar disorder diagnosis (Soutullo et al. 2009).

Obsessive Compulsive Disorder (OCD)

In an Italian study of 98 children with bipolar disorder, OCD was prevalent in 54.1% (Masi et al. 2006). In the US, the prevalence was 18% for female patients and 13% for male patients (Biederman et al. 2004).

Anxiety

Among 98 Italian children with bipolar disorder, the prevalence of generalized anxiety disorder was 37.7% (Masi et al. 2006). In a UK cohort of children and adolescents with bipolar disorder (n=35), the prevalence of morbid anxiety, worry, or panic was 33.3% in those under 13 years of age and 38.5% in those aged 13 to 18 years (Chan et al. 2011).

Module SII. Nonclinical Part

Olanzapine is an atypical antipsychotic that demonstrates a broad pharmacologic profile across a number of receptor systems associated with 5-HT2A, 5-HT2C, 5-HT3, dopamine D1, dopamine D2, α-1-adrenergic, histamine H1, and 5 muscarinic receptor subtypes. An extensive series of single-dose, repeat-dose, genetic toxicity, carcinogenicity, and developmental and reproduction studies was conducted to support clinical trials with oral olanzapine before the marketing authorisation was first granted in Europe. Additionally, subchronic studies were conducted in dogs in support of the rapid-acting intramuscular (RAIM) indication, which was first approved in the European Union (EU) in July 2001. Toxicology studies (chronic toxicity in the dog, embryofoetal development in rats and rabbits, genotoxicity studies, and a rat carcinogenicity study) were also conducted with olanzapine pamoate, a long-acting injection (LAI) formulation first approved in the EU in November 2008.

Table SII.1 below outlines safety findings from nonclinical studies conducted prior to granting of marketing authorization of olanzapine in 1996 in the EU and nonclinical studies supporting the marketing authorizations of the RAIM and LAI formulations in July 2001 and November 2008, respectively.

Table SII.1. Key Safety Findings from Nonclinical Studies and Relevance to Humans

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
• Single and repeat-dose toxicity o Salient features were sedation and systemic toxicity secondary to elevated prolactin concentrations. Leukopaenia was observed in rat, mouse, and dog models; however, no evidence of bone marrow toxicity was observed. o Olanzapine pamoate (LAI): injection site reactions indicative of inflammation in rats and dogs	In clinical use, somnolence has been very commonly reported, while blood dyscrasias have been reported infrequently. Hyperprolactinaemia has been observed in human use. However, olanzapine is generally well tolerated in patients based on evidence, gained over 17years on the market and extensive postmarketing exposure. These nonclinical safety findings have been appropriately addressed in labelling (CDS and SmPC).
• Reproductive toxicity o Oestrus cycles and reproduction parameters were affected at high doses.	There are no adequate and well-controlled studies in pregnant women. This safety finding has been appropriately addressed in labelling; olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus (CDS and SmPC).
• Developmental toxicity o No evidence of teratogenicity in rats and rabbits; some delays in foetal development and transient decreased activity in offspring (rat).	Clinical trials and extensive postmarketing exposure have failed to identify any potential teratogenicity in human use.
• Genotoxicity o Olanzapine is not mutagenic or clastogenic o Pamoic acid (re: LAI formulation) was positive in Chinese Hamster Ovary chromosomal aberration assay	Weight-of-evidence assessment of genetic toxicology tests supports lack of genotoxic hazard to humans
• Carcinogenicity o Olanzapine oral: Increased incidence of mammary gland tumour in female rats and mice consistent with effects due to elevated prolactin levels in rodents. o Olanzapine pamoate: No increase in tumour incidence in rats when compared to vehicle control group	Prolactin-mediated endocrine tumours are a common, particular finding in rats and mice treated with agents that increase prolactin secretion; this does not appear to have direct or known human significance.

Key Safety Findings from Nonclinical Studies and Relevance to Humans

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
General safety pharmacology • Cardiovascular o A decrease in mean arterial pressure has been observed, which may indicate a potential for hypotensive effects. o In a canine Purkinje fibres model, a 16% decrease in the action potential duration at 50% (but not 95%) repolarization was observed at 10 µM. No significant changes on the maximum rate of rise of action potential, or on the effective refractory period. o Low potential risk of cardiac QT interval prolongation (hERG) at high plasma concentrations of olanzapine; however, other antipsychotics dose-dependently blocked the hERG channel in vitro (Crumb et al. 2006) to a greater degree than olanzapine. • Nervous system o Sedation; potential for proconvulsive activity	The potential for orthostatic hypotension in patients has been appropriately labelled in the SmPC and CDS. In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥500 milliseconds [msec] at any time postbaseline in patients with baseline QTcF <500 msec) were uncommon (0.1% to 1%) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. The potential for QTc prolongation is addressed in the SmPC and the safety profile of olanzapine in relation to QTc prolongation has remained unchanged over 17 years on the market and extensive postmarketing exposure in over 42 million patients. The potential for sedation and seizure has been appropriately labelled in the SmPC and CDS.
Mechanisms for drug interactions	See Module SVII.4.1
Other toxicity-related information or data	None

Abbreviations: CDS = Core Data Sheet; QTcF = QT interval as corrected by Fridericia's formula; SmPC = Summary of Product Characteristics.

SII.1. Conclusions on Nonclinical Data

Table SII.2. Important Safety Concerns Based on Nonclinical Data

Safety Concerns
Important Identified Risks (Confirmed by Clinical Data)
o Hyperprolactinaemia in adolescents o Sedation in adolescents
Important Potential Risks (Not Refuted by Clinical Data or that are of Unknown Significance)
None
Missing Information
None

Module SIII. Clinical Trial Exposure

SIII.1. Brief Overview of Development

Olanzapine, a thienobenzodiazepine derivative (selective monoaminergic antagonist), is an atypical antipsychotic developed by Eli Lilly and Company (Lilly). Oral olanzapine for the treatment of schizophrenia (marketed as Zyprexa®) received European Union (EU) approval on 27 September 1996. Oral olanzapine is also indicated for the acute and maintenance treatment of manic or mixed episodes associated with bipolar I disorder. Additionally, a rapid-acting intramuscular (RAIM) injection formulation of olanzapine (Zyprexa Intramuscular), indicated for agitation associated with schizophrenia and bipolar I mania, received approval in the United States (US) on 29 March 2004 and in the EU on 02 July 2001.

Olanzapine long-acting injection (LAI) is intended for the treatment and maintenance treatment of adult patients with schizophrenia. Olanzapine LAI received first approval in the EU on 19 November 2008 and received approval in the US on 11 December 2009.

SIII.2. Clinical Trial Exposure

The adult oral placebo-controlled data are from 13 placebo-controlled studies with 1786 patients aged 18 years or greater exposed to at least one dose of olanzapine. The adult oral overall integrated data are from 91 studies with 13 089 patients aged 18 years or greater exposed to at least one dose of olanzapine.

The adolescent oral placebo-controlled data are from 4 placebo-controlled studies with 196 patients <18 years of age exposed to at least one dose of olanzapine. The adolescent oral overall integrated data are from 7 studies with 695 patients <18 years of age exposed to at least one dose of olanzapine.

The RAIM adult placebo-controlled data are from 5 placebo-controlled studies with 597 patients aged 18 years or greater. The RAIM adult overall integrated data are from 9 studies with 815 patients aged 18 years or greater.

The olanzapine LAI adult placebo-controlled data are from 1 study with 305 patients aged 18 years or greater. The olanzapine LAI adult overall integrated studies data are from 8 studies with 2054 patients aged 18 years or greater.

Table SIII.1. Duration of Exposure to Oral Olanzapine, Adult Population by Indication

Schizophrenia Placebo-Controlled Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	547	162.5
≥1 month (30 days)	272	147.9
≥3 months (90 days)	126	129.7
≥6 months (180 days)	96	119.1
≥9 months (270 days)	75	107.1
≥1 year (365 days)	57	92.1
≥1.5 years (547 days)	30	58.8
≥2 years (730 days)	15	33.1
Total	547	162.5
Schizophrenia Overall Integrated Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	9629	4761.4
≥1 month (30 days)	7573	4660.4
≥3 months (90 days)	4392	4190.3
≥6 months (180 days)	2974	3684.1
≥9 months (270 days)	1592	2890.2
≥1 year (365 days)	1171	2510.3
≥1.5 years (547 days)	842	2128.4
≥2 years (730 days)	659	1801.5
Total	9629	4761.4
Bipolar Placebo-Controlled Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	695	57.4
≥1 month (30 days)	246	35.4
≥3 months (90 days)	0	0
≥6 months (180 days)	0	0
≥9 months (270 days)	0	0
≥1 year (365 days)	0	0
≥1.5 years (547 days)	0	0
≥2 years (730 days)	0	0
Total	695	57.4
Bipolar Overall Integrated Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	2343	599.6
≥1 month (30 days)	1542	561.3
≥3 months (90 days)	643	420.2
≥6 months (180 days)	417	335.7
≥9 months (270 days)	208	201.6
≥1 year (365 days)	94	103.0
≥1.5 years (547 days)	0	0
≥2 years (730 days)	0	0
Total	2343	599.6

Table SIII.2. Duration of Exposure to Oral Olanzapine (Totals), Adult Population

Adult Population Placebo-Controlled Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	1786	312.2
≥1 month (30 days)	940	270.6
≥3 months (90 days)	181	143.8
≥6 months (180 days)	96	119.1
≥9 months (270 days)	75	107.1
≥1 year (365 days)	57	92.1
≥1.5 years (547 days)	30	58.8
≥2 years (730 days)	15	33.1
Total	1786	312.2
Adult Population Overall Integrated Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	13089	5596.8
≥1 month (30 days)	10029	5449.1
≥3 months (90 days)	5334	4733.3
≥6 months (180 days)	3423	4036.5
≥9 months (270 days)	1800	3091.8
≥1 year (365 days)	1265	2613.3
≥1.5 years (547 days)	842	2128.4
≥2 years (730 days)	659	1801.5
Total	13089	5596.8

Table SIII.3. Duration of Exposure to Oral Olanzapine, Adolescent Population by Indication

Schizophrenia Placebo-Controlled Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	88	16.9
≥1 month (30 days)	68	15.9
≥3 months (90 days)	11	9.1
≥6 months (180 days)	10	8.7
≥9 months (270 days)	9	8.0
≥1 year (365 days)	0	0
≥1.5 years (547 days)	0	0
≥2 years (730 days)	0	0
Total	88	16.9
Schizophrenia Overall Integrated Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	262	92.2
≥1 month (30 days)	224	90.1
≥3 months (90 days)	138	79.3
≥6 months (180 days)	76	53.6
≥9 months (270 days)	14	17.4
≥1 year (365 days)	4	8.6
≥1.5 years (547 days)	2	5.8
≥2 years (730 days)	2	5.8
Total	262	92.2
Bipolar Placebo-Controlled Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	106	5.7
≥1 month (30 days)	1	0.1
≥3 months (90 days)	0	0.0
≥6 months (180 days)	0	0.0
≥9 months (270 days)	0	0.0
≥1 year (365 days)	0	0.0
≥1.5 years (547 days)	0	0.0
≥2 years (730 days)	0	0.0
Total	106	5.7
Bipolar Overall Integrated Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	429	184.2
≥1 month (30 days)	357	180.4
≥3 months (90 days)	249	165.9
≥6 months (180 days)	186	144.6
≥9 months (270 days)	92	91.5
≥1 year (365 days)	54	55.6
≥1.5 years (547 days)	0	0.0
≥2 years (730 days)	0	0.0
Total	429	184.2

Table SIII.4. Duration of Exposure to Oral Olanzapine (Totals), Adolescent Population

Adolescent Population Placebo-Controlled Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	196	23.1
≥1 month (30 days)	71	16.4
≥3 months (90 days)	11	9.1
≥6 months (180 days)	10	8.7
≥9 months (270 days)	9	8.0
≥1 year (365 days)	0	0.0
≥1.5 years (547 days)	0	0.0
≥2 years (730 days)	0	0.0
Total	196	23.1
Adolescent Population Overall Integrated Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	695	277.3
≥1 month (30 days)	584	271.5
≥3 months (90 days)	389	246.0
≥6 months (180 days)	262	198.2
≥9 months (270 days)	106	108.9
≥1 year (365 days)	58	64.2
≥1.5 years (547 days)	2	5.8
≥2 years (730 days)	2	5.8
Total	695	277.3

Table SIII.5. Duration of Exposure to Olanzapine Long-Acting Injection (LAI) (Totals)

Olanzapine LAI Placebo-Controlled Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	305	41.1
≥1 month (30 days)	279	39.9
≥3 months (90 days)	0	0.0
≥6 months (180 days)	0	0.0
≥9 months (270 days)	0	0.0
≥1 year (365 days)	0	0.0
≥1.5 years (547 days)	0	0.0
≥2 years (730 days)	0	0.0
Total	305	41.1
Olanzapine LAI Overall Integrated Studies		
Duration of Exposure (at least)	**Persons**	**Person-time (years)**
At least one dose	2054	3511.5
≥1 month (30 days)	1988	3508.3
≥3 months (90 days)	1419	3431.9
≥6 months (180 days)	1011	3258.4
≥9 months (270 days)	942	3218.1
≥1 year (365 days)	884	3168.5
≥1.5 years (547 days)	783	3044.5
≥2 years (730 days)	691	2879.4
Total	2054	3511.5

Table SIII.6, Table SIII.7, Table SIII.8, and Table SIII.9 present the counts of the modal dose categories of the patients studied.

Table SIII.6. Exposure to Oral Olanzapine by Modal Dose Category and Indication, Adult Population

Schizophrenia Placebo-Controlled Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	158	55.6
>5 mg to ≤10 mg	115	20.3
>10 mg to ≤15 mg	166	27.3
>15 mg to ≤20 mg	108	59.4
>20 mg	0	0.0
Total	547	162.5
Schizophrenia Overall Integrated Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	933	434.6
>5 mg to ≤10 mg	3155	1333.6
>10 mg to ≤15 mg	2181	1051.5
>15 mg to ≤20 mg	2832	1768.9
>20 mg	481	167.5
Total	9582	4756.0
Bipolar Placebo-Controlled Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	174	16.0
>5 mg to ≤10 mg	271	20.7
>10 mg to ≤15 mg	118	9.9
>15 mg to ≤20 mg	131	10.8
>20 mg	1	0.0
Total	695	57.4
Bipolar Overall Integrated Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	491	141.4
>5 mg to ≤10 mg	736	188.9
>10 mg to ≤15 mg	524	124.6
>15 mg to ≤20 mg	587	144.5
>20 mg	5	0.1
Total	2343	599.6

Table SIII.7. Exposure to Oral Olanzapine by Modal Dose Category (Totals), Adult Population

Total Population Placebo-Controlled Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	637	124.7
>5 mg to ≤10 mg	556	68.8
>10 mg to ≤15 mg	323	43.6
>15 mg to ≤20 mg	269	75.1
>20 mg	1	0.0
Total	1786	312.2
Total Population Overall Integrated Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	1888	697.8
>5 mg to ≤10 mg	4323	1599.4
>10 mg to ≤15 mg	2861	1201.8
>15 mg to ≤20 mg	3484	1924.8
>20 mg	486	167.6
Total	13042	5591.4

Table SIII.8. Exposure to Oral Olanzapine by Modal Dose Category and Indication, Adolescent Population

Schizophrenia Placebo-Controlled Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	15	3.0
>5 mg to ≤10 mg	32	6.5
>10 mg to ≤15 mg	25	5.8
>15 mg to ≤20 mg	16	1.6
>20 mg	0	0.0
Total	88	16.9
Schizophrenia Overall Integrated Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	39	11.6
>5 mg to ≤10 mg	93	35.7
>10 mg to ≤15 mg	72	25.4
>15 mg to ≤20 mg	58	19.5
>20 mg	0	0.0
Total	262	92.2
Bipolar Placebo-Controlled Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	15	0.7
>5 mg to ≤10 mg	56	3.0
>10 mg to ≤15 mg	24	1.4
>15 mg to ≤20 mg	11	0.6
>20 mg	0	0.0
Total	106	5.7
Bipolar Overall Integrated Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	112	35.7
>5 mg to ≤10 mg	139	58.0
>10 mg to ≤15 mg	99	46.5
>15 mg to ≤20 mg	78	43.9
>20 mg	0	0.0
Total	428	184.1

Table SIII.9. Exposure to Oral Olanzapine by Modal Dose Category (Totals), Adolescent Population

Total Population Placebo-Controlled Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	30	3.6
>5 mg to ≤10 mg	89	9.8
>10 mg to ≤15 mg	49	7.2
>15 mg to ≤20 mg	28	2.5
>20 mg	0	0.0
Total	196	23.1
Total Population Overall Integrated Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	153	47.5
>5 mg to ≤10 mg	233	94.0
>10 mg to ≤15 mg	171	71.9
>15 mg to ≤20 mg	137	63.9
>20 mg	0	0.0
Total	694	277.3

Table SIII.10. Exposure to Olanzapine Long-Acting Injection (LAI), Oral Olanzapine Dose Equivalents, by Dose (Totals)

Olanzapine LAI Placebo-Controlled Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	0	0.0
>5 mg to ≤ 10 mg	7	1.1
>10 mg to ≤ 15 mg	191	25.7
>15 mg to ≤ 20 mg	27	2.0
>20 mg	80	12.2
Total	305	41.1
Olanzapine LAI Overall Integrated Studies		
Dose of Exposure	**Persons**	**Person-time (years)**
≤5 mg	109	71.6
>5 mg to ≤10 mg	279	596.3
>10 mg to ≤15 mg	1276	2099.8
>15 mg to ≤20 mg	96	133.7
>20 mg	294	610.1
Total	2054	3511.5

Table SIII.11. Exposure to Oral Olanzapine by Age Group, Gender, and Indication, Adult Population

Schizophrenia Placebo-Controlled Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 to <30 years	134	27	33.8	11.5
≥30 to <40 years	141	33	45.5	10.9
≥40 to <50 years	95	34	22.4	14.0
≥50 to <65 years	38	42	12.1	9.9
≥65 years	0	3	0.0	2.4
Total	408	139	113.8	48.8
Schizophrenia Overall Integrated Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 to <30 years	1834	720	927.0	341.7
≥30 to <40 years	1940	907	983.7	466.0
≥40 to <50 years	1617	963	784.8	454.8
≥50 to <65 years	816	723	372.8	348.5
≥65 years	42	67	25.9	56.1
Total	6249	3380	3094.3	1667.2
Bipolar Placebo-Controlled Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 to <30 years	64	85	5.2	6.3
≥30 to <40 years	82	103	6.1	8.9
≥40 to <50 years	82	115	6.7	8.9
≥50 to <65 years	65	83	5.4	7.9
≥65 years	2	14	0.2	1.6
Total	295	400	23.7	33.7
Bipolar Overall Integrated Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 to <30 years	254	331	59.4	79.4
≥30 to <40 years	264	382	67.6	101.7
≥40 to <50 years	270	385	64.4	104.8
≥50 to <65 years	184	218	47.8	59.7
≥65 years	17	38	4.8	10.0
Total	989	1354	244.0	355.6

Table SIII.12. Exposure to Oral Olanzapine by Age Group and Gender (Totals), Adult Population

Adult Population Placebo-Controlled Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 to <30 years	268	278	51.1	47.4
≥30 to <40 years	272	235	60.2	36.1
≥40 to <50 years	215	224	34.1	36.2
≥50 to <65 years	118	152	20.1	22.2
≥65 years	4	20	0.5	4.3
Total	877	909	165.9	146.2
Adult Population Overall Integrated Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 to <30 years	2192	1295	1010.9	480.2
≥30 to <40 years	2300	1490	1070.7	611.0
≥40 to <50 years	1984	1523	864.9	598.1
≥50 to <65 years	1075	1056	433.6	429.0
≥65 years	63	111	31.4	67.0
Total	7614	5475	3411.5	2185.3

Table SIII.13. Exposure to Oral Olanzapine by Age Group, Gender, and Indication, Adolescent Population

Schizophrenia Placebo-Controlled Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
12 years	1	1	0.9	0.2
13 years	2	3	1.0	0.2
14 years	10	3	2.4	0.4
15 years	14	5	2.4	0.5
16 years	20	8	5.4	1.0
17 years	15	6	2.1	0.5
Total	62	26	14.2	2.7
Schizophrenia Overall Integrated Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
12 years	2	4	1.0	0.8
13 years	9	8	3.0	2.0
14 years	15	9	5.6	3.0
15 years	31	14	10.8	4.0
16 years	55	16	25.7	4.3
17 years	74	25	25.2	6.9
Total	186	76	71.3	20.9
Bipolar Placebo-Controlled Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
12 years	0	0	0.0	0.0
13 years	14	8	0.8	0.5
14 years	11	16	0.6	0.8
15 years	20	11	1.2	0.6
16 years	10	7	0.5	0.4
17 years	5	4	0.2	0.2
Total	60	46	3.3	2.4
Bipolar Overall Integrated Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
12 years	1	0	0.0	0.0
13 years	47	26	21.4	10.2
14 years	34	44	12.4	17.5
15 years	48	49	20.7	18.1
16 years	45	50	22.6	21.0
17 years	54	31	26.2	14.1
Total	229	200	103.3	80.8

Table SIII.14. Exposure to Oral Olanzapine by Age Group and Gender (Totals), Adolescent Population

Adolescent Population Placebo-Controlled Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
12 years	1	1	0.9	0.2
13 years	16	11	1.8	0.7
14 years	21	19	3.0	1.2
15 years	35	17	3.8	1.3
16 years	30	15	5.9	1.3
17 years	20	10	2.4	0.7
Total	123	73	17.7	5.4
Adolescent Population Overall Integrated Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
12 years	3	4	1.0	0.8
13 years	56	34	24.3	12.2
14 years	49	53	18.0	20.5
15 years	80	64	31.8	22.6
16 years	100	67	48.3	25.3
17 years	128	57	51.5	21.1
Total	416	279	174.9	102.5

Table SIII.15. Exposure to Rapid-Acting Intramuscular (Totals) by Age Group and Gender

RAIM Population Placebo-Controlled Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 to <30 years	82	41	N/A	N/A
≥30 to <40 years	93	51	N/A	N/A
≥40 to <50 years	59	48	N/A	N/A
≥50 to <65 years	41	53	N/A	N/A
≥65 years	52	77	N/A	N/A
Total	327	270	N/A	N/A
RAIM Population Overall Integrated Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 to <30 years	142	48	N/A	N/A
≥30 to <40 years	133	67	N/A	N/A
≥40 to <50 years	87	63	N/A	N/A
≥50 to <65 years	59	62	N/A	N/A
≥65 years	62	92	N/A	N/A
Total	483	332	N/A	N/A

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

Note: RAIM is designed for very short-term use and is generally dispensed as single doses. Person-time is not calculated for this formulation.

Table SIII.16. Exposure to Olanzapine Long-Acting Injection (Totals) by Age Group and Gender

Olanzapine LAI Population Placebo-Controlled Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 to <30 years	58	10	8.3	1.5
≥30 to <40 years	58	16	7.5	2.1
≥40 to <50 years	64	34	8.4	4.4
≥50 to <65 years	40	20	5.5	2.7
≥65 years	4	1	0.5	0.1
Total	224	81	30.2	10.9
Olanzapine LAI Population Overall Integrated Studies				
Age Group	**Persons**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 to <30 years	363	120	704.3	236.2
≥30 to <40 years	399	167	669.1	232.1
≥40 to <50 years	409	217	624.6	400.7
≥50 to <65 years	214	148	314.9	301.2
≥65 years	8	9	11.6	16.9
Total	1393	661	2324.4	1187.1

Abbreviation: LAI = long-acting injection.

Table SIII.17. Exposure to Oral Olanzapine by Ethnic or Racial Origin, and Indication, Adult Population

Schizophrenia Placebo-Controlled Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	448	141.6
African	62	9.7
Hispanic	22	4.0
Asian	9	4.1
Other	6	3.1
Total	547	162.5
Schizophrenia Overall Integrated Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	6269	3356.2
African	1536	609.8
Hispanic	758	310.7
Asian	917	384.6
Other	149	100.1
Total	9629	4761.4
Bipolar Placebo-Controlled Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	566	47.7
African	67	3.7
Hispanic	51	5.1
Asian	8	0.6
Other	3	0.3
Total	695	57.4
Bipolar Overall Integrated Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	1714	439.0
African	277	63.4
Hispanic	188	59.8
Asian	99	11.4
Other	65	25.9
Total	2343	599.6

Table SIII.18. Exposure to Oral Olanzapine by Ethnic or Racial Origin (Totals), Adult Population

Adult Population Placebo-Controlled Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	1390	251.9
African	188	21.0
Hispanic	161	26.9
Asian	29	7.4
Other	18	4.9
Total	1786	312.2
Adult Population Overall Integrated Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	8827	3966.9
African	1918	690.3
Hispanic	1081	409.2
Asian	1034	401.2
Other	229	129.1
Total	13089	5596.8

Table SIII.19. Exposure to Oral Olanzapine by Ethnic or Racial Origin, and Indication, Adolescent Population

Schizophrenia Placebo-Controlled Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	64	12.1
African	18	2.6
Hispanic	5	2.1
Asian	0	0.0
Other	1	0.1
Total	88	16.9
Schizophrenia Overall Integrated Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	212	69.1
African	34	16.4
Hispanic	11	4.4
Asian	0	0.0
Other	5	2.2
Total	262	92.2
Bipolar Placebo-Controlled Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	71	3.8
African	13	0.7
Hispanic	17	1.0
Asian	0	0.0
Other	5	0.3
Total	106	5.7
Bipolar Overall Integrated Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	330	145.3
African	48	17.0
Hispanic	30	11.0
Asian	4	3.6
Other	17	7.3
Total	429	184.2

Table SIII.20. Exposure to Oral Olanzapine by Ethnic or Racial Origin (Totals), Adolescent Population

Adolescent Population Placebo-Controlled Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	137	16.3
African	31	3.3
Hispanic	22	3.1
Asian	0	0.0
Other	6	0.4
Total	196	23.1
Adolescent Population Overall Integrated Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	545	215.3
African	82	33.5
Hispanic	41	15.4
Asian	5	3.7
Other	22	9.5
Total	695	277.3

Table SIII.21. Exposure to Rapid-Acting Intramuscular (Totals) by Ethnic or Racial Origin

RAIM Population Placebo-Controlled Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	411	N/A
African	94	N/A
Hispanic	18	N/A
Asian	52	N/A
Other	22	N/A
Total	597	N/A
RAIM Population Overall Integrated Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	493	N/A
African	208	N/A
Hispanic	20	N/A
Asian	53	N/A
Other	41	N/A
Total	815	N/A

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

Note: RAIM is designed for very short-term use and is generally dispensed as single doses. Person-time is not calculated for this formulation.

Table SIII.22. Exposure to Olanzapine Long-Acting Injection (LAI) (Totals) by Ethnic or Racial Origin

Olanzapine LAI Population Placebo-Controlled Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	173	23.7
African	108	14.2
Hispanic	19	2.5
Asian	4	0.7
Other	1	0.1
Total	305	41.1
Olanzapine LAI Population Overall Integrated Studies		
Ethnic/Racial Origin	**Persons**	**Person-time (years)**
Caucasian	1344	2316.0
African	312	298.1
Hispanic	259	608.2
Asian	129	282.9
Other	10	7.4
Total	2054	3511.5

Exposure data by special population and indication and in special populations (total) are not available (Table SIII.23 and Table SIII.24).

Table SIII.23. Exposure by Special Population and Indication, All Formulations

Schizophrenia: Not available		
	Persons	**Person-time (years)**
Pregnant women	-	-
Lactating women	-	-
Renal impairment	-	-
Hepatic impairment	-	-
Cardiac impairment	-	-
Subpopulations with genetic polymorphisms	-	-
Immuno-compromised	-	-
Bipolar I Disorder: Not available		
	Persons	**Person-time (years)**
Pregnant women	-	-
Lactating women	-	-
Renal impairment	-	-
Hepatic impairment	-	-
Cardiac impairment	-	-
Subpopulations with genetic polymorphisms	-	-
Immuno-compromised	-	-

Table SIII.24. Exposure in Special Populations (Total), All Formulations

Total population: Not available		
	Persons	**Person-time (years)**
Pregnant women	-	-
Lactating women	-	-
Renal impairment	-	-
Hepatic impairment	-	-
Cardiac impairment	-	-
Subpopulations with genetic polymorphisms	-	-
Immuno-compromised	-	-

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Limitations of Adverse Drug Reaction Detection Common to Clinical Trial Development Programmes

Table SIV.1. Ability to Detect Adverse Reactions (Limitation of Trial Programme), Oral Olanzapine and RAIM

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
That are rare	Approximately 13 750 adult and adolescent patients have been exposed over the entire clinical programme	For adults, not applicable due to extensive clinical experience. For patients <18 years old, there are limited data from the clinical trial programme and limited real world clinical experience as the product is not approved for use in the EU (only approved in this age group in 3 countries).
Due to prolonged exposure	A total of 659 adult patients have been exposed to olanzapine for at least 2 years or longer. A total of 58 adolescent patients have been exposed to olanzapine for at least 1 year or longer.	For adults, not applicable due to extensive clinical experience. For patients <18 years old, there are limited data from the clinical trial programme and limited real world clinical experience as the product is not approved for use in the EU (only approved in this age group in 3 countries).
Due to cumulative effects	There is no evidence of cumulative effects with olanzapine, such as specific organ toxicity.	No cumulative effects were identified during the clinical development programme. Due to the relatively short duration of clinical trials by design, the clinical trial programme was not tailored to detect cumulative effects. However, after >42 million postmarketing exposures, and after 17 years on the market, there has been no evidence of any specific organ toxicity due to cumulative effects.
That have a long latency	There is no long-term follow-up information following exposure in clinical trials.	It is unknown, from clinical trial data, if ADRs occurring with long latency could occur after exposure to olanzapine. However, after >42 million postmarketing exposures and over 17 years of real-world experience on the market, there has been no signal with respect to adverse effects of long latency.

Abbreviations: ADR = adverse drug reaction; RAIM = rapid-acting intramuscular.

Table SIV.2. Ability to Detect Adverse Reactions (Limitation of Trial Programme), Olanzapine LAI

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
That are rare	Approximately 2054 adult patients have been exposed over the entire clinical program.	After >57 000 global postmarketing exposures, and after >5 years on the market in the EU, there has been no evidence of any rare AEs not previously identified with treatment with olanzapine LAI. The characterization of the relatively uncommon AE of post-injection syndrome events was completed in the postmarketing observational study F1D MC-B034.
Due to prolonged exposure	A total of 691 adult patients have been exposed to olanzapine LAI for at least 2 years. A long term open-label safety study exposed patients to olanzapine LAI for up to 6 years of treatment without identification of AEs specific to long term exposure.	After >57 000 global postmarketing exposures, and after >5 years on the market in the EU, there has been no evidence of any specific AEs due to prolonged exposure.to olanzapine LAI.
Due to cumulative effects	There is no evidence of cumulative effects with olanzapine, such as specific organ toxicity.	No cumulative effects were identified during the clinical development program. In a long term open-label safety study steady-state olanzapine plasma concentrations remained consistent over time, with no evidence of continuing accumulation of olanzapine over the course of 6 years of treatment. After >57 000 post-marketing exposures, and after >5 years on the market, there has been no evidence of any specific organ toxicity due to cumulative effects.
That have a long latency	There is no long-term follow-up information following exposure in clinical trials.	It is unknown from clinical trial data if ADRs occurring with long latency could occur after exposure to olanzapine LAI. However, after >57 000 postmarketing exposures and >5 years of real-world experience on the market, there has been no signal with respect to adverse effects of long latency.

Abbreviations: ADR = adverse drug reaction; AE = adverse event; LAI = long-acting injection.

SIV.2. Effect of Exclusion Criteria in the Clinical Trial Development Plan

All Formulations

In the olanzapine (oral, rapid-acting intramuscular [RAIM], and long-acting injection [LAI]) clinical development programme, the primary population studied was adults aged 18 years and older. Patients 12 to 17 years old have also received oral olanzapine in clinical trials.

All studies generally used a common set of exclusion criteria, most of which were intended to ensure safety and minimize risk in a research setting. As the product has been approved and

marketed for >17 years, these criteria have changed over this time as a result of the identification of new safety signals. In general, the following have been excluded from olanzapine studies.

- Patients with serious acute medical conditions,
- Patients with a history of a seizure disorder without a clear, resolved aetiology,
- Patients with serious hepatic or renal impairment,
- Patients with leukopenia,
- Patients with increased serum prolactin prior to treatment,
- Patients who are actively suicidal,
- Patients with ongoing alcohol or drug dependence/abuse,
- Patients who were pregnant or breastfeeding,
- A number of medications including primarily medications with psychoactive effects that could confound efficacy analyses (for example, antidepressants or antipsychotics) and medications that could have unwanted pharmacodynamics or other interactions with olanzapine.

Over the course of greater than 17 years that olanzapine has been on the market, and in light of the extensive postauthorisation experience with >42 million estimated postmarketing patient exposures worldwide, including the completion of observational pharmacoepidaemiology studies investigating specific potential risks such as sudden cardiac death, the preauthorisation phase population limitations are either less relevant, or have been adequately addressed in the labelling, or have not highlighted any safety concerns in clinical practice.

Table SIV.3. Exclusion Criteria that will Remain as Contraindications

Criteria	Implications for Target Population
Hypersensitivity	In patients known to be hypersensitive to olanzapine or other constituents of the product, severe allergic reactions may occur.
Patients with known risk of narrow-angle glaucoma	In patients with narrow angle glaucoma, an anticholinergic effect of olanzapine may worsen glaucoma.

Table SIV.4. Exclusion Criteria that are NOT Proposed to Remain as Contraindications

Criteria	Reason for Being an Exclusion Criterion	Justification for Not Being a Contraindication
Patients with a history of seizure disorder	Ensure safety and minimize risk in a research setting.	The SmPC includes an appropriate special warning and precautions for use. There is no evidence, from both the clinical development programme and after extensive postmarketing experience, that olanzapine should be contraindicated in patients with this condition, or that the absence of such a contraindication imposes an increased risk.
Patients with serious hepatic or renal impairment	Ensure safety and minimize risk in a research setting.	The SmPC includes an appropriate special warning and precautions for use. There is no evidence, from both the clinical development programme and after extensive postmarketing experience, that olanzapine should be contraindicated in patients with this condition, or that the absence of such a contraindication imposes an increased risk.
Patients with leukopenia/neutropenia	Ensure safety and minimize risk in a research setting.	The SmPC includes an appropriate special warning and precautions for use. There is no evidence, from both the clinical development programme and after extensive postmarketing experience, that olanzapine should be contraindicated in patients with this condition, or that the absence of such a contraindication imposes an increased risk.
Patients with increased serum prolactin	Ensure safety and minimize risk in a research setting.	The SmPC includes an appropriate special warning and precautions for use. There is no evidence, from both the clinical development programme and after extensive postmarketing experience, that olanzapine should be contraindicated in patients with this condition, or that the absence of such a contraindication imposes an increased risk.
Patients who are actively suicidal	Ensure safety and minimize risk in a research setting.	The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.
Patients with ongoing alcohol or drug dependence/abuse	Ensure safety and minimize risk in a research setting. Could confound efficacy/safety analyses.	In nonclinical and clinical trial experience, as well as after extensive postmarketing experience, there is no evidence of abuse potential.

Exclusion Criteria that are NOT Proposed to Remain as Contraindications

Criteria	Reason for Being an Exclusion Criterion	Justification for Not Being a Contraindication
Patients who were pregnant or breastfeeding	Ensure safety and minimize risk in a research setting.	The SmPC includes pregnancy/lactation information. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition, or postnatal development. To date, clinical trial data and extensive postmarketing experience have not raised a signal or concern warranting a contraindication. Olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Patients should be advised not to breastfeed an infant if they are taking olanzapine.
Patients taking medications with psychoactive effects	Could confound efficacy/safety analyses.	The SmPC includes drug interaction information. There appears to be no evidence, after extensive postmarketing experience, of a specific safety concern warranting a contraindication.
Patients taking medications that could have unwanted pharmacodynamic or other interactions with olanzapine	Ensure safety and minimize risk in a research setting. Could confound efficacy/safety analyses.	The SmPC includes drug interaction information. To date, clinical trial data and extensive postmarketing experience have not raised a specific concern warranting a contraindication.

Abbreviation: SmPC = summary of product characteristics.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Prior to exposure in the marketplace, data with respect to children, elderly, patients who are pregnant or breastfeeding, patients with renal or hepatic impairment, patients with other relevant comorbidities, or patients of different racial or ethnic origin were considered limited. However, olanzapine has now been used in clinical practice for over 17 years. The cumulative number of patient exposures is estimated to be over 42 million patients in all age and gender groups, with and without pre-existing conditions for long periods of time. Oral olanzapine has an estimated 28 million patient-years of exposure. Due to the late stage in its lifecycle and the vast real-world clinical experience with the product, knowledge of the safety profile of olanzapine today exceeds any limitations of the clinical trial development programme.

SIV.3.1. Children

Oral Olanzapine or Rapid-Acting Intramuscular (RAIM)

There are no data for patients <18 years of age for all formulations in the molecules original preauthorisation phase. Since this time the preauthorisation phase, the population <18 years of age has been studied with the oral formulation.

Olanzapine is not licensed for use in patients <18 years of age in the European Union (EU); therefore, it is considered off-label use. Data indicate that olanzapine is being used to treat patients <18 years of age as considered necessary and appropriate by the prescribers for individual patients under their care. Olanzapine use in patients <18 years of age is approved in 3 countries and the use in this age group accounts for approximately 2% of olanzapine use globally.

Spontaneous adverse event (AE) reports within these populations have been assessed periodically as part of Lilly's ongoing safety surveillance processes as well as within the periodic safety update reports (PSURs) which have been compiled and submitted since 1997. No new specific safety issues have been identified relating to patients <18 years of age.

Olanzapine Long-Acting Injection (LAI)

The use of olanzapine LAI in the treatment of patients <18 years of age with schizophrenia has not been studied in clinical trials and Lilly does not intend to conduct studies with olanzapine LAI in patients <18 years of age. The SmPC indicates that the safety and efficacy of olanzapine LAI has not been established in patients younger than 18 years of age. Postmarketing use of olanzapine LAI in the treatment of patients <18 years of age has been reported in 6 patients (Section SV1.6.2.).

SIV.3.2. Elderly

Oral Olanzapine and Rapid-Acting Intramuscular (RAIM)

Postmarketing olanzapine exposure in patients >65 years old includes approximately 6.9 million patients. There are limited data for the population ≥76 years of age (with the exception of studies of dementia-related psychosis). Spontaneous AE reports within these populations have been assessed periodically as part of Lilly's ongoing safety surveillance processes as well as within the PSURs which have been compiled and submitted since 1997. No new specific safety issues have been identified relating to the elderly patient populations.

Elderly patients have not been excluded from oral olanzapine trials. A total of 174 patients ≥65 years of age have been enrolled in olanzapine clinical trials. While results indicated a similar safety profile of olanzapine in elderly patients with schizophrenia compared with younger patients with schizophrenia, a different safety profile was suggested in elderly patients with dementia-related psychosis as compared with younger patients.

The summary of product characteristics (SmPC) warning/precaution section contains the statement: "Olanzapine is not approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident."

Olanzapine Long-Acting Injection (LAI)

Only 17 patients have been enrolled in olanzapine LAI clinical trials at ≥65 years of age. The SmPC includes a statement that olanzapine LAI has not been systematically studied in elderly patients and is not recommended for treatment in the elderly population unless a well-tolerated and effective dose regimen using oral olanzapine has been established. Olanzapine LAI is not recommended to be started in patients >75 years or for the treatment of patients with dementia-related psychosis. An explanation about the risk of cerebrovascular AEs among elderly patients with dementia is included in the SmPC.

SIV.3.3. Pregnant or Breastfeeding Women

All Formulations

Women who were pregnant or breastfeeding and women of childbearing potential not using a medically accepted means of contraception (all formulations and indications) were excluded. However, in 1 study with 6 healthy, lactating women who were given oral olanzapine, olanzapine was excreted in breast milk. Mean infant exposure (mg/kg) at steady state was estimated to be 1.8% of the maternal olanzapine dose (mg/kg).

Spontaneous AE reports within these populations have been assessed periodically as part of Lilly's ongoing safety surveillance processes as well as within the PSURs which have been compiled and submitted since 1997. No new specific safety issues have been identified relating to pregnant or breastfeeding women.

SIV.3.4. Patients with Hepatic Impairment

All Formulations

Transient, asymptomatic elevations of hepatic aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) have been seen commonly, especially in early treatment. Caution should be exercised and follow-up organised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with preexisting conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicines. In cases where hepatitis (including hepatocellular, cholestatic, or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

SIV.3.5. Patients with Renal Impairment

All Formulations

Patients with renal impairment have been studied during the clinical trial development programme. In patients with renal impairment (creatinine clearance <10 mL/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 vs 32.4 hours) or clearance (21.2 vs 25.0 L/hour). A mass balance study showed that approximately 57% of radiolabelled olanzapine appeared in urine, principally as metabolites.

SIV.3.6. Patients with Other Relevant Comorbidities

All Formulations

Exclusion criteria have prevented olanzapine from being extensively studied in patients with comorbid disease. Although no studies in patients with diabetes or metabolic syndrome (obesity, hypertension, dyslipidaemia, and glucose intolerance) have been completed, the increased prevalence of diabetes and metabolic syndrome in patients diagnosed with schizophrenia or bipolar disorder has been described for many years (Bushe and Holt 2004). The risk of diabetes in patients diagnosed with schizophrenia is elevated compared with that of the general population. In patients diagnosed with schizophrenia, the lifetime prevalence rate of diabetes was 11.5% and the current prevalence rate was 10.9% (Argo et al. 2011).

Patients with schizophrenia or bipolar disorder have an increased risk of metabolic syndrome. Metabolic syndrome was found to be present in 51.6% of women and 36.0% of men with schizophrenia, while metabolic syndrome was present in 25.1% and 19.7% of healthy women and men, respectively (McEvoy et al. 2005).

Psychotropic drugs prescribed to patients with schizophrenia or bipolar disorder can induce or exacerbate some modifiable risk factors associated with diabetes (Newcomer 2006). Weight gain, hypertension, hyperglycaemia, and diabetes are all potential adverse effects associated with antipsychotic treatment. Antipsychotic medications are also associated with metabolic effects including alterations in plasma of total cholesterol, triglycerides, and glycosylated haemoglobin (Lieberman et al. 2005).

SIV.3.7. Patients with a Disease Severity Different from the Inclusion Criteria in the Clinical Trial Population

All Formulations

Not relevant.

SIV.3.8. Subpopulations Carrying Known and Relevant Polymorphisms

All Formulations

Not relevant.

SIV.3.9. Patients of Different Racial and/or Ethnic Origin

All Formulations

In clinical trials, examination of the population subset race did not reveal any differential responsiveness on the basis of this subgrouping. In vivo studies have shown that exposures are similar among Japanese, Chinese, and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

SIV.4. Conclusions on the Populations Not Studied and other Limitations of the Clinical Trial Development Programme

Table SIV.5. Safety Concerns due to Limitations of the Clinical Trial Programme

		Outstanding Concern?
Safety Concern	**Comment**	**Yes/No**
None		

Module SV. Postauthorisation Experience

SV.1. Action Taken by Regulatory Authorities and/or Marketing Authorisation Holders for Safety Reasons

Since the last European Union (EU) Risk Management Plan (RMP), no significant actions have been taken, or are proposed, as a result of new safety information.

Table SV.1. Detailed Description of Actions Taken since Last Update to this Module

Safety Issue: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	
Background to Issue	Cumulative review on drug reaction with eosinophilia and systemic symptoms (DRESS) based on case reports in EudraVigilance and from published case reports in the literature requested by PRAC on 08 December 2015
Evidence Source	Lilly database
Action Taken	DRESS text added to Company Core Data Sheet (CCDS) in warnings and precautions and spontaneous ADR section on 26 January 2016. Related SmPC and PL updates pending. On 10 May 2016, FDA issued a Drug Safety Communication warning about the risk of DRESS with olanzapine and mandated addition of a new warning to the drug labels for all olanzapine-containing products that describes this severe condition known as DRESS.
Countries Affected	Global impact
Date(s) of Action	Global label updates initiated following CCDS update. Timing of local updates proceeding according to local requirements.

Abbreviations: ADR = adverse drug reaction; FDA = Food and Drug Administration; PL = patient leaflet; PRAC = Pharmacovigilance Risk Assessment Committee; SmPC = Summary of Product Characteristics.

Table SV.2 through Table SV.9 summarise cumulative significant regulatory actions that have been taken since the International Birth Date for olanzapine. Regulatory actions are presented by safety concern.

Table SV.2. Cumulative List of Actions Taken, Metabolic, All Formulations

Metabolic			
Countries	**Action Taken**	**Comment**	**Date(s)**
EU, Iceland, Norway	Metabolic monitoring frequency examples added to the Special Warnings and Precautions section of the SmPC.	Label update requested by the CHMP as a result of assessment of PSURs 24 and 25 and RMP v3.	CHMP request January 2011; Variation submitted April 2011; Variation approved November 2011
US	Significant updates made to the Warnings for hyperglycaemia, hyperlipidaemia, and weight gain. Updates to the Warnings for hyperprolactinaemia. As part of this action, a new medication guide was created – this guide is considered a REMS.		Submitted in March 2009
EU, Iceland, Norway	The Special Warnings and Precautions Section of the SmPC was updated to align with the texts of the recently approved Depot formulation with respect to recommendations for monitoring patients for glucose, lipids and weight as well as promoting awareness of appropriate metabolic monitoring by distributing guidelines.	Requested by the CHMP.	Variation submitted November 2008; Variation approved March 2009
Taiwan	MoH requested updates to the Special Warnings and Precautions concerning hyperglycaemia and diabetes.		Initiated: 29 August 2008 Approved: 02 February 2009
EU, Iceland, Norway	Submitted label updates to the Undesirable Effects Section of the SmPC to include new data on the extent of changes observed over time in lipids, glucose and bodyweight in both adults and adolescents.	New pooled analyses of glucose, lipids, and weight gain using Lilly longer term clinical trial data in the adult and adolescent patient populations were conducted.	Variation submitted March 2008; Variation approved July 2008
US	Submitted label updates.		December 2007
Rest of World	Submitted label updates.		Q1 2008
US	Submitted Changes Being Effected supplement. Sent Dear Healthcare Professional letter.	Placebo- and comparator-controlled data analyses regarding glucose, lipids and weight gain.	October 2007
EU, Iceland, Norway	Submitted label updates to the Special Warnings and Precautions and Undesirable Effects Sections of the SmPC.		Variation submitted September 2007; Variation approved January 2008
Rest of World	Submitted label updates.		Changes submitted between April and August 2007

Cumulative List of Actions Taken, Metabolic, All Formulations

Metabolic			
Countries	**Action Taken**	**Comment**	**Date(s)**
US	Submitted label updates.	New analyses for fasting Triglyceride and cholesterol data.	19 September 2006
EU, Iceland, Norway	Submitted label updates to the Special Warnings and Precautions and Undesirable Effects Sections of the SmPC.		Variation submitted April 2007; Variation approved September 2007
Rest of World	Submitted label updates.		Q3 2007
US	During label negotiations with the FDA for approval of bipolar maintenance indication, FDA requested the following revisions to the existing USPI text on Hyperglycaemia and Diabetes Mellitus, and requested that this paragraph be moved to a more prominent location within the WARNINGS section. (Deletions in strikethrough, and additions underlined.). These changes are in line with the Wording found in the core data sheet. ~~The available data are insufficient to provide reliable estimates of differences in hyperglycaemia related adverse event risk among the marketed atypical antipsychotics.~~ Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at ~~baseline~~ the beginning of treatment and periodically during treatment.	Changes initiated by the FDA. A Dear Doctor Letter was issued by Lilly informing prescribers of these changes and distributed on 01 March 2004.	DDL sent March 2004; Label change submitted September 2004
Japan	Changes regarding glucose related events were made to the Japan label as requested by the MHLW.		April 2002
EU, Iceland, Norway	At CPMP request following review of PSUR 5, a number of safety changes were submitted including the addition of the terms “acidosis” and “coma” with respect to hyperglycaemia; and reference to cases of hepatitis in the Special Warnings and Precautions Section.		Variation submitted June 2000 Variation approved December 2000

Cumulative List of Actions Taken, Metabolic, All Formulations

Metabolic			
Countries	**Action Taken**	**Comment**	**Date(s)**
EU, Iceland, Norway	Following PSUR3, a Type II variation was submitted to add a warning concerning hyperglycaemia/diabetes to the SmPC. During the review of this variation, CPMP requested the addition of a general statement of care on the need to monitor schizophrenic patients during the early weeks of treatment in the Warnings Section. Patients should be closely monitored during this period, since an improvement in the patient's clinical condition may take several days to some weeks.		Variation submitted December 1998; Variation approved July 1999

Abbreviations: CHMP = Committee for Medicinal Products for Human Use; DDL = Dear Doctor Letter; EU = European Union; FDA = Food and Drug Administration; MHLW = Ministry of Health, Labour, and Welfare; MoH = Ministry of Health; PSUR = periodic safety update report; Q = quarter; REMS = Risk Evaluation and Mitigation Strategy; RMP = risk management plan; SmPC = summary of product characteristics; US = United States; USPI = United States Package Insert; v = version.

Table SV.3. Cumulative List of Actions Taken, Cardiovascular, All Formulations

Cardiovascular			
Countries	**Action Taken**	**Comment**	**Date(s)**
Japan	Addition of 'electrocardiogram QT prolonged' in the section of adverse drug reactions.	Due to the accumulation of spontaneous cases of suspected QT prolongation, spontaneous labelling update was suggested by PMDA.	Discussion with PMDA was held December 2012. Label update was completed in April 2013
Canada	Health Canada requested that the Product Monograph be updated to include the addition of a warning concerning QT intervals.	During this review Health Canada requested class labelling for all atypicals regarding the risk related to arrhythmia as a warning and precautions.	Health Canada requests received August 2010; Label change submitted September 2010; Label approved October 2010
US	FDA requested mortality data from Lilly studies to evaluate the relationship between exposure to atypical antipsychotic drugs and risk of sudden cardiac death. FDA issued Complete Response (CR) Letter to Lilly Sudden Cardiac Death prior approval supplement and did not approve. Lilly withdrew Sudden Cardiac Death PAS and communicated this in a formal letter.	None	Information request letter dated March 2010 FDA formal letter (CR) July 2012 Lilly submitted withdrawal letter July 2013
EU, Iceland, Norway	Addition of a new warning regarding sudden cardiac death	Label updates initiated by Lilly following updates to the olanzapine CDS.	Variation submitted August 2009; Variation approved December 2009
US			Submitted October 2009; Rejected July 2012
Switzerland			Submitted October 2009 Approved September 2010
Rest of world			Submissions started in January 2010, with timing dependent on reference country approval date
New Zealand	Medsafe request to include additional information on risk of QT prolongation. Revised wording proposed for Interactions and Adverse Effects Sections.	Medsafe requested label change following their review of data sheets for antipsychotic medications.	Medsafe request: March 2009 Wording agreed: November 2009 Implemented: March 2010

Cumulative List of Actions Taken, Cardiovascular, All Formulations

Cardiovascular			
Countries	**Action Taken**	**Comment**	**Date(s)**
EU, Iceland, Norway	A type II variation was submitted to update the Special Warnings and Precautions and Undesirable Effects Sections of the SmPC with regard to information about QTc prolongation.	A safety review for QTc prolongation was submitted in July 2004 by Lilly upon request from the EMA.	Variation submitted February 2005; Variation approved August 2005

Abbreviations: CDS = Core Data Sheet; CHMP = Committee for Medicinal Products for Human Use; CR = Complete Response; EMA = European Medicines Agency; EU = European Union; FDA = Food and Drug Administration; PMDA = Pharmaceuticals and Medical Devices Agency, Japan; SmPC = summary of product characteristics; US = United States.

Table SV.4. Cumulative List of Actions Taken, Dermatological, All Formulations

Dermatological			
Countries	**Action Taken**	**Comment**	**Date(s)**
Global	A Type lB variation was submitted to add DRESS as an adverse event to the SmPC.	A safety review for DRESS was submitted in December 2015 by Lilly upon request from the EMA.	Variation submitted June 2016; On 10 May 2016, FDA issued a Drug Safety Communication warning about the risk of DRESS with olanzapine and mandated addition of a new warning to the drug labels for all olanzapine-containing products

Abbreviations: DRESS = drug reaction with eosinophilia and systemic symptoms; EMA = European Medicines Agency; FDA = Food and Drug Administration; SmPC = summary of product characteristics.

Table SV.5. Cumulative List of Actions Taken, Class Labelling, All Formulations

Class Labelling			
Countries	**Action Taken**	**Comment**	**Date(s)**
Canada	Class labelling requested regarding cardiometabolic risks in paediatrics, and the risk of VTE.	Health Canada requested the updates based on signal assessments conducted on atypical antipsychotics.	Request received November 2012; Label change submitted December 2012
EU, Iceland, Norway	Class labelling requested regarding the risk of neonatal drug withdrawal syndrome.	Request received following PhVWP/CHMP review.	Request received June 2011; Variation submitted August 2011; Variation approved October 2011
Australia		Label update initiated by Therapeutic Goods Administration.	Request received March 2011; Approved: June 2011
US		USPI update initiated by FDA as antipsychotic class labelling change and based upon FDA review of AERS data through October 2008.	Request received: August 2010; Lilly responded with prior approval labelling submission September 2010 and followed by discussions with FDA leading to FDA Approval Letter dated December 2010.
Rest of world		Label updates following USPI updates per local MoH request	Submissions started in select countries in January 2011, with exact timing depending on US approval date.
Canada		In addition to the neonatal class labelling, Health Canada also recommended updates to the entire class of antipsychotics, based on signal assessments of atypical antipsychotics and diabetic ketoacidosis (DKA), of atypical antipsychotics and hyperprolactinaemia and bone mineral density (BMD), and of atypical antipsychotics and risk of agranulocytosis.	Request received June 2011; Notifiable Change on July 2011; No Objection Letter issued by Health Canada for updated Product Monograph on August 2011.

Cumulative List of Actions Taken, Class Labelling, All Formulations

Class Labelling			
Countries	**Action Taken**	**Comment**	**Date(s)**
Japan	PMDA requested class labelling regarding cautions for hypoglycaemia and agranulocytosis.	None	December 2009
US	Added warning for leukopenia, neutropenia, and agranulocytosis to USPI.	FDA mandated class labelling for all antipsychotics.	Requested: April 2009 Label Change Approved: August 2009
Taiwan	According to randomised controlled trials and retrospective cohort studies in elderly patients with dementia-related psychosis, conventional and atypical antipsychotic drugs treatment is associated with higher incidence of death compared with placebo.	MoH mandated request to International Research-Based Pharmaceutical Manufacturers Association.	August 2008
South Africa	Class labelling requested regarding a new warning on hyperglycaemia and diabetes mellitus.	Upon request of the MoH.	Submitted March 2005
US		Request followed review conducted by FDA of available data.	FDA request received September 2003; Labelling change submitted September 2003
New Zealand		None	MoH request received February 2002; Label changes submitted June 2003
Canada		The change was initiated by Health Canada as part of an ongoing review of safety data into this class of antipsychotics.	Approved March 2003
Australia		Request made following the mandate by the Japanese MHLW to expand the olanzapine label regarding hyperglycaemia and diabetes, of which Lilly advised the Australian MoH.	Communications between April 2002 and August 2002

Abbreviations: AERS = Adverse Event Reporting System; BMD = bone mineral density; CHMP = Committee for Medicinal Products for Human Use; DKA = diabetic ketoacidosis; EU = European Union; FDA = Food and Drug Administration; MHLW = Ministry of Health, Labour, and Welfare; MoH = Ministry of Health; PhVWP = Pharmacovigilance Working Party; PMDA = Pharmaceuticals and Medical Devices Agency, Japan; US = United States; USPI = United States Package Insert; VTE = venous thromboembolism.

Table SV.6. Cumulative List of Actions Taken, Post-Injection Syndrome, Olanzapine LAI

Post-Injection Syndrome, Olanzapine LAI			
Countries	**Action Taken**	**Comment**	**Date(s)**
US	On 18 June 2013 the FDA issued a Drug Safety Communication stating that the agency was 'investigating two unexplained deaths in patients who received an intramuscular injection of the antipsychotic drug Zyprexa Relprevv (olanzapine LAI)'. The patients died 3-4 days after receiving an appropriate dose of the drug, well after the 3-hour post-injection monitoring period required under the Zyprexa Relprevv REMS. Both patients were found to have very high olanzapine blood levels after death. Lilly issued a Dear Health Care Provider letter to all participants in the US Zyprexa Relprevv Patient Care Program informing them of the details of the cases. As a result of discussions with the FDA, Lilly conducted an animal study to explore potential post mortem redistribution of olanzapine concentrations following treatment with olanzapine LAI. These data demonstrated an increase in olanzapine blood concentrations after death in dogs administered olanzapine pamoate monohydrate, thus providing evidence for post-mortem redistribution of olanzapine.	None	Met with FDA on 22 May 2013; FDA issued Drug Safety Communication on 18 June 2013; Lilly sent DHCP letter on 24 June 2013; nonclinical study was initiated 07 March 2014 and was submitted to the FDA 30 September 2014. On 23 March 2015 the FDA issued Drug Safety Communication to report that their review of a study undertaken to determine the cause of elevated blood LAI levels in these two patients was inconclusive. The FDA did not recommend any changes to the current prescribing or use of LAI.

Abbreviations: FDA = Food and Drug Administration; LAI = long-acting injection; REMS = Risk Evaluation and Mitigation Strategy.

Table SV.7. Cumulative List of Actions Taken, Concomitant Use of Benzodiazepines, Haemodynamic Effects, RAIM

Concomitant Use of Benzodiazepines, Haemodynamic Effects, RAIM			
Countries	**Action Taken**	**Comment**	**Date(s)**
Australia	In addition to Lilly's initiated label updates regarding the concomitant use of benzodiazepines, subsequent to this submission, the Therapeutic Goods Administration requested Lilly to highlight information that the simultaneous use of intramuscular olanzapine and parenteral benzodiazepines is not recommended due to the potential for excessive sedation and cardiorespiratory depression by including a Contraindication to this effect.	Warning updated regarding the concomitant use of benzodiazepines.	February 2011
EU, Iceland, Norway	Type II variation submitted to update the Special Warnings and Precautions Section of the SmPC.		Variation submitted September 2010; Variation approved February 2011
South Africa	In response to the affiliate's submission of multiple olanzapine CDS changes the MCC requested updates to the Contraindications and Warnings Sections of the label.		September 2005
US	Haemodynamic Effects: Addition of safety data on hypotension and bradycardia associated with intramuscular olanzapine for injection in premarketing studies was added to PRECAUTIONS (general)	Change initiated by Lilly.	March 2004
EU, Iceland, Norway, Australia, New Zealand, South Africa, Switzerland	Label changes were made in the EU, Iceland and Norway and Canada with information relating to the safe use of olanzapine IM. In addition, Dear Healthcare Professional letters were sent in the EU, Australia, New Zealand, South Africa, and Switzerland to provide clarity on the safe use of olanzapine IM. Following discussion with Health Canada, Lilly proactively distributed olanzapine IM safety-related educational materials to health care professionals in Canada.	None	Label changes submitted during August and September 2004 Dear Doctor Letters sent between September and December 2004
EU, Iceland, Norway	Changes to the SmPC relating to the safe use of olanzapine IM included updates to sections 4.2, 4.4, 4.5 and 4.8 to provide increased clarity and emphasis about the maximum daily dose and the recommended proper use including the concomitant use with other medicinal products such as benzodiazepines, as well as the need for appropriate observation following treatment.	None	Variation submitted October 2004; Variation approved February 2005

Abbreviations: CDS = core data sheet; DHCP = Dear Healthcare Professional Letter; EU = European Union; FDA = Food and Drug Administration; IM = intramuscular; MCC = Medicines Control Council; PSUR = periodic safety update report; RAIM = rapid-acting intramuscular; SmPC = summary of product characteristics; US = United States.

Table SV.8. Cumulative List of Actions Taken, Elderly Patients with Dementia, All Formulations

Elderly Patients with Dementia			
Countries	**Action Taken**	**Comment**	**Date(s)**
Rest of World	Submitted label updates	Safety experience in elderly patients with dementia-related psychosis.	Q2 2006
Korea Food and Drug Administration (KFDA)	Korean label change as follows: 1. Warning 2. Olanzapine is not approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration.	Initiated by KFDA – Consolidated label change order.	March 2009
Japan	Package insert updated with the following: Paralytic ileus added in the clinically adverse reaction section. Revised the language concerning the risk of increased mortality in the elderly with dementia to include typical antipsychotics.	PMDA requested label changes regarding paralytic ileus and risk of increased mortality in elderly patients with dementia.	January 2009
South Africa	Label changed with additions to Warnings regarding Discontinuation reactions, Fatalities associated with IM use, and Safety experience in elderly patients with dementia-related psychosis.		Recommendations received October and August 2005 Finalized December 2006
Canada	Added class labelling to Product Monograph following public advisory and Dear Health Care Professional letter issued by Health Canada.		Q2 2006

Cumulative List of Actions Taken, Elderly Patients with Dementia, All Formulations

Elderly Patients with Dementia			
Countries	**Action Taken**	**Comment**	**Date(s)**
Japan	Lilly informed health care professionals in Japan of the FDA Talk Paper of 11 April 2005: "FDA Issues Public Health Advisory for Antipsychotic Drugs used for Treatment of Behavioural Disorders in Elderly Patients." Following the above letter to health care professionals, Lilly voluntarily changed the local labelling (Other Precautions section) in this matter.		Health care professionals letters sent April 2005; Label updated July 2005
US	FDA issued a Public Health Advisory to alert health care providers, patients, and patient caregivers to new safety information on the use of atypical antipsychotic drugs and the risk of increased mortality in elderly patients with dementia-related psychosis. In addition, FDA also requested that Lilly issue a Dear Healthcare Professional letter at the time of the labelling change. Final Printed Labelling for olanzapine based on FDA's 17 August 2005 letter requesting additional changes to our Boxed Warning, Bolded Warning, and Geriatric Use section of labelling related to increased mortality in elderly patients with dementia-related psychosis.		Public alert issued April 2005; DHCP letter sent May 2005; Label change submitted May 2005
EU, Iceland, Norway	Following review by the rapporteur, changes were requested to be made to the SmPC. The changes were to add warnings on mortality in elderly patients with dementia related psychosis and/or disturbed behaviours and cerebrovascular adverse events.	Following the initiation of Type II variation to include changes relating to CVAE and Mortality, this was changed to an Urgent safety Restriction upon the recommendation of the CPMP on 24 February 2004 and implemented on 02 March 2004. A Dear Doctor Letter was distributed to prescribers in the EU on 08 March 2004 (appended). Identical label changes were also made to the SmPCs for Norway and Iceland simultaneously and Accession countries labels were updated in line with these changes.	Variation submitted February 2004; Variation approved July 2004

Cumulative List of Actions Taken, Elderly Patients with Dementia, All Formulations

Elderly Patients with Dementia			
Countries	**Action Taken**	**Comment**	**Date(s)**
Australia	The text in line with that of the Core data sheet regarding CVAE and mortality was added to the Australian Product Information on 01 March 2004. A Dear Doctor Letter informing prescribers of these changes was sent out on 02 March 2004 (appended)	The Dear Doctor Letter was initiated by Lilly Australia.	March 2004
New Zealand	MoH were advised of the CVAE/Mortality in elderly patients with dementia related Core Data Sheet changes. The text used was identical to that in the CDS. This was added directly to the existing MoH Data Sheets.	A Dear Doctor letter was sent informing Physicians of the new information on 02 March 2004.	New Data Sheets dated 28 February 2004 formally submitted on 01 March 2004.
Switzerland	Swiss Medic requested on 10 March 2004 that changes to the SmPC for Switzerland relating to CVAE and mortality should be in line with the text agreed with the EMA for the EU (as highlighted above) and that a Dear Doctor Letter should be sent informing prescribers of these changes.	EU SmPC wording and Dear Doctor Letter utilised.	March 2004
Canada (Health Canada)	Lilly Canada submitted a Notifiable Change submission to update the Product Monograph with the new safety information from the Core Data Sheet (ie CVAE and mortality). A Dear Healthcare Professional Letter (DHPL) and Public Advisory (PA) were issued in Canada regarding CVAEs.	Health Canada requested Lilly Canada to issue a DHPL and PA on CVAEs to be consistent with Risperdal who were also requested to issue a DHPL on CVAEs in Canada in October 2002.	DHPL sent and PA issued March 2004
US	During label negotiations with the FDA for approval of the bipolar maintenance indication, FDA requested the addition of language on Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia in the WARNINGS section.	Changes initiated by the FDA. A Dear Doctor Letter informing prescribers about CVAE and Mortality in elderly patients was sent out proactively by Lilly on 26 January 2004.	DDL sent January 2004; Label change submitted February 2004

Abbreviations: CDS = core data sheet; CPMP = Committee for Proprietary Medicinal Products; CVAE = Cerebrovascular Adverse Event; DDL = Dear Doctor Letter; DHPL = Dear Healthcare Professional Letter; EU = European Union; FDA = Food and Drug Administration; IM = intramuscular; KFDA = Korean Food and Drug Administration; MoH = Ministry of Health; PA = public advisory; PMDA = Pharmaceuticals and Medical Devices Agency, Japan; Q = quarter; SmPC = summary of product characteristics; US = United States; USPI = United States Package Insert.

Table SV.9. Cumulative List of Actions Taken, Medication Error, All Formulations

Medication Error			
Countries	**Action Taken**	**Comment**	**Date(s)**
US	Dear Health Care Professional letter for Zyprexa was sent to physicians and pharmacies. Eli Lilly and Company has received reports, in the US, of medication dispensing or prescribing errors between Zyprexa (olanzapine) and the antihistamine Zyrtec (cetirizine HCl) marketed by Pfizer. These reports include instances where Zyprexa was incorrectly dispensed for Zyrtec and vice versa. Lilly had been in numerous discussions with FDA on this issue since November 2002 when Lilly had submitted a "Changes Being Effected Supplement" which provided for changes to the bottle label for Zyprexa to assist in reducing the potential for medication errors involving Zyprexa and Zyrtec.	None	Dear Health Care Professional letter for Zyprexa was sent in January 2005

Abbreviations: FDA = Food and Drug Administration; US = United States.

SV.2. Nonstudy Postauthorisation Exposure

SV.2.1. Method used to Calculate Exposure

Worldwide sales of olanzapine oral, olanzapine IM (rapid acting), and olanzapine LAI were obtained for the cumulative time period ending on 30 September 2013. The sales data include both Lilly brand olanzapine oral as well as generic olanzapine oral from other manufacturers. These data are the basis for calculating global patient exposure estimates for olanzapine. The methodology for estimating exposure for olanzapine oral and olanzapine IM (rapid acting) uses internal bulk sales data, samples distributed, IMS Midas days of therapy and standard units, IMS National Disease and Therapeutic Index data, IMS National Prescription Audit, and IMS age and gender data. A weighted average of the total possible days of therapy from the internal bulk sales data and the IMS Midas data was determined. The possible days of therapy were then factored by an average length of therapy and average courses of treatment, assumptions to determine the estimated patient exposure estimate for each country or region. In order to calculate patient exposure for olanzapine LAI, the cumulative product sales data are divided by estimates for average patient dose and average length of therapy in order to estimate the cumulative number of patients exposed to olanzapine LAI and the cumulative patient-years of exposure. The patient dosing and length of therapy information are obtained from the Zyprexa Relprevv (olanzapine LAI) patient care program registry being conducted in the USA. Other common assumptions, such as the amount of drug not ingested and the amount of product in inventory, were not included; thus, the resulting patient exposure estimates do not account for product that may not have reached patients.

SV.2.2. Exposure

Table SV.10. Postmarketing Exposure by Age Group and Gender

Olanzapine ORAL				
	Persons			
Age group (years)	Male	Female	Not Reported	Total[a]
0-17	488 000	219 000	7 000	715 000
18-64	17 911 000	12 330 000	152 000	30 393 000
≥65	2 340 000	4 526 000	37 000	6 905 000
Not Reported	196 000	151 860	93 000	441 000
Total[a]	20 936 000	17 228 000	291 000	38 456 000

[a] Totals may not sum due to independent rounding.

Table SV.11. Postmarketing Exposure by Indication

Indication	Persons	Exposure
N/A		

Abbreviation: N/A = not available.

Table SV.12. Postmarketing Exposure by Route of Administration

Route of Administration	Patients	Patient-Years
Olanzapine Oral	38 456 000	28 442 000
Olanzapine IM (rapid acting)	4 124 000	N/A
Olanzapine Long-Acting Injection	57 100	28 400

Abbreviations: IM = intramuscular; N/A = not available.

Table SV.13. Postmarketing Exposure by Dose

Indication	Persons	Exposure
N/A		

Abbreviation: N/A = not available.

Table SV.14. Postmarketing Exposure by Country/Region

Olanzapine Oral		
	Patients	**Patient-Years**
Europe	14 883 000	11 008 000
Japan	3 502 000	2 590 000
United States	12 983 000	9 602 000
Other Countries	7 085 000	5 240 000
Worldwide[a]	38 456 000	28 442 000
Olanzapine IM (Rapid Acting)		
	Patients	**Patient-Years**
Europe	665 000	N/A
Japan	25 000	N/A
United States	1 517 000	N/A
Other Countries	1 915 000	N/A
Worldwide[a]	4 124 000	N/A
Olanzapine Long-Acting Injection (LAI)		
	Patients	**Patient-Years**
Europe	50 000	24 101
United States	4700	2600
Other Countries	3400	1600
Worldwide[a]	57 100	28 400

Abbreviations: IM = intramuscular; N/A = not available.

[a] Worldwide totals may not sum due to independent rounding.

SV.3. Postauthorisation Use in Populations not Studied in Clinical Trials

Table SV.15. Postmarketing Use in Paediatric Populations

Estimated Use	Number	Comment on any Variation in Benefit or Risk from Overall Target Population
○ **Preterm newborns** ○ **Neonates (birth to 27 days)** ○ **Infants and toddlers (1 to 23 months)** ○ **Children (2 years to eg 11 years)** ○ **Adolescents (eg 12 to 18 years)**	-	Not available.
Data Source		
Method of Calculation		

Table SV.16. Postmarketing Use in Elderly Populations

Estimated Use	Number	Comment on any Variation from Overall Target Population
○ **65 – 74 years** ○ **75 – 84 years** ○ **85 + years**	Oral: 1992 (ages 60-69) RAIM: 511 (ages 65-79) LAI: 141 (ages >65) Oral: 1948 (ages 70-79) Oral: 2259 (ages 80+) RAIM: 497 (ages 80+)	None
Data Source: Oral: GPRD, Final study report for F1D-MC- B042; LAI: Final study report for F1D-MC-B034; RAIM: Final study report for Characteristics and Outcomes in Hospitalized Patients Treated with Intramuscular Antipsychotics: Analysis of a US Hospital Database		
Method of Calculation: Frequency from cohort of 20 954 patients exposed to olanzapine for F1D-MC-B042; count of patients enrolled for at least 1 injection in F1D-MC-B034 over age 65; Cohort of 2984 exposed to olanzapine RAIM for Characteristics and Outcomes in Hospitalized Patients Treated with Intramuscular Antipsychotics: Analysis of a US Hospital Database		

Abbreviations: GPRD = General Practice Research Database; LAI = long-acting injection; RAIM = rapid-acting intramuscular; US = United States.

Table SV.17. Postmarketing Use in Pregnant or Breast Feeding Women

Estimated Use	Number	Comment on any Variation from Overall Target Population
○ **Pregnant** ○ **Breastfeeding**	-	Not available.
Data Source		
Method of Calculation		

Table SV.18. Postmarketing Use in Patients with Hepatic Impairment

Estimated Use with Hepatic Impairment	Number	Comment on any Variation from Overall Target Population
○ **Mild** ○ **Moderate** ○ **Severe**	-	Not available.
Data Source		
Method of Calculation		

Table SV.19. Postmarketing Use in Patients with Renal Impairment

Estimated Use with Renal Impairment	Number	Comment on any Variation from Overall Target Population
○ **Mild** ○ **Moderate** ○ **Severe**	-	Not available.
Data Source		
Method of Calculation		

Table SV.20. Other Postmarketing Use

Estimated Use	Number	Comment on any Variation from Overall Target Population
○ **Mild** ○ **Moderate** ○ **Severe**	-	Not available.
Data Source		
Method of Calculation		

SV.4. Postauthorisation Off-Label Use

Table SV.21. Off-Label Use in European Union

Off-Label Category	Country	Source of Information	Comment
Not available.			

SV.5. Epidemiological Study Exposure

Table SV.22. Epidemiological Studies

Study Title and Study Type	Objective(s)	Population Studied	Duration	Number of Persons and Person Time	Comment
F1D-MC-B042: Risk of Cardiac Mortality (including Sudden Cardiac Death) in Atypical Antipsychotic Users (retrospective cohort)	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 3 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	UK adult population aged 18 years or older from the General Practice Research Database	1995 to November 2010	Olanzapine: 20 954 Non-user Psychiatric comparison group: 193 920 The matched general population comparison group 62 720 Cardiac Mortality Outcome – Olanzapine (current use): 26 765 Non-user Psychiatric comparison group: 201 055 The general population comparison group: 544 726	Final study report submitted with Olanzapine LAI (Pamoate) RMP v9.0 on 25 November 2011
F1D-MC-B034: Post-Injection Syndrome in Patients with Schizophrenia Receiving Olanzapine Long-Acting Injection (prospective cohort)	1. To estimate the incidence per injection and per patient of post- injection syndrome events in schizophrenia patients receiving olanzapine LAI 2. To further characterize the clinical presentation, including the outcomes of post-injection syndrome events 3. To identify potential risk factors associated with post-injection syndrome events 4. Characterise hospitalisation at baseline (previous 6- or 12-month) and postbaseline	Adult patients with schizophrenia whose physician has decided to treat with olanzapine LAI	07 April 2009 to 04 December 2015	3858 patients from 24 countries enrolled for a total of 103 505 injections	Final study report complete on 29 June 2016. Report in Annex 9.

Abbreviations: AMI = acute myocardial infarction; EU = European Union; ICU = intensive care unit; IM = intramuscular; LAI = long-acting injection; PCD = Perspective Comparative Database; PSUR = Periodic Safety Update Report; RAIM = rapid-acting intramuscular; REMS = Risk Evaluation and Mitigation Strategy; RMP = Risk Management Plan; SCD = sudden cardiac death; UK = United Kingdom; US = United States; v = version.

Module SVI. Additional EU Requirements

SVI.1. Potential for Harm from Overdose

Oral Olanzapine or Rapid-Acting Intramuscular

The lifetime risk of suicide attempt among patients with schizophrenia is approximately 50%, and the risk of completed suicide is 5% to 13% (Nyman and Johnson 1986; Meltzer and Fatemi 1995; Green et al. 2003; Palmer et al. 2005). In a study that examined suicide in patients with schizophrenia, most suicide attempts (81%) were made with medication overdose (Altamura et al. 2003).

There is limited clinical trial experience with olanzapine overdose. In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or electrocardiogram (ECG). Vital signs were usually within normal limits following overdoses.

During postmarketing, there have been reports of acute and chronic overdoses of olanzapine through routine pharmacovigilance. Very common symptoms reported in olanzapine overdose (>10% incidence) include tachycardia, agitation/ aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Other medically significant sequelae of olanzapine overdose include delirium, convulsion, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (<2% of overdose cases), and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg of oral olanzapine but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

Olanzapine Long-Acting Injection

The likelihood of overdose with olanzapine LAI is considered to be minimal, because it is administered by an HCP; however, 3 potential scenarios were considered: the patient obtains the drug directly from the pharmacy and administers it without an HCP; an HCP administers olanzapine LAI more frequently than recommended (eg, 405 mg every 2 weeks rather than every 4 weeks); or the patient takes oral antipsychotic medications (including oral olanzapine) while receiving olanzapine LAI.

Based on an analysis of SAEs, TEAEs, and discontinuations due to AEs in patients supplemented with oral olanzapine in an olanzapine LAI study, the addition of oral olanzapine to the existing olanzapine LAI regimen did not appear to significantly affect tolerability. However, the SmPC recommends that if oral olanzapine supplementation is clinically indicated, the total dose of olanzapine (olanzapine LAI plus oral olanzapine) should not exceed 20 mg/day.

Although the potential risk of overdose with suicidal intention exists with many marketed drug products, the risk is significantly reduced with injectable depot formulations, given their method of distribution and administration (Barnes and Curson 1994; Altamura et al. 2003). Reported cases of olanzapine overdose, potentially high concentrations of olanzapine have generally been well tolerated (Palenzona et al. 2004; Morgan et al. 2007).

SVI.2. Potential for Transmission of Infectious Agents

Oral Olanzapine

Based on extensive postmarketing experience, there does not appear to be a risk of transmission of infectious agents with olanzapine.

Olanzapine Long-Acting Injection and Rapid Acting Intramuscular

As with other injectable medications, there is a small risk for contamination resulting from the injection. This risk is minimal because the drug is administered by a HCP.

SVI.3. Potential for Misuse for Illegal Purposes

All Formulations

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behaviour, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Extensive postmarketing clinical experience does not suggest a potential for systematic misuse of olanzapine for illegal purposes. If stolen, like any drug, olanzapine has a potential for misuse.

SVI.4. Potential for Medication Errors

SVI.4.1. Description of Medication Errors during the Clinical Trial Programme

In the light of the extensive postauthorisation experience, with >42 million estimated postmarketing patient exposures worldwide, medication errors during clinical trials are considered less relevant. See Section SVI.4.4 for description of medication errors with marketed product.

Table SVI.1. Description of Medication Errors during the Clinical Trial Programme

Olanzapine				
Description of Error	Number of Occurrences	Analysis of Cause	Steps taken to Prevent	Comment
Not available.				

SVI.4.2. Preventive Measures for the Final Products Being Marketed

Section 6.4 of the SmPC includes special precautions for storage. In the olanzapine patient information leaflet (PIL), patients are informed to only take other medicines while taking olanzapine if their doctor tells them they can, particularly medications for Parkinson's disease, carbamazepine, fluvoxamine, or ciprofloxacin.

Oral Olanzapine

Patients are informed to swallow olanzapine tablets whole with water, not to take 2 doses in 1 day, and how to store olanzapine properly.

Olanzapine Long-Acting Injection/Rapid-Acting Intramuscular

The 2 intramuscular formulations of olanzapine have distinct packaging that clearly differentiates the products in a clinical setting. There are differences in trade name, the reconstitution process, injection dosage, volume, colour of suspension, size of needle, and size of vial. Additionally, the patient populations and the medical settings where the 2 drugs are administered also differ (acute agitation in an emergency room setting versus chronic, nonagitated patients in a routine clinical setting). Current postmarketing clinical experience does not suggest that this type of medication error has occurred.

SVI.4.3. Effect of Device Failure

Not applicable.

SVI.4.4. Reports of Medication Errors with the Marketed Products

Table SVI.2. Reports of Medication Errors with the Marketed Product(s)

Description of Error	Number of Occurrences	Analysis of Cause	Steps Taken to Prevent	Comment
RAIM Olanzapine				
Wrong dosing (route of administration, amount, frequency, schedule)	47	Patients received incorrect dose, route of administration, frequency, schedule, technique; prescribing and dispensing errors	SmPC clearly describes the proper dosing, frequency, and route of administration	Based on the postmarketing exposure of ~4 million patients, medication errors are very rarely reported for RAIM olanzapine. Reviews of these spontaneous reports have not revealed any new safety concerns or any significant new information indicative of systemic errors involving the prescribing, dispensing, or administration of RAIM olanzapine.
Wrong patient	2	Cause of error not reported	N/A	
Wrong technique	3	Not specified	Labelling provides administration technique	

Reports of Medication Errors with the Marketed Product(s)

Description of Error	Number of Occurrences	Analysis of Cause	Steps Taken to Prevent	Comment
ORAL Olanzapine				
Wrong dosing (route of administration, amount, frequency, schedule)	506	Patients received incorrect dose, route of administration, frequency, schedule, technique; prescribing and dispensing errors	SmPC clearly describes the proper dosing, frequency, and route of administration.	Based on the postmarketing exposure of ~38 million patients, medication errors are very rarely reported for olanzapine. Reviews of these spontaneous reports have not revealed any new safety concerns or any significant new information indicative of systemic errors involving the prescribing, dispensing, or administration of oral olanzapine.
Wrong patient	82	There have been a limited number of exposures to children and adults	Labelling clearly states that the product must be stored out of the sight and reach of children. To prevent confusion in patients taking multiple medications, olanzapine tablets have a unique shape, colour, and printing.	
Wrong technique	199	Splitting tablets	Package leaflet states to swallow the tablet whole. To discourage patients from splitting tablets, the tablets are not scored.	
Poor quality drug administered	21	Expired drug taken	Package leaflet states that the product should not be used after expiry date	
Suspected counterfeit drug	4	N/A	Package leaflet describes the unique shape, colour, and printing on the tablets.	

Reports of Medication Errors with the Marketed Product(s)

Description of Error	Number of Occurrences	Analysis of Cause	Steps Taken to Prevent	Comment
Olanzapine LAI				
Wrong dosing (route of administration, amount, frequency, schedule)	133	Patients received incorrect dose, route of administration, frequency, schedule, technique; prescribing and dispensing errors	CDS clearly describes the proper dosing, frequency, and route of administration	Based on the postmarketing exposure of >57 000 patients, medication error is rarely reported for olanzapine LAI. Reviews of these spontaneous reports have not revealed any new safety concerns or any significant new information indicative of systemic errors involving the prescribing, dispensing, or administration of olanzapine LAI.
Wrong patient	20	Reconstitution errors resulted in accidental topical exposure to HCP.	Labelling provides reconstitution technique.	
Wrong technique	24	Alternative injection sites were reported.	Labelling provides administration technique.	
Poor quality drug administered	1	Expired drug taken	Package leaflet states that the product should not be used after expiry date.	

Abbreviations: CDS = Core Data Sheet; LAI = long-acting injection; N/A = not applicable; RAIM = rapid-acting intramuscular; (~) = approximately.

SVI.5. Potential for Off-Label Use

In the review of the spontaneous postmarketing reports, off-label use is considered as prescriptions for the treatment of any indications other than approved indications or olanzapine use in patients younger than 18 years of age in the European Union (EU).

Oral Olanzapine or Rapid-Acting Intramuscular

The majority of spontaneous cases with off-label indications involving adults and patients with unknown age have been reported from the United States (US), similar to the geographic distribution of use of olanzapine. Of the case reports with off-label indications for olanzapine, approximately one-third were considered serious, which has a slightly higher percentage rate compared with all spontaneous case reports of olanzapine. The most frequently reported adverse events (AEs) in those case reports with off-label use of olanzapine include diabetes mellitus, weight increased, diabetes mellitus non-insulin-dependent, hyperglycaemia, somnolence, pancreatitis, oedema peripheral, hypertension, and tremor. The highest proportions of the events are from the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOC) metabolism and nutrition disorders, investigations, nervous system disorders, psychiatric disorders, and general disorders and administration site conditions. The distribution pattern of these AEs in the cases with off-label use of olanzapine has been similar to those in all spontaneous case reports of olanzapine.

Based on the spontaneous AE reporting data, it is known that olanzapine has been prescribed for off-label use. However, the AE profile in spontaneous case reports did not differ from the event profile in spontaneous cases with labelled use of olanzapine. No specific safety signal was identified among those patients who used olanzapine for unapproved indications.

Olanzapine Long-Acting Injection

At the time of submission and early authorisation of LAI, it was considered by the MAH that this formulation could be used off label in bipolar disorder, acutely agitated/severely psychotic patients or olanzapine naïve patients. These situations were addressed in the SmPC respectively:

Section 4.4 of the SmPC contains the following warning:

"Zypadhera should not be used to treat patients with schizophrenia who are in an acutely agitated or severely psychotic state such that immediate symptom control is warranted."

Section 4.2 of the SmPC contains the following recommendation:

"Patients should be treated initially with oral olanzapine before administering Zypadhera, to establish tolerability and response."

It appears from the following data, that these concerns have not been realized in practice.

There have been 27 spontaneous and postmarketing study reports for treatment of conditions other than approved indications in adults. The indications were: bipolar disorder (10), psychosis (4), anorexia (3), paranoia (3), aggressive behaviour (1), attention-deficit disorder/addiction (1), borderline personality disorder (1), depression with mania (1), obsessive compulsive disorder (1), post-traumatic stress disorder (1), and schizoaffective disorder (1); reported AEs were consistent with the known profile of olanzapine. In addition, there have been 6 reports in a patient younger than 18 years of age as described below (Section SVI.6.2).

SVI.6. Specific Paediatric Issues

SVI.6.1. Issues Identified in Paediatric Investigation Plans

Not applicable.

Table SVI.3. Issues Identified in Paediatric Investigation Plans

Olanzapine		
Issue (Safety or Efficacy)	**Background**	**Relevance to Indications covered in this RMP and how, if appropriate, it will be addressed.**
Not applicable.		

SVI.6.2. Potential for Paediatric Off-Label Use

Oral Olanzapine or Rapid-Acting Intramuscular

Olanzapine is licensed in the US for use in adolescent patients (13 through 17 years of age) for the treatment of manic or mixed episodes associated with bipolar I disorder or schizophrenia, and as described in the safety specification, its safety has been systematically evaluated in both short-term and long-term clinical studies. However, olanzapine is not licensed for use in patients <18 years of age in the EU, and hence the potential for off-label use in the paediatric population in the EU does exist.

Approximately 2% of postmarketing global olanzapine exposure is estimated to be among patients <18 years of age. In addition to analysis of the adolescent data from clinical studies previously presented in this Safety Specification, Lilly regularly and periodically examines the postmarketing data in this population within the context of the PSURs. Specific safety issues unique to patients <18 years of age have not been identified in these reviews, as the general profile (ie, the types of spontaneously reported events) is similar to that seen in an adult population.

Olanzapine Long-Acting Injection

The use of olanzapine LAI in the treatment of patients <18 years of age with schizophrenia has not been studied in clinical trials, nor are studies in this population intended. There have been 6 spontaneous postmarketing reports of patients <18 years of age treated with olanzapine LAI for schizophrenia. The reporting rate for off label use is extremely low and specific safety issues based on these few case reports do not highlight any specific safety issue in this subpopulation.

The current SmPC clearly states that olanzapine LAI has not been studied in patients <18 years of age.

SVI.7. Conclusions

Table SVI.4. Safety Concerns for this Module

Safety Concerns from this Module	
Safety Concern	**Comment**
None.	None.

Module SVII. Important Identified and Potential Risks

SVII.1. Newly Identified Important Safety Concerns (Since this Module was Last Submitted)

Table SVII.1. Newly Determined Important Safety Concerns (since this Module was Last Submitted)

None	
Details	Not applicable
Source	
New studies proposed in pharmacovigilance plan?	
New risk minimisation actions proposed?	

SVII.2. Recent Study Reports with Implications for Important Safety Concerns

Olanzapine LAI

Since the last RMP, one study has completed (F1D-MC-B034 [B034]) which addressed an important identified risk: post-injection syndrome. B034 was a prospective, observational, postauthorisation safety study designed to estimate the per-injection and per-patient incidence of post-injection syndrome in real-world clinical practice outside of the US. Secondary objectives included: further characterize the clinical presentation, including outcomes, of post-injection syndrome; identify potential risk factors associated with post-injection syndrome; and characterise hospitalization at baseline (previous 6 and 12 months) and postbaseline. B034 enrolled 3858 patients with schizophrenia receiving olanzapine LAI from 24 countries for a total of 103 505 injections. Post-injection syndrome occurred in 0.044% of injections (n=46) and 1.17% of patients (n=45). Data from B034 reinforce that the rates, timing for the onset of and recovery from post-injection syndrome, and severity of post-injection syndrome events are not greater than observed in controlled clinical trials.

SVII.3. Details of Important Identified and Potential Risks from Clinical Development and Postauthorisation Experience (including Newly Determined)

All important identified and potential risks for oral olanzapine are also risks for olanzapine LAI.

Table SVII.2. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk Weight Gain (Adults and <18 Years of Age)	
Frequency with 95% CI	**Clinical Trial Data** **Adult-Short-term Overall Olanzapine Analysis** *(includes data from oral olanzapine and olanzapine LAI placebo-controlled trials up to 12 weeks treatment)* In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg (5.7 lb) compared to an average of 0.3 kg (0.6 lb) weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients (N=1983) gained at least 7% of their baseline weight, which was statistically significantly different compared with 3% of placebo-treated patients, with a median exposure to event of 8 weeks. Of the olanzapine-treated patients (N=1983), 4.2% gained at least 15% of their baseline weight, which was statistically significantly different compared with 0.3% of placebo-treated patients, with a median exposure to event of 12 weeks. Patients in all BMI categories gained significant amounts of weight. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients (N=2056) and in no placebo-treated patients. **Long-term Overall Olanzapine Analysis** *(includes data from oral olanzapine and olanzapine LAI trials with at least 48 weeks of treatment)* There were 65% of patients who gained ≥7% of their baseline body weight, >30% patients gained at least ≥15%, and >10% gained at least ≥25% of their baseline body weight. The mean weight gain was 5.6 kg (12.3 lb) (median exposure of 573 days, N=2021). Discontinuation due to weight gain occurred in 0.4% of olanzapine-treated patients following at least 48 weeks of exposure. **Long-term Olanzapine LAI Analysis** (up to 192+ weeks of treatment) In clinical trials, the percentage of patients who experienced ≥7% weight gain by treatment duration was as follows: 26.6% by 72 weeks, 30.2% by 120 weeks, 31.3% by 144 weeks, 32.2% by 168 weeks, and 34.1% by 192 + weeks. **<18 years of Age** In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescent patients (aged 13 to 17 years), clinically significant weight gain was observed across all baseline BMI categories, but mean changes in weight were greater in adolescents with BMI categories above normal at baseline. Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to 0% of placebo-treated patients. **Weight Gain with Olanzapine Use in Adolescents (aged 13 to 17 years) from 4 Placebo-Controlled Trials**

	Olanzapine-treated patients (N=197)	**Placebo-treated patients (N=112)**
Mean change in body weight from baseline (median exposure = 3 weeks)	4.6 kg (10.1 lb)	0.3 kg (0.7 lb)
Percentage of patients who gained at least 7% of baseline body weight	40.6% (median exposure to 7% = 4 weeks)	9.8% (median exposure to 7% = 8 weeks)
Percentage of patients who gained at least 15% of baseline body weight	7.1% (median exposure to 15% = 19 weeks)	2.7% (median exposure to 15% = 8 weeks)

Identified Risk Weight Gain (Adults and <18 Years of Age)	
	In long-term studies (at least 24 weeks), the mean weight gain was 11.2 kg (24.6 lb); median exposure of 201 days, N=179). The percentages of adolescents who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 89%, 55%, and 29%, respectively. Among adolescent patients, mean weight gain by baseline BMI category was 11.5 kg (25.3 lb), 12.1 kg (26.6 lb), and 12.7 kg (27.9 lb), respectively, for normal (N=106), overweight (N=26) and obese (N=17). Following at least 24 weeks of exposure, discontinuation due to weight gain occurred in 2.2% of olanzapine-treated patients. **Cumulative Spontaneous Postmarketing Data (through 30 September 2013):** **Adults:** In patients ≥18 years, events related to weight gain in the olanzapine spontaneous database are considered "rarely reported" (≥0.01% to <0.10%) based on an estimated patient exposure to olanzapine of over 37 million patients ≥18 years. The majority of events related to weight gain were reported as weight increased, metabolic disorder, increased appetite, or obesity. Approximately 15.6% of the weight-gain-related events were considered to be serious with approximately 0.1% of the events having a fatal outcome. **<18 years of Age:** In patients <18 years of age, events related to weight gain in the olanzapine spontaneous database are considered "uncommonly reported" (≥0.1% to <1.0%) based on an estimated patient exposure to olanzapine of 715 000. The majority of events related to weight gain were reported as weight increased, increased appetite, hyperphagia or obesity. Approximately 9.1% of the weight-gain-related events were considered to be serious with approximately 0.1% of the events having a fatal outcome
Seriousness/outcomes	**Clinical Trial** ***Adult long-term data summary:*** • In pooled analyses of long-term olanzapine exposures from controlled and uncontrolled trials (at least 48 weeks), both the magnitude of weight gain and the proportion of patients who experienced clinically significant weight gain were greater than in analyses of short-term exposures (median of 7 weeks). • The percentages of patients who gained at least 15% or 25% of their baseline body weight with long-term exposure were very common (≥10%). • The mean rate of weight increase slowed with long-term exposure. ***<18 Years of age summary:*** • In pooled analyses of long-term olanzapine exposures from controlled and uncontrolled trials (at least 24 weeks), both the magnitude of weight gain and the proportion of adolescent patients who experienced clinically significant weight gain were greater than in adolescent patients with short-term exposures (median of 3 weeks), and adult patients with comparable exposures. • Approximately half of adolescent patients gained at least 15% of their baseline body weight and almost a third gained at least 25% with long-term exposure. • Among adolescent patients, mean weight gain was greatest in patients who were overweight or obese at baseline.

Identified Risk Weight Gain (Adults and <18 Years of Age)	
	Cumulative Spontaneous Postmarketing Data (through 30 September 2013): ***Adult*** • Approximately 15.6% of the weight-gain-related events were considered to be serious • Approximately 0.1% of the weight gain-related events had a fatal outcome. ***<18 Years of Age*** • Approximately 9.1% of the weight-gain-related events were considered to be serious. • One of the weight-gain-related events had a fatal outcome.
Severity and nature of risk	**Clinical Trial** ***Adult*** • In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients (N=1983) gained an average of 2.6 kg, which was statistically significantly different compared with an average 0.3 kg weight loss in placebo-treated patients with a median exposure of 6 weeks. ***<18 Years of Age*** • In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescent patients (aged 13 to 17 years), olanzapine-treated patients (N=197) gained an average of 4.6 kg, which was statistically significantly different compared with an average of 0.3 kg in placebo-treated patients (N=112) with a median exposure of 3 weeks. • Mean increase in weight in adolescents (4.6 kg over 3 weeks median duration of exposure) was greater than in adults (2.6 kg over 7 weeks median duration of exposure). **Cumulative Spontaneous Postmarketing Data (through 30 September 2013):** ***Adult*** • In patients ≥18 years, the majority of events related to weight gain were reported as weight increased, metabolic disorder, increased appetite, or obesity. ***<18 Years of Age*** • In patients <18 years, the majority of events related to weight gain were reported as weight increased, increased appetite, hyperphagia or obesity.
Background incidence/prevalence	**Schizophrenia Adult** The CLAMORS study in Spain of 1452 patients aged 18-74 years (mean age 40.7) with some form of schizophrenia found the prevalence of obesity BMI (≥30 kg/m^2) to be 30.8% (Arango et al. 2011) In patients with schizophrenia in a study from Portugal (N=125, aged ≥18 years), prevalence of overweight or obesity was high and similar in cases and controls: 64.2% versus 69% respectively (Ferreira et al. 2010) Prevalence of psychotropic drug-induced weight gain (≥10% of initial weight) in a Swiss psychiatric population (N=196, aged 18-65) was 47% and prevalence of obesity (BMI ≥30 kg/m^2) was 38%. 87 of the 196 patients had some form of schizophrenia (Choong et al. 2012).

Identified Risk Weight Gain (Adults and <18 Years of Age)	
	Schizophrenia Adolescent In a UK study of 5 863 adolescents aged 15-16 years, 16.9% were overweight (20.4% female, 14.4% male) and 6.8% were obese (8.3% female, 5.7% male). Overweight was defined using the International Obesity Task Force criteria (Wardle et al. 2006) **Bipolar Disorder (BD) Adult** A study of outpatient claims data from 5 primary health centres in Spain found that, among bipolar patients (n=128), the prevalence of obesity (BMI ≥30 kg/m^2) was 43.8% (Sicras-Mainar et al. 2008). **Bipolar Disorder (BD) Adolescent** Among 1841 child and adolescent (<17 years old) bipolar patients in a US claims database, prevalence of obesity or weight gain was 10.7% compared to 8.6% in the general population (n=4500) (Jerrell et al. 2010).
Risk groups or risk factors	The increased risk of clinically significant weight gain relative to the general population has been documented to be pre-existing in the population of patients for whom olanzapine is indicated. In patients with schizophrenia, including those treated with antipsychotics, prevalence of overweight or obesity ranged from 29-64% (Gasquet et al. 2008; Ferreira et al. 2010; Correll et al. 2010). Antipsychotic-naïve patients with schizophrenia have been shown to have impaired glucose tolerance, increased insulin resistance and increased visceral fat distribution compared with normal controls (Thakore et al. 2002; Venkatasubramanian et al. 2007; Fernandez-Egea et al. 2009). Various epidemiological risk factors for second-generation antipsychotic weight gain include abnormal BMI, younger age, female gender, and non-white race (Roerig et al. 2011).
Potential mechanisms	The exact mechanism is unknown, but the following are implicated: impairments in plasma leptin secretion, histamine antagonism, serotonin antagonism, muscarinic antagonism, genetic polymorphism, increased appetite, and decreased satiety. Ghrelin has been reported to be associated with metabolic changes, in combination with leptin, during olanzapine treatment (Kim et al. 2008).
Preventability	Strategies implemented to mitigate, and attempt to prevent, the risk of weight gain in patients treated with olanzapine include: appropriate labelling and communications to healthcare professionals (HCPs) through education and encouragement to counsel patients, and direct communication to patients through medication guides. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines.
Impact on individual patient	Weight gain is a reversible condition which can be managed through diet and exercise or with clinical assistance. However, if left unmanaged, clinically significant amounts of weight gain could potentially be life shortening (Jakicic et al. 2001).
Potential public health impact of safety concern	Olanzapine is associated with clinically significant weight gain, (mean increases and increased percentage of patients shifting upwards in category) during short- and long-term treatment, the impact of which needs to be taken into consideration, especially with the rising background incidence of weight-related problems (overweight and obesity) in the general population, including children, adolescents, and individuals with schizophrenia. This may suggest a potential public health safety issue. However, the overall public health impact would be minimal/negligible given the prevalence of schizophrenia, the percentage of the patients on olanzapine and of those who do develop weight gain.

Identified Risk Weight Gain (Adults and <18 Years of Age)	
Evidence source	• Clinical Trial Data • Spontaneous Postmarketing Data • Hedley et al. 2004
MedDRA terms	Weight increased

Abbreviations: BMI = body mass index; CI = confidence interval; EU = European Union; HCP = healthcare professional; LAI = long-acting injection; MedDRA = Medical Dictionary for Regulatory Activities.

[a] The short-term overall olanzapine analysis includes data from oral olanzapine and olanzapine LAI placebo-controlled trials with up to 12 weeks of treatment.

[b] The long-term overall olanzapine analysis includes data from oral olanzapine and olanzapine LAI trials with at least 48 weeks of treatment.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk Glucose Dysregulation (Adults and <18 Years of Age)	
Frequency with 95% CI	**Clinical Trial Data** **Adult** **Short-term Overall Olanzapine Analysis** *(includes data from oral olanzapine and olanzapine LAI placebo-controlled trials up to 12 weeks treatment)* In an analysis of 13 double-blind, placebo-controlled adult studies with olanzapine monotherapy, 5 of the studies provided fasting data with treatment duration up to 12 weeks. In patients with baseline normal fasting glucose levels (<100 mg/dL), 2.2% (N=543) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 3.4% (N=293) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 17.4% (N=178) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 11.5% (N=96) of those treated with placebo. Greater mean changes in fasting glucose levels were seen in patients treated with olanzapine (N=769) compared with placebo (N=411): 2.76 mg/dL versus 0.17 mg/dL. The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline. These patients had a statistically significantly greater (0.04%; N=89) mean increase in HbA1c compared with placebo (-0.06%; N=85). **Long-term Overall Olanzapine Analysis** *(includes data from oral olanzapine and olanzapine LAI trials with at least 48 weeks of treatment)* For patients exposed to olanzapine for at least 48 weeks, the mean change in fasting glucose was 4.2 mg/dL (N=487). In an analysis of patients who completed 9-12 months of olanzapine therapy, mean change in fasting and nonfasting glucose levels continued to increase over time, with a slowing in the rate of change after approximately 6 months of therapy. In pooled analyses of short- and long-term olanzapine exposures from controlled and uncontrolled trials (86 studies), the proportion of patients who experienced categorical changes from baseline in glucose (from normal to high or from borderline to high) increased over time, with earlier shifts among patients whose baseline glucose was borderline. **<18 Years of Age** In patients with baseline normal fasting glucose levels (<100 mg/dL), zero out of 124 (0%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 2 out of 14 (14.3%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus zero out of 13 (0%) of those treated with placebo. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a greater mean change from baseline in fasting glucose levels compared to placebo (2.68 mg/dL vs -2.59 mg/dL). The mean change in fasting glucose for adolescents exposed at least 24 weeks was 3.1 mg/dL (N=121).

Identified Risk Glucose Dysregulation (Adults and <18 Years of Age)	
	Cumulative Spontaneous Postmarketing Data (through 30 September 2013): **Adults:** Events related to glucose dysregulation in the olanzapine spontaneous database are "rarely reported" (≥0.01% to <0.10%) in patients ≥18 years of age based on estimated patient exposure to olanzapine of over 37 million patients ≥18 years of age. The majority of the events related to glucose dysregulation were reported as diabetes mellitus, type 2 diabetes mellitus, or hyperglycaemia. Approximately 19.6% of the glucose dysregulation events were considered to be serious with approximately 0.6% having a fatal outcome. **<18 Years of Age:** Events related to glucose dysregulation in the olanzapine spontaneous database are "rarely reported" (≥0.01% to <0.10%) in patients <18 years of age based on estimated patient exposure to olanzapine of 715 000 patients <18 years of age. The majority of the glucose dysregulation events were reported as diabetes mellitus, hyperglycaemia, or blood glucose increased. Approximately 31.4% of the glucose dysregulation related events were considered to be serious with approximately 1.6% having a fatal outcome.
Seriousness/outcomes	**Clinical Trial** ***Adult*** • No deaths reported in clinical trial data were associated with hyperglycaemia or DM. ***Adult long-term data summary:*** • Adult patients treated with olanzapine had mean increases in fasting and nonfasting glucose. • In a subset analysis of patients who completed 9-12 months of olanzapine therapy, the mean change in blood glucose increased over time, with a slowing in the rate of change after approximately 6 months of therapy. • In pooled analyses of short- and long-term olanzapine exposures from controlled and uncontrolled trials (86 studies), the proportion of patients who experienced categorical changes from baseline in glucose (from normal to high or from borderline to high) increased over time, with earlier shifts among patients whose baseline glucose was borderline. ***<18 Years of Age Summary*** • In pooled analyses of olanzapine exposures from controlled and uncontrolled trials (at least 24 weeks), changes in glucose from normal at baseline to high were uncommon (<1% and ≥0.1%). • Adolescent patients treated with olanzapine had mean increases in fasting and nonfasting glucose. • The mean increases observed in adolescents were similar to those observed in adults treated with olanzapine. **Cumulative Spontaneous Postmarketing Data (through 30 September 2013):** ***Adult*** • Approximately 19.6% of the glucose dysregulation-related events were considered to be serious. • Approximately 0.6% of the glucose dysregulation-related events had a fatal outcome.

Identified Risk Glucose Dysregulation (Adults and <18 Years of Age)	
	<18 Years of Age • Approximately 31.4% of the glucose dysregulation-related events were considered to be serious. • Approximately 1.6% of the glucose dysregulation-related events had a fatal outcome.
Severity and nature of risk	**<u>Clinical Trial</u>** ***Adult*** *Short-Term Overall Olanzapine Analysis (Up to 12 Weeks)[a]:* • In an analysis of 13 double-blind placebo-controlled adult studies with olanzapine monotherapy, 5 of the studies provided fasting data with treatment duration up to 12 weeks. In these 5 studies: o Greater mean changes in fasting glucose levels were seen in patients treated with olanzapine (N=769) compared with placebo (N=411) (2.76 mg/dL vs 0.17 mg/dL). o These patients had a statistically significantly greater (0.04%; N=89) mean increase in HbA1c compared with placebo (-0.06% N=85). *Long-Term Overall Olanzapine Analysis (At Least 48 Weeks of Treatment)[b]:* • Adult patients treated with olanzapine had mean increases in fasting and nonfasting glucose. • Increases were greatest for patients with normal baseline values. • In a subset analysis of patients who completed 9 to 12 months of olanzapine therapy, the mean change in blood glucose increased over time, with a slowing in the rate of change after approximately 6 months of therapy. • In pooled analyses of short- and long-term olanzapine exposures from controlled and uncontrolled trials (86 studies), the proportion of patients who experienced categorical changes from baseline in glucose (from normal to high or from borderline to high) increased over time, with earlier shifts among patients whose baseline glucose was borderline. ***<18 Years of Age*** • In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, olanzapine (N=138) was associated with a statistically significantly greater mean change in fasting glucose levels compared with placebo (N=66) (2.68 mg/dL vs -2.59 mg/dL). • Increases in fasting glucose were similar in adolescents and adults treated with olanzapine; however, the difference between olanzapine and placebo groups was greater in adolescents compared with adults **<u>Cumulative Spontaneous Postmarketing Data (through 30 September 2013):</u>** ***Adult*** • In patients ≥18 years, the majority of events related to glucose dysregulation were reported as diabetes mellitus, type 2 diabetes mellitus, or hyperglycaemia. ***<18 Years of Age*** • In patients <18 years of age, the majority of events related to glucose dysregulation were reported as diabetes mellitus, hyperglycaemia, or blood glucose increased.

Identified Risk Glucose Dysregulation (Adults and <18 Years of Age)	
Background incidence/prevalence	**SchizophreniaAdult** **Incidence:** In the European First-Episode schizophrenia trial encompassing 14 countries, the incidence rate of new DM cases over a 52-week follow-up period was 0.82% (Fleischhacker et al. 2013). By individual country, a Swedish national cohort study of 8277 patients with schizophrenia and followed for 7 years (2003-2009), found the incidence of DM to be 12.5% in females and 11.0% in males compared to 5.1% and 6.4%, respectively, in the general population (Crump et al. 2013b), and incidence of type 1 and 2 diabetes in 16 079 Danish schizophrenia patients was 2.98/1000 PY compared to 0.54% in controls from 1995 to 2007 (Laursen et al. 2011a). **Prevalence:** Results from the WHO World Health Survey of 28 291 people exhibiting at least 1 psychotic symptom found the prevalence of diabetes mellitus (DM) to be 4.99%. In people with a lifetime diagnosis of schizophrenia or psychosis, the prevalence of DM was higher in those with current psychotic symptoms (7.3% vs 5.2%; OR=1.65) suggesting that the persistence of symptoms over time could play a central role (Nuevo et al. 2011). In Europe, a meta-analysis (32 publications, 13 383 unique patients, 24 countries) found the prevalence of diabetes in patients with schizophrenia to be 2.1% in unmediated patients, 1.3% in first episode patients and 12.8% in chronic schizophrenia patients (Mitchell et al. 2013). A German study from 2006-2008 found the prevalence of DM to be 5.6% in 642 patients with schizophrenia and measured glucose levels ≥115 mg/dL in 14.1%. DM in the German general population was 9.4% suggesting many in the schizophrenia population are unaware of somatic health status (Kraemer et al. 2011). When diabetes mellitus was identified by type, the 12 country European METEOR study found the prevalence of DM in 2270 patients aged 18+ with schizophrenia between 2006 and 2007 was 3.8%; 0.3% for Type 1 and 3.5% for Type 2 (Falissard et al. 2011). The CLAMORS study in Spain of 1452 patients aged 18-74 years with some form of schizophrenia found the prevalence of Diabetes (type I, type II) and glucose ≥126 mg/dL to be 7.6% and Glucose intolerance 6.5% (Arango et al. 2011) and the prevalence of type 2 diabetes was increased in first hospitalized schizophrenia compared to hospitalized controls (11.3% vs 6.3%) in a UK study of 679 schizophrenia patients (Schoepf et al. 2012). **Schizophrenia Adolescent** **Prevalence:** Diabetes mellitus (DM) is present in less than 1% of the world's population of children and adolescents (Wild et al. 2004; CDC 2011). A hospital based study in Leeds, England of 677 children attending a diabetic clinic had a prevalence of type 2 diabetes of 0.01 per 1000 for ages 0-14 years and 0.09 per 1000 for ages 15-19 years and was seen more commonly in south Asians (Feltbower et al. 2003).

Identified Risk Glucose Dysregulation (Adults and <18 Years of Age)	
	BipolarDisorder(BD)Adult In a Swedish national cohort study of 6618 patients with BD, the prevalence of diabetes mellitus was 9.8% in women and 12.0% in men compared to 4.8% and 6.0% in the general population (Crump et al. 2013a). **BipolarDisorder(BD)Adolescent** Among 1841 child and adolescent (<17 years old) bipolar patients in a US claims database, prevalence of type 2 diabetes mellitus was 2.3% compared to 1.9% in the general population (n=4500) (Jerrell et al. 2010).
Risk groups or risk factors	The increased risk of clinically significant weight gain relative to the general population has been documented to be preexisting in the population of patients for whom olanzapine is indicated. Patients with schizophrenia appear to be at increased risk of diabetes (Bushe and Holt 2004) and metabolic syndrome (Mendelson 2008) relative to the general public. Some epidemiological studies also suggest an increased risk of hyperglycaemia-related outcomes in patients treated with atypical antipsychotics in general (Carlson et al. 2006; Lambert et al. 2006; Kessing et al. 2010). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline, including those patients diagnosed with diabetes mellitus or who met criteria suggestive of hyperglycaemia, and these patients had a greater increase in HbA1c compared to placebo. In a database study using US claims data, an approximately three-fold higher prevalence of diabetes was found among adolescents (13-17) with schizophrenia or bipolar disorder, 0.83%, compared to the general population, 0.30. A four-fold higher increase was seen in the incidence of diabetes, 424.3 per 100 000 person years (PY), compared to the general population, 90.0 per 100 000 PY (Enger et al. 2004).
Potential mechanisms	There are numerous studies that have assessed the possible mechanisms for blood glucose changes associated with the use of atypicals, including olanzapine, with a focus on the critical role of insulin secretion and insulin action (Sowell et al. 2003; Hardy et al. 2007; Haupt et al. 2007; Manu et al. 2013). The results of these studies do not provide a clear understanding of any such changes and, in fact, contradictory results have been seen even in similarly designed experiments. Weight gain is a known risk for glucose dysregulation; however, there is no definite association that changes in weight mediate glucose changes in patients treated with olanzapine. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor.
Preventability	People at high risk for type 2 diabetes mellitus can prevent or delay the onset of the disease. People with prediabetes who lose 5%-7% of body weight and get at least 150 minutes a week of moderate physical activity can reduce the risk of developing type 2 diabetes by 58% (CDC 2012). Strategies implemented to mitigate, and attempt to prevent, the risk of glucose dysregulation in patients treated with olanzapine include: appropriate labelling and communications to healthcare professionals (HCPs) through education, and encouragement to counsel patients, and direct communication to patients through medication guides. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines.
Impact on individual patient	Although type II diabetes can be clinically managed through diet and use of glucose-lowering agents, it is a serious and potentially life-threatening condition which requires continual monitoring and can increase the risk of developing retinopathy and cardiovascular disease (Home et al. 2002). Along with obesity and dyslipidaemia, glucose dysregulation can predispose a patient to metabolic syndrome, which is associated with an increased risk of developing type 2 diabetes mellitus and cardiovascular disease (Eckel et al. 2005). An international study conducted by Meltzer et al. (2011) showed that adult schizophrenia patients treated with olanzapine had

Identified Risk Glucose Dysregulation (Adults and <18 Years of Age)	
	a higher incidence of increased glucose levels (≥100 mg/dL) at 22.3% versus placebo at 17.7% (Meltzer et al. 2011). Similarly, US child and adolescent patients taking olanzapine for schizophrenia or other mood disorders had incident hyperglycaemia (≥100 mg/dL) at a rate of 2.2% versus 0.0% in the untreated comparison group (Correll et al. 2009).
Potential public health impact of safety concern	Olanzapine's association with glucose dysregulation, given the background risk, and an at-risk population suggests a potential public health safety issue. However the overall public health impact would be minimal/negligible given the prevalence of schizophrenia, the percentage of the patients on olanzapine and of those who do develop glucose dysregulation.
Evidence source	• Clinical Trial Data • Spontaneous Postmarketing Data
MedDRA terms	Hyperglycaemia/new onset diabetes mellitus (SMQ: Narrow)

Abbreviations: CDC = Centers for Disease Control and Prevention; DM = diabetes mellitus; MedDRA = Medical Dictionary for Regulatory Activities; PY = person years; SMQ = standardised MedDRA queries; US = United States; WHO = World Health Organization.

[a] The short-term overall olanzapine analysis includes data from oral olanzapine and olanzapine LAI placebo-controlled trials with up to 12 weeks of treatment.

[b] The long-term overall olanzapine analysis includes data from oral olanzapine and olanzapine LAI trials with at least 48 weeks of treatment.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk Dyslipidaemia (Adults and <18 Years of Age)	
Frequency with 95% CI	**ClinicalTrialData** **Adult** In an analysis of 13 double-blind placebo-controlled adult studies with olanzapine monotherapy, 5 of the studies provided fasting data with treatment duration up to 12 weeks. In these 5 studies: **Fasting Triglyceride Level:** The percentage of adult patients who had an increase of ≥50 mg/dL in their fasting triglyceride level was significant compared with placebo (N=754 vs 402; 39.6% vs 26.1%). The percentage of patients who went from a normal to high value was significantly greater than placebo (N=457 vs 251; 9.2% vs 4.4%) and the percentage of patients who went from borderline to a high value was significantly greater than placebo (N=135 vs 65; 39.3% vs 20.0%). **Fasting Total Cholesterol Level:** The percentage of adult patients who had an increase of ≥40 mg/dL in their fasting cholesterol level was significant compared with placebo (N=745 vs 402; 21.6% vs 9.5%). The percentage of patients who went from normal to high was not significantly greater than placebo (N=392 vs 207; 2.8% vs 2.4%) and the percentage of patients who went from borderline to a high was statistically significantly greater than placebo N=222 versus 112; 23% versus 12.5%. **Fasting LDL Cholesterol Level:** The percentage of patients who had an increase of ≥30 mg/dL in their fasting LDL cholesterol level was significant compared with placebo (N=536 vs 304; 23.7% vs 14.1%). The percentage of patients who went from a normal to high was not significantly greater than placebo (N=154 vs 82; 0% vs 1.2%) and the percentage of patients who went from a borderline to a high was not significantly greater than placebo (N=302 vs 173; 10.6% vs 8.1%). **Long-term Overall Olanzapine Analysis** (*includes data from oral olanzapine and olanzapine LAI trials with at least 48 weeks of treatment)* In long-term studies (at least 48 weeks), patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.6 mg/dL, 2.5 mg/dL, and 18.7 mg/dL, respectively; and a mean decrease in fasting HDL cholesterol of 0.16 mg/dL. In an analysis of patients who completed 12 months of therapy, the mean nonfasting total cholesterol did not increase further after approximately 4-6 months. Cumulative proportions of patients shifting from normal levels at baseline increased over time and time-to-event for total cholesterol was earlier in patients who were borderline at baseline (appeared to occur within first year of treatment). **<18 Years of Age** In an analysis of 3-placebo-controlled olanzapine monotherapy studies of adolescent patients, statistically significantly greater mean increase was observed for the olanzapine-treated patients (N=138; 12.87 mg/dL) compared with those administered placebo (N=66; 1.3 mg/dL) for the fasting total cholesterol (28.35 mg/dL) and (1.07 mg/dL) for the fasting triglycerides. Increases in fasting total cholesterol, LDL cholesterol, and triglycerides were generally greater in adolescents than in adults treated with olanzapine; however, the differences between olanzapine and placebo were similar between adolescents and adults. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients for fasting HDL cholesterol.

Identified Risk Dyslipidaemia (Adults and <18 Years of Age)	
	Cumulative SpontaneousPostmarketing Data (through 30 September2013): **Adult** Events related to increased cholesterol and increased triglycerides in the olanzapine spontaneous database are "rarely reported" (≥0.01% to <0.10%) in patients ≥18 years of age based on an estimated patient exposure to olanzapine of over 37 million patients ≥18 years of age. The majority of the events related to increased cholesterol and increased triglycerides were reported as blood triglycerides increased or blood cholesterol increased. Approximately 8.9% of the increased cholesterol or increased triglycerides related events were considered to be serious and none of the increased cholesterol or increased triglycerides related events had a fatal outcome. **<18 Years of Age** Events related to increased cholesterol or increased triglycerides in patients <18 years of age in the olanzapine spontaneous database are "rarely reported" (≥0.01% to <0.10%) based on estimated patient exposure to olanzapine of 715 000 patients <18 years of age. The majority of the events related to increased cholesterol or increased triglycerides were reported as blood cholesterol increased or blood triglycerides increased. Approximately 5.3% of the events were considered to be serious and none of the events had a fatal outcome.
Seriousness/ outcomes	**ClinicalTrial:** ***Adult*** Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. ***Adult Summary*** • Adult patients treated with olanzapine had mean increases in fasting and nonfasting total cholesterol, LDL cholesterol, and triglycerides. • In additional analyses performed to depict the pattern of changes in total cholesterol over time in adults treated with olanzapine, the range of increase in nonfasting cholesterol at various time-points was between 4 and 12 mg/dL, and there was no consistent pattern of increase over time. • In pooled analyses of short- and long-term olanzapine exposures from controlled and uncontrolled trials, the proportion of patients who experienced categorical changes from baseline in total cholesterol (from normal to high or from borderline to high) increased over time, with earlier shifts observed among patients whose baseline total cholesterol was borderline. • The proportion of patients who experienced categorical changes in HDL (from normal to low or from borderline to low), LDL or triglycerides (from normal to high or from borderline to high) was greater in patients with at least 48 weeks exposure than in patients with short-term exposure (up to 12 weeks). ***<18 Years of Age Summary*** • Adolescent patients treated with olanzapine had mean increases (larger than those seen in the adult patients) in fasting and nonfasting total cholesterol, LDL cholesterol, and triglycerides

Identified Risk Dyslipidaemia (Adults and <18 Years of Age)	
	• Increases in fasting total cholesterol, LDL cholesterol, and triglycerides were generally greater in adolescents than in adults treated with olanzapine in long-term data (at least 24 weeks) trials. **<u>Cumulative Spontaneous Postmarketing Data (through 30 September 2013):</u>** ***Adult*** • Approximately 8.9% of the increased cholesterol or increased triglycerides related events were considered to be serious. • None of the increased cholesterol or increased triglycerides related events had a fatal outcome. ***<18 Years of Age*** • Approximately 5.3% of the increased cholesterol or increased triglycerides related events were considered to be serious • None of the increased cholesterol or increased triglycerides related events had a fatal outcome.
Severity and nature of risk	ClinicalTrial: ***Adult*** *Short-Term Overall Olanzapine Analysis (Up to 12 Weeks)[a]:* In an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine- treated patients had statistically significant increases from baseline in mean fasting total cholesterol (N=744 vs 402), LDL cholesterol (N=535 vs 304), and triglycerides (N=744 vs 402) of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL, respectively, compared with decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. *Long-Term Overall Olanzapine Analysis (At Least 48 Weeks of Treatment)[b]:* Dyslipidaemia continued to be observed with longer term exposure to olanzapine. Cumulative proportions of patients shifting from normal levels at baseline increased over time. Time-to-event for total cholesterol was earlier in patients who were borderline at baseline (appeared to occur within first year of treatment). ***<18 Years of Age*** In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, statistically significantly greater mean increase was observed for the olanzapine-treated patients (N=138; 12.87 mg/dL) compared with those administered placebo (N=66; 1.3 mg/dL) for the fasting total cholesterol (28.35 mg/dL) and (-1.07 mg/dL) for the fasting triglycerides. Increases in fasting total cholesterol, LDL, cholesterol, and triglycerides were generally greater in adolescents than in adults treated with olanzapine; however, the differences between olanzapine and placebo were similar between adolescents and adults. CumulativeSpontaneousPostmarketing Data (through30 September2013): ***Adult*** In patients ≥18 years, the majority of events related to increased cholesterol and increased triglycerides were reported as blood triglycerides increased or blood cholesterol increased. ***<18 Years of Age*** In patients <18 years, the majority of events related to increased cholesterol or increased triglycerides were reported as blood cholesterol increased or blood triglycerides increased.

Identified Risk Dyslipidaemia (Adults and <18 Years of Age)	
Background incidence/ prevalence	**SchizophreniaAdult** A meta-analysis (32 publications, 13 383 unique patients, 24 countries) found the prevalence of triglycerides >150 mg/dL in patients with schizophrenia to be 16.9% in unmediated patients, 19.6% in first episode patients and 41.1% in chronic schizophrenia patients. Prevalence of decreased HDL cholesterol in patients with schizophrenia was 20.4% in unmediated patients, 21.9% in first episode patients and 44.7% in chronic schizophrenia patients (Mitchell et al. 2013). A German study from 2006-2008 found the prevalence of lipid disorders to be 6.7% in 642 patients with schizophrenia. Measured triglycerides ≥150 mg/dL were 52.5% and HDL cholesterol ≤40 mg/dL were 11.4%. Lipid disorders in the general population were 23.4%, suggesting many in the schizophrenia population are unaware of somatic health status (Kraemer et al. 2011). The CLAMORS study in Spain of 1452 patients aged 18-74 years with some form of schizophrenia found the prevalence of total cholesterol ≥200 mg/dL to be 46.7%, HDL cholesterol <45 (males) or <50 (females) mg/dL to be 33.9%, hypertriglyceridemia to be 34.3%, and dyslipidaemia to be 27% (Arango et al. 2011). In patients with schizophrenia in a study from Portugal (N=125, aged ≥18 years), prevalence of laboratory dyslipidaemia was 52.0% versus 36.2% (OR=1.92) in controls and 59.1% versus 53.3 % for clinical dyslipidaemia. Major contributor to dyslipidaemia was low HDL-C with prevalence of 43.1% in cases and 17.4% in controls (Ferreira et al. 2010). **SchizophreniaAdolescent** **Prevalence** Range from 3 studies in the United States and 1 in Belgium (Jago et al. 2006; Duncan et al. 2004; Freedman et al. 1999; Nawrot et al. 2004) • TC >200 mg/dL ranged from 4 % - 17% • LDL-C >130 mg/dL range from 3.9% - *8% (Freedman et al. 1999 used a threshold of TG >130 mg/dL) • HDL-C <35 mg/dL range from 11%-*23.4% (*Duncan et al. 2004 used threshold of HDL-C <40 mg/dL) • TG >110 mg/dL range from 8% -23.2% **BipolarDisorder(BD)Adult** In a Swedish national cohort study of 6618 patients with BD, the prevalence of lipid disorders was 2.7% in women and 3.7% in men; similar rates were seen in the general population, 2.4% in women and 3.5% in men (Crump et al. 2013a). **BipolarDisorder(BD)Adolescent** Among 1841 child and adolescent (<17 years old) bipolar patients in a US claims database, prevalence of dyslipidaemia was 2.7% compared to 10.8% in the general population (n=4500) (Jerrell et al. 2010).

Identified Risk Dyslipidaemia (Adults and <18 Years of Age)	
Risk groups or risk factors	Patients with schizophrenia appear to have a higher baseline prevalence of hyperlipidaemia than the general population (Correll et al. 2010; Ferreira et al. 2010) in addition to low rates of diagnosis and treatment (Bresee et al. 2010). Epidemiological risk factors for dyslipidaemia in the schizophrenic patient population include prevalence of obesity, male gender, and older age (Bresee et al. 2010). In a database study using US claims data, an approximately three-fold higher prevalence of dyslipidaemia was found among adolescents (13-17) with schizophrenia or bipolar disorder compared to the general population. A four-fold higher increase was seen in the incidence of dyslipidaemia compared to the general population (Enger et al. 2004). The risk of dyslipidaemia with olanzapine treatment is also higher in adolescents than in adults.
Potential mechanisms	Unknown, but potentially related to weight gain, insulin resistance, and the inhibition of lipid metabolism.
Preventability	The management of dyslipidaemia requires a comprehensive strategy to control lipid levels and to address associated metabolic abnormalities and modifiable risk factors such as hypertension, diabetes, obesity, and cigarette smoking. A healthy diet, regular exercise may help to reduce high cholesterol (Jellinger et al. 2012). Prompt recognition through appropriate labelling and communications to HCPs (through education and/or "Dear healthcare provider" letters) will help address the risk of dyslipidaemia. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines.
Impact on individual patient	Hyperlipidaemia is associated with increased risk of coronary artery disease, which is potentially life-threatening, and, along with obesity and glucose dysregulation, can predispose a patient to metabolic syndrome.
Potential public health impact of safety concern	Olanzapine's association with dyslipidaemia (ie, increased mean changes in lipid levels or an increase in proportions of patients going from normal to borderline to high lipid levels) needs to be taken into account when considering treatment given the high background incidence of dyslipidaemia in patients with schizophrenia and the general population as it may suggest a potential public health impact. However the overall public health impact would be minimal/negligible given the prevalence of schizophrenia, the percentage of the patients on olanzapine and of those who do develop alterations in the lipid profile.
Evidence source	• Clinical Trial Data • Spontaneous postmarketing data
MedDRA terms	Dyslipidaemia (SMQ: Narrow)

Abbreviations: BD = bipolar disorder; HCP = healthcare provider; HDL = high-density lipoprotein; LDL = low density lipoprotein; MedDRA = Medical Dictionary for Regulatory Activities; OR = odds ratio; SMQ = standardised MedDRA queries; TC = total cholesterol; US = United States.

[a] The short-term overall olanzapine analysis includes data from oral olanzapine and olanzapine LAI placebo-controlled trials with up to 12 weeks of treatment.

[b] The long-term overall olanzapine analysis includes data from oral olanzapine and olanzapine LAI trials with at least 48 weeks of treatment.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk Sedation (<18 Years of Age)	
Frequency with 95% CI	**ClinicalTrialData:** In the overall olanzapine exposure combined database, 158 of 454 (34.8%) olanzapine-treated patients reported at least 1 sedation- related event. Sedation (14.1%) and somnolence (19.82%) were the most frequently reported sedation-related AEs. Five patients (1.1%) discontinued from a study due to a sedation-related AE. In short-term, placebo-controlled trials in adolescent patients treated with oral olanzapine (doses ≥2.5 mg), sedation was reported with an incidence of ≥5% and reported at least twice as frequently as placebo-treated patients. The percentage of adolescent patients with schizophrenia who experienced a sedation-related event in a 6-week trial was 39% (N=72) in olanzapine-treated patients compared to 9% (N=35) placebo-treated patients. In a 3-week trial, the percentage of adolescent patients with bipolar I disorder who experienced a sedation-related event was 48% (N=107) compared to 9% (N=54) placebo-treated patients. **CumulativeSpontaneousPostmarketingData(through 30September2013):** Events related to sedation in patients <18 years of age in the olanzapine spontaneous database are considered "rarely reported" (≥0.01% to <0.10%) based on an estimated patient exposure to olanzapine of 715 000 patients <18 years of age. The majority of the events were reported as somnolence, fatigue, sedation, or hypersomnia. Approximately 12.5% of the events were considered to be serious and none of the events had a fatal outcome.
Seriousness/outcomes	**ClinicalTrial** • Olanzapine-treated adolescent patients reported sedation 1.9 times and somnolence 1.7 times more frequently than olanzapine- treated adult patients. There is limited information on whether this translates into clinically meaningful differences in long- term outcomes. **Cumulative SpontaneousPostmarketing Data (through30 September2013):** Of the events potentially related to sedation in patients <18 years: • 12.5% were considered to be serious. • None had a fatal outcome.
Severity and nature of risk	**ClinicalTrial** • In the Acute Placebo-Controlled Combined Database, statistically significantly more olanzapine-treated patients compared with placebo-treated patients reported at least 1 sedation-related AE (44.13% olanzapine vs 8.99% placebo; p<.001). There were no patients who discontinued from a study due to a sedation-related AE. **CumulativeSpontaneous PostmarketingData(through 30 September2013):** Of the events related to sedation reported in patients <18 years of age: • The majority were reported as somnolence, fatigue, sedation, or hypersomnia

Identified Risk Sedation (<18 Years of Age)	
Background incidence/prevalence	**SchizophreniaAdolescent** Sedation is an important AE with antipsychotics because it may exacerbate negative symptoms associated with schizophrenia (Whitaker and Rao 1992). Fatigue/sedation was reported for all evaluated drugs in a review of published studies of atypical antipsychotics in children and adolescents: clozapine: 40%, risperidone: 31%, olanzapine: 20%, quetiapine: 24%, and ziprasidone: 54%) (Cheng-Shannon et al. 2004). **BipolarDisorder(BD)Adult** In a placebo controlled US trial of quetiapine in 55 adults with bipolar II disorder, the incidence of sedation/somnolence was 20% in the placebo arm, n=25, and 53.3% in the treatment arm, n=30 (Suppes et al. 2013). **BipolarDisorder(BD)Adolescents** Rates not well characterized in the literature for adolescents. Prevalence and mortality rates are not well characterized in the general population as this is usually reported as an AE.
Risk groups or risk factors	Sedation or somnolence is dose-related in patients taking conventional and second-generation antipsychotics, but most often affects children and adolescents (Jerrell et al. 2008; Cheng-Shannon et al. 2004). Additionally, the odds of being diagnosed with sedation/somnolence has been found to be significantly higher in youth taking multiple antipsychotic medications, SSRIs, and those with pre-existing central nervous system and cardiovascular disorders (Jerrell et al. 2008). Olanzapine-treated adolescent patients reported sedation 1.9 times and somnolence 1.7 times more frequently than olanzapine-treated adults.
Potential mechanisms	Antihistamine effect.
Preventability	Olanzapine labelling and medication guide raises awareness that compared to patients from adult clinical trials, adolescents are likely to experience increased sedation and that patients should be counselled about the long-term risks associated with olanzapine. Sedation with olanzapine treatment is neither predictable nor preventable.
Impact on individual patient	In children and adolescents, sedation can potentially impact ability to participate in the educational setting. For this reason, it is recommended that patients take their olanzapine dose in the evening so that peak sedation occurs during hours of sleep. For many patients, sedation will become more tolerable after the first weeks of treatment. However, some patients do choose to discontinue the medication as a result of continued sedation. In the two adolescent registration trials (3 and 6 weeks duration) and their respective open-label extension periods (each 26 weeks), sedation-related adverse events were reported less frequently after the first 3-6 weeks of treatment. The majority of these events were mild or moderate in severity, regardless of study period, with only 2 patients discontinuing due to sedation-related events.

Identified Risk Sedation (<18 Years of Age)	
Potential public health impact of safety concern	The risk of sedation is very specific to the individual prescribed olanzapine, and there is no public health impact of the same.
Evidence source	• Clinical Trial Data • Spontaneous Postmarketing Report
MedDRA terms	Sedation

Abbreviations: AE = adverse event; BD = bipolar disorder; MedDRA = Medical Dictionary for Regulatory Activities; SSRI = selective serotonin reuptake inhibitor; US = United States.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk Hepatic-Related Events (<18 years of age)	
Frequency with 95% CI	**ClinicalTrialData:** In placebo–controlled trials of adolescent patients with schizophrenia or bipolar I disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at any time, were observed in laboratory analytes compared to placebo: elevated ALT (≥3X ULN in patients with ALT at baseline <3X ULN), (12% vs 2%); elevated AST (28% vs 4%); low total bilirubin (22% vs 7%); and elevated GGT (10% vs 1%). In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from <3 time ULN at baseline to ≥3 times ULN) were observed in 12% (22/192) of patients exposed to olanzapine compared to 2% (2/109) of patients exposed to placebo. ALT elevations ≥5 times ULN were observed in 4% (8/192) of olanzapine-treated patients, compared to 1% (1/109) of placebo-treated patients. No adolescent patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule. **CumulativeSpontaneousPostmarketingData(through30September2013):** Events related to hepatic changes in patients <18 years of age in the olanzapine spontaneous database are considered "rarely reported" (≥0.01% to <0.10%) based on an estimated patient exposure to olanzapine of 715 000 patients <18 years of age. The majority of the events were reported as alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, hepatic enzyme increased, or liver function test abnormal. Approximately 25.5% of the events reported were considered to be serious and 0.3% had a fatal outcome.
Seriousness/outcomes	**ClinicalTrial** • No patients met the criteria for Hy's Rule (ALT ≥3 times ULN and TBILI ≥2 ULN). • 8.6% of patients had at least 1 hepatic-related AE in the overall olanzapine exposure combine database. Eight patients (1.8%) discontinued from a study due to a hepatic-related AE. All hepatic-related AEs were limited to elevated hepatic enzymes. **Cumulative Spontaneous Postmarketing Data through 30 September 2013** Of the events potentially related to hepatic changes identified in patients <18 years, • 25.5% were considered to be serious. • 0.3% had a fatal outcome.
Severity and nature of risk	Based on placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from <3 times ULN at baseline to ≥3 times ULN) were observed 6 times more frequently in the olanzapine-treated patients (N=192) compared to placebo-treated patients (N=109). ALT elevations ≥5 times ULN were observed 4 times more frequently in olanzapine-treated patients (N=192) compared to placebo-treated patients (N=109).
	ClinicalTrial Mean change from baseline to endpoint for ALT, AST, and GGT was statistically significantly higher for olanzapine-treated patients compared with placebo-treated patients, while mean change for TBILI was statistically significantly higher for placebo-treated patients compared with olanzapine-treated patients (ALT [olanzapine: +19.95 U/L; placebo: -3.08 U/L; p<.001], AST [olanzapine: +6.43 U/L; placebo: -2.47 U/L; p=.002], GGT [olanzapine: +7.47 U/L; placebo: -0.43 U/L; p<.001], TBILI [olanzapine: -1.73 umol/L; placebo: +0.78 umol/L; p<.001])

Identified Risk Hepatic-Related Events (<18 years of age)	
	A statistically significantly greater percentage of olanzapine-treated adolescent patients compared with placebo-treated adolescent patients had at least one hepatic-related AE (8.4% olanzapine vs 1.1% placebo; p=.025). However, the incidence of any individual hepatic-related AE was not statistically significantly different between treatment groups. Six olanzapine-treated patients (3.4%) discontinued from a study due to a hepatic-related AE. All hepatic-related AEs were limited to elevated hepatic enzymes and no individual AE was reported in >5% of patients treated with olanzapine. **Cumulative Spontaneous Postmarketing Data through 30 September 2013** Of the events related to hepatic changes reported in patients <18 years of age, The majority were reported as ALT increased, AST increased, hepatic enzyme increased, or liver function test abnormal.
Background incidence/prevalence	Up to 50% of patients treated with atypical antipsychotics have shown asymptomatic elevation of liver enzymes with serious hepatotoxicity being rarely if ever reported (Ozcanli et al. 2006). Rates in the target population are not well characterized in the literature. BU In a Spanish study from 1993 to 1998, the incidence of acute serious liver disease for ages 15-29 years in the general population was 4.05 per 1 000 000 (10^6) inhabitants/year (4.55 for males, 3.55 for females) (Ibáñez et al. 2002). In the age group 15-24 years, incidence rates per 100 000 persons/year of liver enzyme abnormalities by type between 1992 and 1993 in a US study ranged from 0 for biliary pathologies to 5.0 for alcohol, malignancy or viral hepatitis to 15.0 for unknown aetiology, 20.0 for drug associated and 125.2 for mononucleosis (Duh et al. 1999). Prevalence of abnormal liver enzymes among US adolescents (12-18 years) in the general population between 1988 and 1994 (Strauss et al. 2000) Elevated ALT by weight classification: • Normal weight: 1.5% • Overweight (85 < BMI<95th%): 5.0% • Obese (BMI >95th%): 9.5% Elevated GGT by weight classification: • Normal weight: 1.2% • Overweight (85 < BMI <95th%): 1.3% • Obese (BMI >95th%): 3.9%
Risk groups or risk factors	The epidemiological risk factors for hepatic events, specifically NASH, are obesity, Type 2 diabetes mellitus, and hyperlipidaemia (aside from polymedication, alcoholism, and/or drug abuse in combination with antipsychotics which may not be relevant in adolescents); all of these factors are identified risks in long-term antipsychotic use (Ozcanli et al. 2006).
Potential mechanisms	The potential mechanism for hepatic-related changes is unknown.

Identified Risk Hepatic-Related Events (<18 years of age)	
Preventability	Hepatic-related adverse events observed in adolescent patients treated with olanzapine are thought to be idiosyncratic reactions as their mechanism is unknown. Olanzapine labelling and Medication Guide raise awareness that compared to patients from adult clinical trials, adolescents are likely to have greater increases in hepatic aminotransferase levels and that patients should be counselled about the long-term risks associated with olanzapine.
Impact on individual patient	Due to the presence of risk factors such as polymedication, alcoholism and/or drug abuse, hepatic tolerance of atypical antipsychotics is an issue in short and long term schizophrenia treatment (Mouradian-Stamatiadis et al. 2002).
Potential public health impact of safety concern	Mild to moderate transient elevations are not concerning from a public health perspective as these are not predictive of more severe hepatic injury.
Evidence source	• Clinical Trial Data • Spontaneous Postmarketing Data
MedDRA terms	Liver related investigations, signs and symptoms (SMQ: Narrow)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; NASH = nonalcoholic steatohepatitis; SMQ = standardised MedDRA Queries; TBILI = total bilirubin; ULN = upper limit of normal

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk Hyperprolactinaemia (<18 years of age)	
Frequency with 95% CI	**ClinicalTrialData:** In the acute placebo-controlled combined database for patients <18 years of age, there was a statistically significantly greater incidence of treatment–emergent abnormally high prolactin levels in olanzapine-treated patients compared with placebo-treated patients at any time (47.4% olanzapine vs 6.8% placebo; p<0.001). Olanzapine-treated patients <18 years of age had a statistically significant higher incidence of treatment-emergent abnormal high prolactin values than olanzapine-treated adults (55.5% patients <18 years of age vs 29.0% adults; p<0.001). **CumulativeSpontaneousPostmarketingData(through 30 September 2013):** Events related to hyperprolactinaemia in patients <18 years of age in the olanzapine spontaneous database are considered "rarely reported" (≥0.01% to <0.10%) based on an estimated patient exposure to olanzapine of 715 000 patients <18 years of age. Of the events related to hyperprolactinaemia reported in patients <18 years of age, the majority were reported as galactorrhoea, blood prolactin increased, gynecomastia, amenorrhea, and hyperprolactinaemia. Of the events related to hyperprolactinaemia in patients <18 years of age, approximately 8.3% were considered to be serious and none of the events had a fatal outcome.
Seriousness/outcomes	**ClinicalTrial** Hyperprolactinaemia-related results from the Overall Olanzapine Exposure Combined Database are summarized below: • There was a statistically significant mean increase in prolactin levels from baseline to endpoint (+4.74 ug/L; p<.001). • 54.7% of patients had a treatment-emergent abnormally high prolactin level. • 4.6% of patients had a TEAE related to prolactin elevation. One patient (0.6%) discontinued from a study to a hyperprolactinaemia-related AE. **Cumulative SpontaneousPostmarketingDatathrough 30 September 2013** Of the events potentially related to hyperprolactinaemia identified in patients <18 years, • 8.3% were considered to be serious. • None had a fatal outcome.
Severity and nature of risk	In placebo-controlled olanzapine monotherapy studies in patients <18 years of age (up to 6 weeks) with schizophrenia or bipolar I disorder (manic or mixed episodes), changes from normal to high prolactin occurred more frequently (approximately 7 times) in olanzapine-treated patients <18 years of age related to placebo-treated patients <18 years of age. **Clinical Trial** **In the acute placebo-controlled combined database:** • Olanzapine-treated patients had a statistically significantly greater mean increase in prolactin levels from baseline to endpoint compared with placebo treated patients (olanzapine: +11.44 ug/L; placebo: -0.16 ug/L; p<.001). • There was not a statistically significant difference between olanzapine-treated patients and placebo-treated patients in the incidence of TEAEs related to prolactin elevation (2.8% olanzapine vs 5.6% placebo; p=.308). There were no patients who discontinued from a study due to a hyperprolactinaemia-related AE. • Olanzapine-treated patients <18 years of age had a statistically significantly greater mean increase from baseline to endpoint in prolactin levels than olanzapine-treated adults (patients <18 years of age: +23.01% URL; adults: -4.19% URL; p=.004).

Identified Risk Hyperprolactinaemia (<18 years of age)	
	Cumulative Spontaneous Postmarketing Data through 30 September 2013 • Of the events related to hyperprolactinaemia reported in patients <18 years of age, the majority were reported as galactorrhoea, blood prolactin increased, gynecomastia, amenorrhea, and hyperprolactinaemia
Background incidence/prevalence	Rates in the target population are not well characterized in the literature. **General Population <18 years of age:** Frequency of hyperprolactinaemia in patients <18 years of age as reported for all evaluated drugs in a review of 176 published studies of atypical second-generation antipsychotics: clozapine: 0%, risperidone: 4% olanzapine: 8%, quetiapine: 1%, and ziprasidone: 23% (Cheng-Shannon et al. 2004). Prevalence and mortality rates are not well characterized in the general population as this usually reported as an AE.
Risk groups or risk factors	The risk factors for hyperprolactinaemia in patients <18 years of age with the schizophrenia and bipolar disorder are not well characterized in the literature. A risk factor for hyperprolactinaemia in the general population is exposure to any drug that affects the hypothalamic dopamine system or the pituitary dopamine receptors, including but not limited to phenothiazines, butyrophenones, metoclopramide, reserpine, tricyclic antidepressants, opiates, verapamil, and large parenteral doses of cimetidine (Mah and Webster 2002). Risk factors specific for hyperprolactinaemia with olanzapine treatment have not been identified.
Potential mechanisms	Neurotransmitters regulate prolactin secretion through the central nervous system at the hypothalamic and tuberoinfundibular dopaminergic system levels (Jerrell et al. 2008). Secretion of prolactin from pituitary lactotroph cells is primarily regulated by tonic inhibition by dopamine; dopamine is secreted from the median eminence of the hypothalamus into the hypothalamic-pituitary portal plexus and transported to the anterior pituitary, where it acts on D2-dopamine receptors on lactotrophs to inhibit prolactin secretion. Antipsychotic medications, including olanzapine, are D2-dopamine receptor antagonists and can therefore raise serum prolactin by blocking this tonic inhibitory effect (Correll and Carlson, 2006).
Preventability	Olanzapine labelling and the Medication Guide raise awareness that compared to patients from adult clinical trials, patients <18 years of age are likely to have greater increases in prolactin levels and that patients should be counselled about the long-term risks associated with olanzapine.
Impact on individual patient	A review of the literature shows that the potential risks linked to the increased rate of hyperprolactinaemia and pituitary enlargement observed in the adolescent population are unclear. A study of adolescents treated with atypical antipsychotics (Staller 2006) concluded that the relevance of sustained, mildly elevated prolactin levels over an extended period of time in developing children is unclear; that only 12% of the AEs in the study were possibly related to sustained elevated prolactin; and that the AEs associated with increased in prolactin may not be relevant or reliable markers in the paediatric population (for example, sexual dysfunction, breast enlargement, and menstrual irregularities. Galactorrhoea, amenorrhea, gynecomastia, and erectile dysfunction have been reported in patients receiving prolactin-elevating compounds. Long-term effects of hyperprolactinaemia on patients <18 years of age are uncertain. Bone loss occurs secondary to hyperprolactinaemia-mediated sex steroid attenuation. A 25% decrease in spinal bone density can be seen in women with hyperprolactinaemia and may be irreversible even with normalization of prolactin levels (Melmed et al. 2011). Long-standing hyperprolactinaemia when associated with hypogonadism may lead to decreased bone density in both females and males.

Identified Risk Hyperprolactinaemia (<18 years of age)	
Potential public health impact of safety concern	The risk (if at all) of hyperprolactinaemia is very specific to the individuals <18 years of age treated with olanzapine, and there is no public health impact.
Evidence source	• Clinical Trial Data • Spontaneous Postmarketing Data
MedDRA terms	Blood prolactin increased

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event; URL = upper range limit.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Potential Risk: Increased Risk of Cardiac Death (Presumed Sudden Cardiac Death)	
Frequency with 95% CI	**CumulativeSpontaneousPostmarketingData(through 30September 2013):** In patients ≥18 years, the event of sudden cardiac death was "very rarely reported" (<0.01%) based on an estimated patient exposure to olanzapine of over 37 million patients ≥18 years. **Post-MarketingPharmacoepidemiologicalStudies:** In a retrospective observational study published in the literature, patients treated with atypical antipsychotics (including olanzapine) or typical antipsychotics had a similar dose-related increase of presumed sudden cardiac death (SCD) compared to non-users of antipsychotics (almost twice the risk than for non-users) (Ray et al. 2009). The primary analysis included 44 218 and 46 089 baseline users of single typical and atypical antipsychotics, respectively. Incidence of Sudden Cardiac Death in patients treated with olanzapine: 3.37 per 1000 PY (n=75) Pharmacoepidaemiology study, F1D-MC-B042, Risk of Cardiac Mortality (including Sudden Cardiac Death) in Atypical Antipsychotic Users. Incidence of Sudden Cardiac Death Primary definition (most restrictive): 1.7 per 1000 PY(95% CI 0.6-3.8) (n=6) Secondary definition: 2.9 per 1000 PY (95% CI 1.4-5.3) (n=10) Tertiary definition: 1.8 per 1000 PY (95% CI 1.0-2.9) (n=15)
Seriousness/outcomes	Mortality
Severity and nature of risk	Cardiac-related deaths (presumed sudden cardiac death)
Background incidence/prevalence	**Schizophrenia Adult** *Cardiac death*: In a Canadian study of 3022 patients with schizophrenia (32.3% were users of atypical antipsychotics), the incidence of cardiac death was 10.8/PYs and 5.3/1000 PYs in the general population. The rate ratio for cardiac death (schizophrenia population vs general population): 2.2 (95% CI = 1.7 - 2.8) (Curkendall et al. 2004). *Sudden Cardiac Death*: In a Canadian study of 3022 patients with schizophrenia (32.3% were users of atypical antipsychotics), incidence of sudden cardiac death was 1 per 1000 PYs (100 per 100 000 PYs) compared to 0.3/1000 PYs (30/100 000 PYs) in the general population (Curkendall et al. 2004). Patients with schizophrenia in the 18-country ZODIAC trial (n = 9077, person years = 6198) found the 1-year mortality incidence of sudden cardiac death to be 0.34% (intent to treat) or 0.40 per 100 person-years (secondary analysis with person time on assigned treatment, n=25 person-years) in the ziprasidone arm (Strom et al. 2011). **BipolarDisorder(BD)** Rates are not well characterized in the literature for adults or patients <18 years of age.

Potential Risk: Increased Risk of Cardiac Death (Presumed Sudden Cardiac Death)	
	In a US general population study, the annual incidence of sudden cardiac arrest was 54/100 000. In the age group <65 years, incidence was 26/100 000 and in those ≥65 years of age it was 281 per 100 000 (Reinier et al. 2006).
Risk groups or risk factors	More than 80% of cases of SCD occur in individuals with CHD. Only in 5% to 10% of cases does SCD occur in the absence of CHD or cardiomyopathy, such as patients with long/short QT syndromes which can precipitate SCD without overt structural changes in the heart. There are also meaningful associations between cigarette smoking, obesity, diabetes, lifestyle, and SCD. Various reports suggest that patients with schizophrenia have a significantly increased burden of cardiovascular disease and diabetes and that cardiovascular mortality contributes to the excess mortality in persons with schizophrenia (Enger et al. 2004; Osborn et al. 2007; Osby et al. 2000; Brown et al. 2010). Study B042 found that incidence of cardiac mortality among patients treated with any antipsychotic was 17.0 per 1000 person-years, patients treated with olanzapine was 7.7 per 1000 person-years and among a non-user psychiatric population was 6.4 per 1000 person-years. In addition, weight gain, glucose and lipid abnormalities, which are associated with an increased risk of cardiovascular disease and are important identified risks for olanzapine and other atypical antipsychotics.
Potential mechanisms	The mechanism(s) for the potential increased risk of cardiac death (presumed SCD) with the use of antipsychotics is not known. A possible association between SCD has been noted with certain antipsychotics that contribute to ventricular repolarisation abnormalities, including potentially fatal ventricular arrhythmias. There is a general consensus that the prolongation of the QTc interval may be a marker of such risk (Haddad and Sharma 2007). However, it is well described and accepted that there are different degrees of risk of prolonging the QT interval associated with different antipsychotics. Lilly's comprehensive review of QTc prolongation reviewed by the CHMP established that the risk of QT prolongation with olanzapine is uncommon (which is a variance to the hypothesis put forward [Ray et al. 2009]). More than 80% of cases of SCD occur in individuals with CHD. Only in 5% to 10% of cases does SCD occur in the absence of CHD or cardiomyopathy, such as patients with long/short QT syndromes which can precipitate SCD without overt structural changes in the heart. There are also meaningful associations between cigarette smoking, obesity, diabetes, lifestyle, and SCD (Wilson et al. 1998). Weight gain, glucose and lipid abnormalities are established risks with the use of atypical antipsychotics, including olanzapine. Various reports suggest that patients with schizophrenia have a significantly increased burden of cardiovascular disease and diabetes and that cardiovascular mortality contributes to the excess mortality in persons with schizophrenia (Enger et al. 2004; Osborn et al. 2007; Osby et al. 2000; Brown et al. 2010). Understanding of these potential mechanisms is unchanged by the completed study B042.
Preventability	Given the absence of a known mechanism for this risk, no measures for either predicting or preventing cardiac death (presumed cardiac death) potentially associated with the use of antipsychotics are known at this time. Current labelling includes a warning that the risk of presumed sudden cardiac death in patients treated with olanzapine is approximately twice the risk in patients not using antipsychotics and comparable to the risk of using atypical antipsychotics. In addition, olanzapine is appropriately labelled for weight gain, glucose and lipid abnormalities, which are associated with an increased risk of cardiovascular disease.
Impact on individual patient	The impact on the individual patient would be a sudden, unexpected death.
Potential public health impact of safety concern	Due to limited evidence and the absence of absolute risk estimates for this potential risk, the public health impact is not known.

Potential Risk: Increased Risk of Cardiac Death (Presumed Sudden Cardiac Death)	
Evidence source	Published literature (Ray et al. 2009)
MedDRA terms	Sudden cardiac death

Abbreviations: BD = bipolar disorder; CHD = coronary heart disease; CHMP = Committee for Medicinal Products for Human Use; CI = confidence interval; PY= person years; SCD = sudden cardiac death; US = United States.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Potential Risk: Risk of Mortality (Rapid-Acting Intramuscular Olanzapine)	
Frequency with 95% CI	**ClinicalTrialData:** No deaths occurred during clinical trials with RAIM. **CumulativeSpontaneousPostmarketingData(through 30September2013):** A fatal outcome in the RAIM olanzapine spontaneous database was "very rarely reported" (<0.01%) in patients ≥18 years of age.
Seriousness/outcomes	**ClinicalTrial** Not applicable. **CumulativeSpontaneousPostmarketingData** Not applicable.
Severity and nature of risk	This important potential risk is specific to the rapid acting IM formulation. The evaluation of this risk is complicated by the increased morbidity and mortality associated with acute agitation. **Risks:** **IM Antipsychotics** • Analysis of the FDA AERS data showed a higher frequency of reported deaths in patients receiving IM antipsychotics (ziprasidone, olanzapine and haloperidol non-decanoate) as compared with patients receiving the oral counterpart, which is consistent with the hypothesis that the acutely agitated patient population might be at a higher risk of suffering medical complications (including increased mortality risk) when compared with the population treated with the same antipsychotics for indications other than acute agitation. **Disease State:** This patient population presents with a higher risk of mortality compared with non-agitated patients (Lilly study conducted using the Premier Perspective Comparative Database [PCD]). **Concurrent Conditions and Concomitant Medications:** • Many of the disease states that can lead to acute agitation are associated with concurrent conditions such as serious medical comorbidities including obesity and recent surgeries, alcohol or drug intoxication, smoking, apnoea/sleep apnoea, use of physical restraints etc. which may increase the risk of adverse events and poor treatment outcomes. • Patients received multiple doses of medications in a short period of time including the use of parenteral benzodiazepines and other antipsychotics. • Concomitant use of benzodiazepines may potentially increase the risk of excessive sedation and cardiorespiratory depression.

Potential Risk: Risk of Mortality (Rapid-Acting Intramuscular Olanzapine)	
	Clinical Trial **Data of IM olanzapine in healthy volunteers in Study F1D-LC-LOAV:** • As reflected in the Digit Symbol Substitution Test (DSST) and somnolence, an additive interaction was observed in the pharmacodynamic responses. Overall, the combination of IM olanzapine (2.5 mg or 5.0 mg) and IM lorazepam (2.0 mg) appeared safe. • The pharmacokinetics of IM olanzapine, unconjugated IM lorazepam, and total IM lorazepam (IM lorazepam plus lorazepam glucuronide) were not significantly affected when administered in combination. There was no pharmacokinetic drug interaction. Thus, it appears that IM olanzapine will not affect the metabolism of compounds that are primarily conjugated with glucuronic acid. Likewise, IM olanzapine clearance is unlikely to be altered by other compounds that are primarily metabolized by this phase II metabolic pathway.
Background incidence/prevalence	**Schizophrenia** In a 25-year mortality study of 370 patients with schizophrenia aged 16-65 in the UK, the all-cause mortality SMR between 1981 and 2006 was as follows: Total: 289 (95% CI: 247-337); Male: 294 (95% CI: 237-361); Female: 283 (95% CI: 221-356) (Brown et al. 2010). For the period 2007-2009, a second UK study (n=7022) found the SMR for schizophrenia to be: Total: 2.25 [95% CI: 2.10-2.51]; Male: 2.78 (2.40-3.19); Female: 1.74 (1.45-2.07) (Chang et al. 2010). Among US hospitalized patients (Internal study report, Premier study 2007): • 4% olanzapine IM • 5% haloperidol IM • 3% ziprasidone IM (Unpublished internal study report: Characteristics and Outcomes in Hospitalized Patients Treated with Intramuscular Antipsychotics: Analysis of a US Hospital Database) **BipolarDisorder(BD)** Rates are not well characterized in the literature for adults or patients <18 years of age.
Risk groups or risk factors	The acutely agitated patient population presents with a higher risk of mortality compared with non-agitated patients. Many of the disease states that can lead to acute agitation are associated with concurrent conditions such as serious medical comorbidities including obesity and recent surgeries, alcohol and drug intoxication, smoking, apnoea/sleep apnoea, use of physical restraints, etc, which may increase the risk of adverse events and poor treatment outcomes (Marder et al. 2010). Concomitant use of benzodiazepines may potentially increase the risk of excessive sedation and cardiorespiratory depression. Patient characteristics that may be specific to RAIM olanzapine have not been identified.
Potential mechanisms	Unknown, but several factors may be involved with the risk of mortality. These factors include the state of agitation itself, age >45 years, metabolic conditions, presence of underlying medical conditions, and polypharmacy (Marder et al. 2010).
Preventability	Strategies implemented to mitigate, and attempt to prevent the risk of mortality in patients treated with RAIM include: appropriate labelling and communication to HCPs, through education, Dear HCP letters, and routine surveillance.

Potential Risk: Risk of Mortality (Rapid-Acting Intramuscular Olanzapine)	
Impact on individual patient	The impact on the individual patient would be death.
Potential public health impact of safety concern	Given the increased morbidity and mortality associated with acute agitation and the confounding factors reported in the cases reviewed although the impact on an individual is serious, the additional public health impact of the potential risk of death with olanzapine rapid acting injection is minimal.
Evidence source	• Clinical Trial Data • Spontaneous Postmarketing Reports
MedDRA terms	Death

Abbreviations: AERS = Adverse Event Reporting System; DSST = Digit Symbol Substitution Test; FDA = Food and Drug Administration; HSP = healthcare professional; IM = intramuscular; PCD = Premier Perspective Comparative Database; PCD = Premier Perspective Comparative Database; RAIM = rapid-acting intramuscular; SMR = standardised MedDRA queries; UK = United Kingdom.

Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Post-Injection Syndrome (Olanzapine Long-Acting Injection)	
Frequency	The incidence rate in clinical trials to date is 0.07% of injections and 1.85% of patients. Cumulatively, in postmarketing Study B034, there were 3858 patients who had received at least 1 injection, and a total of 103 505 injections were administered. As of 31 March 2016 in the Zyprexa Relprevv Patient Care Program, there were 5024 patients who had received at least 1 injection, and a total of 79 040 injections were administered. Based on these 182 545 olanzapine LAI given to 8882 patients, PDSS events (123) occurred in approximately 0.07% of injections and 1.4% of patients in postmarketing studies. Cumulatively, as of 31 March 2016, there were 548 post-injection syndrome events reported spontaneously and 123 from postmarketing studies. Based on the estimated patient exposure to olanzapine LAI as of 31 March 2016, post-injection syndrome events have been reported in approximately 0.66% of patients (671 events in 659 patients [12 patients reported 2 events each]/100 000 patients).
Seriousness/outcomes	• All of the events were considered to be serious. • Of the patients reporting an outcome, 98% who experienced an event fully recovered. The majority reported recovery within 24 to 48 hours, with most recovering within 72 hours.
Severity and nature of risk	• Event onset has taken place in a majority of cases within the first hour post-injection. Events typically started with milder symptoms (such as sedation- and delirium-related events), which progressed in severity over time in some cases. • Signs and symptoms reported with post-injection syndrome events are consistent with many of the AEs reported with an oral olanzapine overdose. These include dizziness, confusion, disorientation, slurred speech, altered gait, weakness, muscle spasms, possible seizure/convulsion, and varying degrees of sedation. • Reporting rates of clinically relevant hemodynamic instability or respiratory depression, including cardiac arrest and arrhythmias, in acute ingestion of an oral olanzapine overdose (as of 30 September 2007) is very rare (<0.01%). • The spontaneous reports were consistent with the clinical trial cases in severity.
Background incidence/prevalence	Post-injection syndrome is unique to olanzapine LAI.
Risk groups or risk factors	No clear risk factors were identified in a pooled analysis of the first 30 post-injection syndrome events in clinical trials. Forward stepwise regression analyses in Study B034 indicate risk factors for post-injection syndrome on the per-injection basis included high dose (odds ratio$_{high:low}$=3.95; p-value=0.006) and male gender (odds ratio$_{female:male}$=0.42; p-value=0.017). BMI also remained in the regression model due to the predetermined level of significance of 0.2 (odds ratio=0.95, p-value=0.143). Analysis on the per-patient level suggests that male gender (odds ratio$_{female:male}$=0.43, p-value=0.20) and total number of injections (odds ratio=1.013, p-value=0.002) are risk factors for the occurrence of at least 1 post-injection syndrome event in the patient over the course of his/her entire treatment.
Potential mechanisms	Clinical signs and symptoms appear to reflect excessive olanzapine concentrations in the systemic circulation, potentially resulting from vascular trauma associated with the IM injection. In association with vascular trauma, the higher solubility of olanzapine LAI in blood would permit a portion of the injected suspension to dissolve too rapidly. The event potentially may involve accidental intravascular injection of a portion of the dose, or a nick/puncture of a blood vessel encountered along the injection needle track to

Identified Risk: Post-Injection Syndrome (Olanzapine Long-Acting Injection)	
	open a portal for more rapid dissolution and absorption of a portion of the IM dose (McDonnell et al. 2010). While the risk factors identified in Study B034 (male gender and high dose) were robust, statistically, the mechanism of action is not understood for either risk factor. The difference in risk across genders is not fully understood, as gender may instead be a proxy for gluteal adiposity and therefore protective of vascular injury during injection. Dose is directly related to volume of injection, and therefore, may represent a greater opportunity for a higher plasma concentration.
Preventability	There are no specific measures known to prevent post-injection syndrome. Although gender and dose were strong risk factors in Study B034, the mechanism of action is not understood for either risk factor, the baseline risk of post-injection syndrome remains low, and there are no clinically relevant risk minimisation actions to take.
Impact on individual patient	For those patients with a post-injection syndrome event, impact on the patient typically involves hospitalization for 1 to 2 days while symptoms resolve. The majority of cases of post-injection syndrome can be managed through observation only or through observation and fluids. However, approximately one third of cases are treated with medications to manage the symptoms of post- injection syndrome and 14% in clinical trials have received other active interventions (such as use of physical restraints, intubation, catheterization, or administration of oxygen).
Potential public health impact of safety concern	Post-injection syndrome events have occurred for 0.07% of olanzapine LAI injections (1.85% of patients) in clinical trials. The rate of post-injection syndrome in real-world use (Study B034) was lower than in clinical trials, 0.04% of injections and 1.17% of patients. Due to the low rate of occurrence and the existing requirement that patients be observed at the healthcare facility for an extended period after the injection so that potential post-injection syndrome can be managed, public health impact of this safety concern is minimal/negligible
Evidence source	IAIV Injection Event Special Safety Topics Report; Summary Clinical Safety; Clinical Overview, 10-Month Safety Update, CHMP Day 180 Response to Major Objection Question 2. IPCD report December 2008. Research article on Post-Injection Delirium/Sedation Syndrome in Patients with Schizophrenia Treated with Olanzapine Long-Acting Injection (Detke et al. 2010; McDonnell et al. 2010). F1D-MC-B034 Final Study Report
MedDRA terms	Post-injection syndrome

Abbreviations: AE = adverse event; BMI = body mass index; CI = confidence interval; IM = intramuscular; LAI = long-acting injection.

SVII.4. Identified and Potential Interactions

SVII.4.1. Overview of Potential for Interactions

All Formulations

Given the primary central nervous system (CNS) effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol. Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents. Olanzapine may antagonize the effects of levodopa and dopamine agonists.

Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 could potentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance; therefore, a dosage increase (for induction) or decrease (for inhibition) may need to be considered for specific drugs.

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit cytochrome P450 1A2 (CYP1A2), 2C9 (CYP2C9), 2C19 (CYP2C19), 2D6 (CYP2D6), and 3A4 (CYP3A4). Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

There are no important identified and potential interactions for olanzapine. Of note, no drug-drug interactions were observed in studies involving concomitant administration of olanzapine with ethanol, warfarin, lithium, valproate, or lorazepam.

A number of postmarketing cardiovascular-related serious adverse events (SAEs), which included some deaths, have been reported in temporal association with RAIM olanzapine treatment. In most cases, it was reported that patients were treated with intramuscular (IM) olanzapine in a manner that was not studied in clinical trials. These situations included the concomitant administration of IM olanzapine and parenteral benzodiazepines or other antipsychotics, as well as the use of IM olanzapine in the presence of significant medical comorbidities or other clinical conditions associated with potentially fatal outcomes.

Olanzapine Long-Acting Injection (LAI)

The olanzapine LAI clinical trial database was analysed with respect to cardiovascular-related events in the presence of benzodiazepines. No apparent clinically significant interaction was observed between benzodiazepine use and olanzapine LAI treatment on cardiovascular or hemodynamic function. However, consistent with oral olanzapine labelling and based on the primary CNS effects of olanzapine, the SmPC for olanzapine LAI indicates that caution should be used when taking olanzapine LAI in combination with other centrally acting medicines or alcohol. Overall outcomes from the postmarketing database are also consistent with labelling.

SVII.4.2. Important Identified and Potential Interactions

Table SVII.3. Important Identified and Potential Interactions

Effect of interaction	Not applicable.
Evidence source	Not applicable.
Possible mechanisms	Not applicable.
Potential health risk	Not applicable.
Discussion	Not applicable.

SVII.5. Pharmacological Class Effects

SVII.5.1. Pharmacological Class Risks already included as Important Identified or Potential Risks

Table SVII.4. Pharmacological Class Risks included as Important Identified or Potential Risks

Risk	Frequency in Clinical Trials of Medicinal Product	Frequency Seen with Other Products in Same Pharmacological Class	Comment
Weight gain (adults and <18 years of age)	Adults: 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight <18 years: 40.6% of olanzapine-treated patients gained at least 7% of their baseline weight	**Molindone[b]:** (mean kg [SD]) • Weight change: 0.3 (2.9) **Quetiapine[a]:** • Weight gain >7%: 24% **Risperidone[a,b]:** • Weight gain[a] >7%: 14% • Weight change[b] (mean kg [SD]): 3.6 [4.0]	None
Glucose dysregulation (adults and <18 years of age)	Adults: (mean change) Fasting glucose: 2.76 mg/dL <18 years: (mean change) Fasting glucose: 2.68 mg/dL	**Molindone[b]:** (mean change [SD]) • Glucose: 0.9 mg/dL (12.0) • Insulin: 1.2 mU/L (7.1) • HOMA-IR: 0.5 mUmMol/L^2 (1.9) **Quetiapine[a]:** (mean change [SE]) • Blood glucose: 3.3 mg/dL (3.1) **Risperidone[a]:** (mean change [SE]) • Blood glucose: -0.4 mg/dL (4.4) **Risperidone[b]** : (mean change [SD]) • Glucose: 1.2 mg/dL (7.3) • Insulin: -2.4 mU/L (19.4) • HOMA-IR: 0.0 mUmMol/L^2 (1.7)	None

Pharmacological Class Risks included as Important Identified or Potential Risks

Risk	Frequency in Clinical Trials of Medicinal Product	Frequency Seen with Other Products in Same Pharmacological Class	Comment
Dyslipidaemia (adults and <18 years of age)	Adults: (mg/dL) • Fasting triglyceride level - increase of ≥50 mg/dL: 39.6% • Fasting total cholesterol level - increase of ≥40 mg/dL: 21.6% • Fasting LDL cholesterol level - increase of ≥30 mg/dL: 23.7% <18 years: (mean change) • Fasting cholesterol: 12.87 mg/dL • Fasting triglycerides: 28.35 mg/dL	**Molindone[b]**: (mean change [SD]) • Total cholesterol: 0.0 mg/dL (16.0) • HDL: 0.3 mg/dL (10.6) • LDL: 0.48 mg/dL (14.5) • Triglycerides: -5.8 mg/dL (44.7) **Quetiapine[a]**: (mean change [SE]) • Total cholesterol: 1.3 mg/dL (4.9) • Triglycerides: 25.6 mg/dL (17.0) **Risperidone[a]**: (mean change [SE]) • Total cholesterol: 4.4 mg/dL (5.3) • Triglycerides: 7.4 mg/dL (11.0) **Risperidone[b]**: (mean change [SD]) • Total cholesterol: -10.2 mg/dL (26.7) • HDL: -4.0 mg/dL (9.4) • LDL: -9.6 mg/dL (22.2) • Triglycerides: 7.1 mg/dL (33.3)	None
Increased risk of cardiac death (presumed sudden cardiac death)	No cardiac deaths have occurred in clinical trials.	Incidence-Rate Ratio (95% CI)[e] Haloperidol: 1.61 (1.16-2.24) Thioridazine: 3.19 (2.41-4.21) Clozapine: 3.67 (1.94-6.94) Quetiapine: 1.88 (1.30-2.71) Risperidone: 2.91 (2.26-3.76)	None
Sedation (<18 years of age)	34.8% olanzapine-treated patients reported at least 1 sedation-related event	**Molindone[b]**: 5% discontinued due to sedation **Quetiapine[a]**: 3% discontinued due to sedation **Risperidone[b]**: 2% discontinued due to sedation	None
Hepatic-related adverse events (<18 years of age)	• Elevated ALT (≥3 times ULN in patients with ALT at baseline <3 times ULN): 12% • Elevated AST: 28% • Low total bilirubin: 22% • Elevated GGT: 10%	**Molindone[b]**: (mean U/L [SD]) • ALT change: -2.8 (14.8) • AST change: -3.2 (10.0) **Quetiapine[d]**: • Elevations in ALT,: common (>1/100 to ≤1/10) • Elevations in AST: uncommon (≥1/1000 to <1/100) • Elevations in GGT levels: common (>1/100 to ≤1/10) • Jaundice: rare (>1/10 000 to ≤1/1000) • Hepatitis: rare (>1/10 000 to ≤1/1000)	None

Pharmacological Class Risks included as Important Identified or Potential Risks

Risk	Frequency in Clinical Trials of Medicinal Product	Frequency Seen with Other Products in Same Pharmacological Class	Comment
		Risperidone[c]: • Transaminases increased: uncommon (≥1/1000 to <1/100) • GGT increased: uncommon (≥1/1000 to <1/100) • Hepatic enzyme increased: uncommon (≥1/1000 to <1/100) • Jaundice: rare (>1/10 000 to ≤1/1000) **Risperidone[b]:** • ALT change (U/L [SD]): -5.2 [19,5] • AST change (U/L [SD]): -2.8 [9,7]	
Hyperprolactinemia (<18 years of age)	47.4% of olanzapine-treated patients experienced treatment–emergent abnormally high prolactin levels	**Molindone[b]:** (mean change [SD]) • Prolactin: -8.8 µg/L (24.9) **Quetiapine[a]:** (mean change [SE]) • Prolactin: -10.8 ng/mL (2.9) **Risperidone[b]:** (mean change [SD]) • Prolactin: 19.5 µg/L (21.5)	None

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; GGT = gamma glutamyltransferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SD = standard deviation; SE = standard error; SmPC = Summary of Medicinal Product Characteristics; ULN = upper limit of normal.

a Stroup et al. 2007 (population between 18 and 65 years old).

b Sikich et al. 2008 (population between 8 and 19 years old).

c Risperidal SmPC, 2015.

d Seroquel SmPC, 2015.

e Ray et al. 2009.

SVII.5.2. Important Pharmacological Class Effects not Discussed Above

Table SVII.5. Important Pharmacological Class Effects (Not Important Identified or Potential Risks)

Potential Risks: Leucopoenia, Neutropenia, and Agranulocytosis	
Seriousness/outcomes	Not available.
Severity and nature of risk	In a study conducted in the UK/Ireland between January 1990 and July 1994, among 6316 patients treated with clozapine the incidence of fatal agranulocytosis was 0.03% (95% CI: 0.006-0.12) (Atkin et al. 1996).
Frequency with other members of the same or similar pharmacological class with 95%CI	Clozapine: Agranulocytosis 0.8% at 1 year (Alvir et al. 1993). In clinical trial and postmarketing experience, events of leukopaenia/neutropaenia have been temporally related to atypical antipsychotic agents.
Risk groups or risk factors	No evidence of a dose relationship to agranulocytosis. Risk factors for clozapine-induced agranulocytosis include older age, female gender and certain ethnic groups (Ashkenazi Jews).
Potential mechanisms	The pathophysiological mechanism is unknown. Clozapine-induced agranulocytosis selectively affects precursors of polymorphonuclear leucocytes in the bone marrow. There is some evidence that it is immunologically mediated (Alvir et al. 1993).
Comment	None.

Abbreviations: CI = confidence interval; UK = United Kingdom.

Module SVIII. Summary of the Safety Concerns

Important risks for olanzapine are also risks for olanzapine LAI.

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

Summary of Safety Concerns for All Formulations of Olanzapine	
Important Identified Risks	• Weight gain • Glucose dysregulation • Dyslipidaemia
Important Potential Risks	• Increased risk of cardiac death (presumed sudden cardiac death)
Missing Information	• N/A
Summary of Safety Concerns Specific to Patients <18 Years of Age	
Important Identified Risks	• Sedation • Hepatic-related events • Hyperprolactinaemia
Important Potential Risks	• N/A
Missing Information	• N/A
Summary of Safety Concerns Specific to RAIM Formulation of Olanzapine	
Important Identified Risks	• N/A
Important Potential Risks	• Risk of mortality
Missing Information	• N/A
Summary of Safety Concerns Specific to LAI Formulation of Olanzapine	
Important Identified Risks	• Post-injection syndrome
Important Potential Risks	• N/A
Missing Information	• N/A

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

Part III. Pharmacovigilance Plan

III.1. Safety Concerns and Overview of Planned Pharmacovigilance Actions

Important risks for oral olanzapine listed below are also risks for olanzapine LAI.

Table III.1. Weight Gain (Adults and <18 Years of Age) and Planned Pharmacovigilance Activities

Weight Gain (Adults and <18 Years of Age)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None identified.	Routine pharmacovigilance	To fulfil marketing authorisation holder legal obligations for pharmacovigilance within Directive 2001/83/EC.

Table III.2. Glucose Dysregulation and Planned Pharmacovigilance Activities

Glucose Dysregulation (Adults and <18 Years of Age) (Olanzapine)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None identified.	Routine pharmacovigilance	To fulfil marketing authorisation holder legal obligations for pharmacovigilance within Directive 2001/83/EC.

Table III.3. Dyslipidaemia and Planned Pharmacovigilance Activities

Dyslipidaemia (Adults and <18 Years of Age) (Olanzapine)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None identified.	Routine pharmacovigilance	To fulfil marketing authorisation holder legal obligations for pharmacovigilance within Directive 2001/83/EC.

Table III.4. Increased Risk of Cardiac Death (Presumed Cardiac Death) and Planned Pharmacovigilance Activities

Increased Risk of Cardiac Death (Presumed Cardiac Death) (Olanzapine)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None identified.	Routine pharmacovigilance	To fulfil marketing authorisation holder legal obligations for pharmacovigilance within Directive 2001/83/EC.
None identified.	Targeted surveillance	To continue to obtain targeted follow-up for the collection and evaluation of complete and quality scientific medical data used in ongoing and focused review and evaluation of spontaneous reports relating to cardiac death that would contribute to appropriate decisions on the risk-benefit profile, as well as ensuring appropriate product labelling.

Table III.5. Sedation and Planned Pharmacovigilance Activities

Sedation (Specific to Patients <18 Years of Age Olanzapine)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None identified.	Routine pharmacovigilance	To fulfil marketing authorisation holder legal obligations for pharmacovigilance within Directive 2001/83/EC.

Table III.6. Hepatic-Related Events and Planned Pharmacovigilance Activities

Hepatic-Related Events (Specific to Patients <18 Years of Age Olanzapine)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None identified.	Routine pharmacovigilance	To fulfil marketing authorisation holder legal obligations for pharmacovigilance within Directive 2001/83/EC.
None identified.	Targeted surveillance	To continue to obtain targeted follow-up for the collection and evaluation of complete and quality scientific medical data used in ongoing and focused review and evaluation of spontaneous reports relating to hepatic events that would contribute to appropriate decisions on the risk-benefit profile, as well as ensuring appropriate product labelling.

Table III.7. Hyperprolactinaemia and Planned Pharmacovigilance Activities

Hyperprolactinaemia (Specific to Patients <18 Years of Age Olanzapine)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None identified	Routine pharmacovigilance	To fulfil marketing authorisation holder legal obligations for pharmacovigilance within Directive 2001/83/EC.

Table III.8. Risk of Mortality and Planned Pharmacovigilance Activities

Risk of Mortality (Rapid-Acting Intramuscular [RAIM])		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None identified.	Routine pharmacovigilance	To fulfil marketing authorisation holder legal obligations for pharmacovigilance within Directive 2001/83/EC.

Table III.9. Post-Injection Syndrome and Planned Pharmacovigilance Activities

Post-Injection Syndrome (Olanzapine LAI)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None identified	Routine pharmacovigilance	To fulfil marketing authorisation holder legal obligations for pharmacovigilance within Directive 2001/83/EC.
None identified	Targeted surveillance	To continue to obtain targeted follow- up for the collection and evaluation of complete and quality scientific medical data used in ongoing and focused review and evaluation of spontaneous reports relating to post-injection syndrome that would contribute to appropriate decisions on the risk- benefit profile, as well as ensuring appropriate product labelling.
Determination of the incidence, potential risk factors, and presentation of post-injection syndrome events in clinical use	Registry - F1D-MC-B041 Zyprexa Relprevv Patient Care Program Registry (US REMS)	To establish long-term safety and safe use of Zyprexa Relprevv through periodic monitoring for the risk of post- injection syndrome events and by enrolling all patients who receive Zyprexa Relprevv in the Zyprexa Relprevv Patient Care Program Registry.

Abbreviation: LAI = long-acting injection.

III.2. Additional Pharmacovigilance Activities to Assess Effectiveness of Risk Minimisation Measures

Table III.10. Assessment of Effectiveness of EU Risk Minimisation Measures, All Formulations

Targeted Surveillance		
Component Measured	**Activities**	**Rationale**
Not applicable.		

III.3. Studies and Other Activities Completed Since Last Update of Pharmacovigilance Plan

Table III.11. Studies and Other Activities Completed since Last Update of Pharmacovigilance Plan

F1D-MC-B034: Post-Injection Syndrome in Patients with Schizophrenia Receiving Olanzapine Long-Acting Injection	
Safety concern(s) risk minimisation measure investigated	Post-injection syndrome
Brief summary of results	Post-injection syndrome occurred in 0.044% of injections and 1.17% of patients. Based on 45 of the 46 confirmed post-injection syndrome events with time-to-onset information, 91.1% (n=41) occurred within 1 hour of injection, 4.4% (n=2) occurred between 1 and 2 hours of injection, 2.2% (n=1) occurred between 2 and 3 hours, and 2.2% (n=1) occurred after 3 hours. Time to recovery from the post-injection syndrome event was within 72 hours for 95.5% of patients (range 6 hours to 11 days). Regression analyses indicate risk factors for post-injection syndrome on the per-injection basis included high dose and male gender. Analysis conducted at the patient level suggest that male gender and total number of injections are risk factors for the occurrence of at least 1 post-injection syndrome event in the patient over the course of his/her entire treatment. Twelve months before enrolling in Study B034, 48% of patients had a psychiatric hospitalization. After enrolment in Study B034, hospitalisations so rarely occurred that the median rate of hospitalization per year was zero, with only 425 (11%) patients with a psychiatric hospitalisation over the course of study participation.
Implications	Study B034 results reinforce that the rates, timing for the onset of and recovery from post-injection syndrome, and severity of post-injection syndrome events are not greater than observed in controlled clinical trials. Rates from clinical development provide the basis for product labelling (USPI and SmPC) and are in part described in Detke et al. 2010. The post-injection syndrome rates were lower and more post-injection syndrome events were identified within 1 hour of injection in Study B034 compared to clinical development—a possible reflection of successful risk minimization activities. The benefit-risk profile of olanzapine LAI continues to remain favourable for adult patients with schizophrenia, and no additional risk minimization activities are warranted.

Abbreviations: LAI = long-acting injection; SmPC = Summary of Medicinal Product Characteristics; USPI = United States Package Insert.

III.4 Details of Outstanding Additional Pharmacovigilance Activities

None.

III.4.1. Imposed Mandatory Additional Pharmacovigilance Activity (Key to Benefit Risk)

Table III.12. Imposed Activities Considered Key to the Benefit-Risk of the Product, All Formulations

	Description of Activity	Milestone(s)	Due Date(s)
	Not applicable.		

III.4.2. Mandatory Additional PhV Activity (Being a Specific Obligation)

Table III.13. Specific Obligations, All Formulations

	Description of activity	Milestone(s)	Due Date(s)
	Not applicable.		

III.4.3. Required Additional Pharmacovigilance Activities to Address Specific Safety Concerns or to Measure Effectiveness of Risk Minimisation Measures

Table III.14. Required Additional Pharmacovigilance Activities, All Formulations

	Description of activity	Milestone(s)	Due Date(s)
1	F1D-MC-B041: Zyprexa Relprevv Patient Care Program Registry (US REMS)	Annual REMS Assessment Report	October

Abbreviations: REMS = Risk Evaluation and Mitigation Strategy; US = United States.

III.4.4 Stated Additional Pharmacovigilance Activities

Table III.15. Stated Additional Pharmacovigilance Activities, Oral Olanzapine and RAIM

	Description of Activity	Expected Date of Report
1	F1D-JE-CS09: Post-marketing surveillance of olanzapine treatment in acutely agitated patients with schizophrenia 24 hours post-injection in Japan	21 July 2017
2	F1D-JE-CS11: Post-marketing surveillance of olanzapine treatment in acutely agitated patients initially treated with olanzapine intramuscular (IM) and followed by oral olanzapine (Japan)	31 July 2017

Table III.16. Stated Additional Pharmacovigilance Activities, Olanzapine Long-Acting Injection (LAI)

	Description of Activity	Expected Date of Report
	None	

III.5. Summary of the Pharmacovigilance Plan

III.5.1. Table of Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Table III.17. Ongoing and Planned Studies Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan, Oral Olanzapine and Rapid-Acting Intramuscular (RAIM)

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
None.				

Table III.18. Ongoing and Planned Studies Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan, Olanzapine Long-Acting Injection (LAI)

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
F1D-MC-B041 Zyprexa Relprevv Patient Care Program Registry (US REMS)	To establish long-term safety and safe use of Zyprexa Relprevv through periodic monitoring for the risk of post-injection syndrome events and by enrolling all patients who receive Zyprexa Relprevv in the Zyprexa Relprevv Patient Care Program Registry	Post-injection syndrome	Ongoing	Not applicable (US Registry; annual assessment reports provided to FDA)

Abbreviations: FDA = Food and Drug Administration; LAI = long-acting injection; REMS = Risk Evaluation and Mitigation Strategy; US = United States.

III.5.2. Table of Completed Studies/Activities from the Pharmacovigilance Plan

Table III.19. Completed Studies from the Postmarketing Pharmacovigilance Development Plan, All Formulations

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 behavioural weight intervention program was superior to a standard behavioural weight intervention program in mitigation of weight gain. The behavioural 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 to the CHMP 06 November 2013.

Completed Studies from the Postmarketing Pharmacovigilance Development Plan, All Formulations

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Completed)	Date of Submission of Final Report
F1D-MC-B034 Post-Injection Syndrome in Patients with Schizophrenia Receiving Olanzapine Long-Acting Injection, Category 3	Estimate the per-injection and per-patient incidence of post-injection syndrome events among patients with schizophrenia receiving olanzapine LAI, characterise the clinical presentation of these events, identify potential risk factors associated with these events, and characterise hospitalisation at baseline (previous 6 or 12 month) and postbaseline.	Post-injection syndrome	Completed	Final study report submitted to EMA and FDA Q3 2016.

Abbreviations: AMI = acute myocardial infarction; BMI = body mass index; CHMP = Committee for Medicinal Products for Human Use; EMA = European Medicines Agency; FDA = Food and Drug Administration; LAI = long-acting injection; PASS = postauthorisation safety study; Q = quarter; SCD = sudden cardiac death.

Part IV. Plans for Postauthorisation Efficacy Studies

IV.1. Applicability to Efficacy to All Patients in the Target Population

All Formulations

Olanzapine has been approved for use in the European Union and worldwide for over 17 years. It has been studied and approved for use in the acute and maintenance treatment of schizophrenia and bipolar disorder. The use of olanzapine in these treatment populations is well understood and studied. There is no evidence that the efficacy of olanzapine is limited to specific populations or subpopulations. The generalizability of the efficacy of olanzapine treatment from the clinical studies to environments outside of the clinical trial setting has been supported by observational and real world studies (Haro et al. 2003; Stroup et al. 2007) which have confirmed similar efficacy in multiple environments outside the clinical study setting. Reviews of extensive postmarketing data collected during the use of olanzapine have not identified any efficacy or safety issues not already identified in the current labelling for the treatment. Clinical trial data have not revealed any variability in the benefits of treatment for subpopulations, in general.

There are no plans for further efficacy studies for olanzapine.

IV.2. Tables of Postauthorisation Efficacy Studies

Table IV.1. Efficacy Studies that are Specific Obligations and/or Conditions of the Market Authorisation, All Formulations

Description of Study (including Objectives and Study Number)	Milestone(s)	Due Date (s)
Not applicable.		

Table IV.2. Other Efficacy/Effectiveness Studies, All Formulations

Description of Study (including Objectives and Study Number)	Milestone(s)	Due Date (s)
Not applicable.		

IV.3. Summary of Postauthorisation Efficacy Development Plan

There are no plans for further efficacy studies in the target population for the currently authorised indications.

Table IV.3. Summary of Post-authorisation Efficacy Development Plan, All Formulations

Study (Type and Study Number)	Objectives	Efficacy Uncertainties Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports
Not applicable.				

IV.4. Summary of Completed Postauthorisation Efficacy Studies for Authorized Indications

Table IV.4. Summary of Completed Postauthorisation Efficacy Studies for Authorised Indications, All Formulations

Study (Type and Study Number)	Objectives	Efficacy Uncertainties Addressed	Status (Completed, Study Report Submitted)	Date of Submission of Final Study Report
F1D-JE-CSOS	Observational study to estimate the all-cause discontinuation rate at 12 months in Japanese patients with acute schizophrenia treated with antipsychotic medications when used as mono-therapy.	Olanzapine's superiority in efficacy, as measured by discontinuation rate and beyond compared to SOC in NSOS.	Complete	31 May 2013

Abbreviations: NSOS = non-safety observational study; SOC = standard of care.

Part V. EU Risk Minimisation Measures

V.1. Risk Minimisation Measures

Table V.1. Risk Minimisation Measures by Safety Concern: Weight Gain

Weight Gain	
Objective(s) of the routine risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	Text in SmPC: Section 4.2 Posology and method of administration *Paediatric population* Olanzapine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in short-term studies of adolescent patients than in studies of adult patients (see sections 4.4, 4.8, 5.1, and 5.2). Text in SmPC: Section 4.4 Special warnings and precautions for use *Adults, under Hyperglycaemia and diabetes* Weight should be monitored regularly, eg, at baseline, 4, 8 and 12 weeks after starting olanzapine treatment and quarterly thereafter. *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). Text in SmPC: Section 4.8 Undesirable effects *Adults* The most frequently (seen in ≥1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose, and triglyceride levels (see section 4.4), glycosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopaenia, neutropenia (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases (see section 4.4), rash, asthenia, fatigue, pyrexia, arthralgia, increased alkaline phosphatase, high gamma glutamyltransferase, high uric acid, high creatine phosphokinase, and oedema. *Listed in Tabulated list of adverse reactions: Adults* Weight gain[1], very common [1]Clinically significant weight gain was observed across all baseline body mass index (BMI) categories. Following short-term treatment (median duration 47 days), weight gain ≥7% of baseline body weight was very common (22.2%); ≥15% was common (4.2%); and ≥25% was uncommon (0.8%). Patients gaining ≥7%, ≥15% and ≥25% of their baseline body weight with long-term exposure (at least 48 weeks) were very common (64.4%, 31.7% and 12.3%, respectively).

Risk Minimisation Measures by Safety Concern: Weight Gain

Weight Gain	
Routine risk minimisation measures (continued)	*Long-term exposure (at least 48 weeks)* The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol, or triglycerides increased over time. In adult patients who completed 9 to 12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months. *Additional information on special populations* In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1%; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥10%) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥7% from baseline body weight in 39.9% of patients. *Paediatric population* Clinically significant weight gain (≥7%) appears to occur more frequently in the adolescent population compared to adults with comparable exposures. The magnitude of weight gain and the proportion of adolescent patients who had clinically significant weight gain were greater with long-term exposure (at least 24 weeks) than with short-term exposure. Weight gain[13], very common [13]Following short-term treatment (median duration 22 days), weight gain ≥7% of baseline body weight (kg) was very common (40.6%); ≥15% of baseline body weight was common (7.1%) and ≥25% was common (2.5%). With long-term exposure (at least 24 weeks), 89.4% gained ≥7%, 55.3% gained ≥15% and 29.1% gained ≥25% of their baseline body weight. **Text in SmPC: Section 5.3 Preclinical safety data** *Acute (Single-Dose) Toxicity* Signs of oral toxicity in rodents were characteristic of potent neuroleptic compounds: hypoactivity, coma, tremors, clonic convulsions, salivation, and depressed weight gain. The median lethal doses were approximately 210 mg/kg (mice) and 175 mg/kg (rats). Dogs tolerated single oral doses up to 100 mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, laboured respiration, miosis, and anorexia. In monkeys, single oral doses up to 100 mg/kg resulted in prostration and, at higher doses, semi-consciousness.
	Comment: Wording regarding this risk has been included in the olanzapine SmPC since 1996.
	Other routine risk minimisation measures None proposed.

Risk Minimisation Measures by Safety Concern: Weight Gain

Weight Gain	
Additional risk minimisation measure(s)	**Objective and justification:** None.
	Proposed actions/component and rationale: None.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessments	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Additional or different risk minimisation activities are not needed for weight gain.

Abbreviations: BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SmPC = summary of product characteristics.

Table V.2. Risk Minimisation Measures by Safety Concern: Glucose Dysregulation

Glucose Dysregulation	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	Text in SmPC: Section 4.4 Special warnings and precautions for use *Hyperglycaemia* and *diabetes* Hyperglycaemia and/or development or exacerbation of diabetes, occasionally associated with ketoacidosis or coma, has been reported uncommonly, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines, eg, measuring of blood glucose at baseline, 12 weeks after starting olanzapine treatment and annually thereafter. Patients treated with any antipsychotic agents, including ZYPREXA/ZYPREXA VELOTAB, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness), and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. **Text in SmPC: Section 4.8 Undesirable effects** *Adults* The most frequently (seen in ≥1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glycosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopaenia, neutropenia (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases (see section 4.4), rash, asthenia, fatigue, pyrexia, arthralgia, increased alkaline phosphatase, high gamma glutamyltransferase, high uric acid, high creatine phosphokinase, and oedema. *Tabulated list of adverse reactions: Adults* Elevated glucose levels[4], common Glycosuria, common [4]Observed for fasting normal levels at baseline (<5.56 mmol/l) which increased to high (≥7 mmol/l). Changes in fasting glucose from borderline at baseline (≥5.56 - < 7 mmol/l) to high (≥7 mmol/l) were very common. *Long-term exposure (at least 48 weeks):* The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol, or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.
	Comment: Wording regarding this risk has been included in the olanzapine SmPC since 1999.
	Other routine risk minimisation measures: None.
Additional risk minimisation measure(s)	**Objective and justification:** None.
	Proposed actions/component and rationale: None.

Risk Minimisation Measures by Safety Concern: Glucose Dysregulation

Glucose Dysregulation	
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessments	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Additional or different risk minimisation activities are not needed for glucose dysregulation.

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; SmPC = summary of product characteristics.

Table V.3. Risk Minimisation Measures by Safety Concern: Dyslipidaemia

Dyslipidaemia	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**Text in SmPC: Section 4.2 Posology and method of administration** *Paediatric population* Olanzapine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in short-term studies of adolescent patients than in studies of adult patients (see sections 4.4, 4.8, 5.1, and 5.2). **Text in SmPC: Section 4.4 Special warnings and precautions for use** *Lipid alterations* Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidaemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic agents, including ZYPREXA/ZYPREXA VELOTAB, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines, eg, at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter. **Text in SmPC: Section 4.8 Undesirable effects** *Tabulated list of adverse reactions:* *Adults* Elevated cholesterol levels[2], common [2]Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline.
	Comment: Wording regarding this risk has been included in the olanzapine SmPC since 2007.
	Other routine risk minimisation measures: None.
Additional risk minimisation measure(s)	**Objective and justification:** None.
	Proposed actions/component and rationale: None.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessments	Not applicable.
Results of effectiveness measurement	Not applicable.

Risk Minimisation Measures by Safety Concern: Dyslipidaemia

Dyslipidaemia	
Impact of risk minimisation	Not applicable.
Comment	Additional or different risk minimisation activities are not needed for dyslipidaemia.

Abbreviations: LDL = low-density lipoprotein; SmPC = summary of product characteristics.

Table V.4. Risk Minimisation Measures by Safety Concern: Sedation (Patients <18 Years of Age)

Sedation (Patients <18 Years of Age)	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**Text in SmPC: Section 4.8 Undesirable effects** *Tabulated list of adverse reactions:* *Paediatric population* Sedation, Very common (including hypersomnia, lethargy, somnolence)
	Comment: Wording regarding this risk has been included in the olanzapine SmPC since 2008.
	Other routine risk minimisation measures: None.
Additional risk minimisation measure(s)	**Objective and justification:** None.
	Proposed actions/component and rationale: None.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessments	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Additional or different risk minimisation activities are not needed for sedation.

Abbreviation: SmPC = summary of product characteristics

Table V.5. Risk Minimisation Measures by Safety Concern: Hepatic-Related Adverse Events (Patients <18 Years of Age)

Hepatic-Related Adverse Events (Patients <18 Years of Age)	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	The SmPC contains text related to hepatic-related adverse events for patients irrespective of age group within various Sections, besides specifically listing hepatic-related adverse events seen in patients <18 years of age. **Text in SmPC: Section 4.2 Posology and method of administration** *Patients with renal and/or hepatic impairment* A lower starting dose (5 mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh class A or B), the starting dose should be 5 mg and only increased with caution. **Text in SmPC: Section 4.4 Special warnings and precautions for use** *Hepatic function* Transient, asymptomatic elevations of hepatic aminotransferases ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised and follow-up organised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicines. In cases where hepatitis (including hepatocellular, cholestatic, or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued. **Text in SmPC: Section 4.8 Undesirable effects** *Tabulated list of adverse reactions: Paediatric population* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4), very common **Text in SmPC: Section 5.2 Pharmacokinetic properties** *Smokers* In smoking subjects with mild hepatic dysfunction, mean elimination half-life (39.3 hours) was prolonged and clearance (18.0 l/hr) was reduced analogous to nonsmoking healthy subjects (48.8 hours and 14.1 l/hr, respectively).
	Comment: Wording specific to patients <18 years of age regarding this risk has been included in the olanzapine SmPC since 2008.
	Other routine risk minimisation measures: None.
Additional risk minimisation measure(s)	**Objective and justification:** None.
	Proposed actions/component and rationale: None.

Risk Minimisation Measures by Safety Concern: Hepatic-Related Adverse Events (Patients <18 Years of Age)

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessments	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Additional or different risk minimisation activities are not needed for hepatic-related events.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; SmPC = summary of product characteristics.

Table V.6. Risk Minimisation Measures by Safety Concern: Hyperprolactinaemia (Patients <18 Years of Age)

Hyperprolactinaemia (Patients <18 Years of Age)	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**Text in SmPC: Section 4.2 Posology and method of administration** *Paediatric population* Olanzapine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in short-term studies of adolescent patients than in studies of adult patients (see sections 4.4, 4.8, 5.1, and 5.2). **Text in SmPC: Section 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). **Text in SmPC: Section 4.8 Undesirable effects** *Tabulated list of adverse reactions: Paediatric population* Elevated plasma prolactin levels[16], very common [16]Elevated plasma prolactin levels were reported in 47.4% of adolescent patients **Text in SmPC: Section 5.1 Pharmacodynamic properties** *Paediatric population* The experience in adolescents (ages 13 to 17 years) is limited to short-term 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 data on maintenance of effect and limited data on long-term safety (see sections 4.4 and 4.8).
	Comment: Wording regarding this risk has been included in the olanzapine SmPC since 2008 for patients <18 years of age.
	Other routine risk minimisation measures: None.
Additional risk minimisation measure(s)	**Objective and justification:** None.
	Proposed actions/component and rationale: None.

Risk Minimisation Measures by Safety Concern: Hyperprolactinaemia (Patients <18 Years of Age)

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessments	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Additional or different risk minimisation activities are not needed for hyperprolactinaemia.

Abbreviations: LDL = low-density lipoprotein; SmPC = summary of product characteristics.

Table V.7. Risk Minimisation Measures by Safety Concern: Potential Increased Risk of Cardiac Death (Presumed Cardiac Death)

Potential Increased Risk of Cardiac Death (Presumed Cardiac Death)	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**Text in SmPC: Section 4.4 Special warnings and precautions for use** *Sudden cardiac death* In postmarketing reports with olanzapine, the event of sudden cardiac death has been reported in patients with olanzapine. In a retrospective observational cohort study, the risk of presumed sudden cardiac death in patients treated with olanzapine was approximately twice the risk in patients not using antipsychotics. In the study, the risk of olanzapine was comparable to the risk of atypical antipsychotics included in a pooled analysis.
	Comment: Wording regarding this risk has been included in the olanzapine SmPC since 2009.
	Other routine risk minimisation measures None.
Additional risk minimisation measure(s)	**Objective and justification:** None.
	Proposed actions/component and rationale: None.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessments	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Additional or different risk minimisation activities are not needed for increased risk of cardiac death (presumed cardiac death).

Abbreviation: SmPC = summary of product characteristics.

Table V.8. Risk Minimisation Measures by Safety Concern: Risk of Mortality (RAIM)

Risk of Mortality (RAIM)	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**Text in SmPC:** Warning in Section 4.4 of the SmPC states that concomitant injection of olanzapine IM and parenteral benzodiazepines is not recommended, and describes the associated signs and symptoms of this combination. Reference is also made in Section 4.5 of the SmPC to the events reported in patients treated with this combination. In Section 4.8 of the SmPC, reference is made to the temporal association of treatment with IM olanzapine with cases of respiratory depression, hypotension or bradycardia and death, mostly in patients who concomitantly received benzodiazepines.
	Comment: Wording regarding this risk has been included in the olanzapine SmPC since 2004.
	Other routine risk minimisation measures None.
Additional risk minimisation measure(s)	**Objective and justification:** None.
	Proposed actions/component and rationale: None.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	None proposed.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessments	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	Additional or different risk minimisation activities are not needed for risk of mortality.

Abbreviation: RAIM = rapid-acting intramuscular.

Table V.9. Risk Minimisation Measures by Safety Concern: Post-Injection Syndrome (Olanzapine LAI)

Post-Injection Syndrome (Olanzapine LAI-Specific)	
Objective(s) of the risk minimization measures	To ensure that prescribers are appropriately informed about this risk through labelling and advised on appropriate patient management.
Routine risk minimization measures	**Text in SmPC: 4.4 Special Warnings and Precautions for Use** Post-injectionsyndrome During pre-marketing clinical studies, reactions that presented with signs and symptoms consistent with olanzapine overdose were reported in patients following an injection of ZYPADHERA. These reactions occurred in <0.1% of injections and approximately 2% 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 and convulsion. In most cases, initial signs and symptoms related to this reaction have appeared within 1 hour following injection, and in all cases full recovery was reported to have occurred within 24 - 72 hours after injection. Reactions occurred rarely (<1 in 1000 injections) between 1 and 3 hours, and very rarely (<1 in 10 000 injections) after 3 hours. Patients should be advised about this potential risk and the need to be observed for 3 hours in a healthcare facility each time ZYPADHERA is administered. Post-marketing reports of post-injection syndrome since the marketing authorization of ZYPADHERA are generally consistent with the experience seen in clinical studies. After each injection, patients should be observed in a healthcare facility by appropriately qualified personnel for at least 3 hours for signs and symptoms consistent with olanzapine overdose. Immediately prior to leaving the healthcare facility, it should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose. If an overdose is suspected, close medical supervision and monitoring should continue until examination indicates that signs and symptoms have resolved. The 3-hour observation period should be extended as clinically appropriate for patients who exhibit any signs or symptoms consistent with olanzapine overdose. For the remainder of the day after injection, patients should be advised to be vigilant for signs and symptoms of overdose secondary to post-injection adverse reactions, be able to obtain assistance if needed, and should not drive or operate machinery (see section 4.7). If parenteral benzodiazepines are essential for management of post-injection adverse reactions, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended (see section 4.5). **Section 4.7 Effects on ability to drive and use machines** Patients should be advised not to drive or operate machinery for the remainder of the day after each injection due to the possibility of a post-injection syndrome event leading to symptoms consistent with olanzapine overdose (see section 4.4). **Section 4.8 Undesirable Effects** Post-injection syndrome reactions have occurred with ZYPADHERA leading to symptoms consistent with olanzapine overdose (see sections 4.2 and 4.4). Clinical signs and symptoms included symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety and other cognitive

<table>
<tr><th colspan="4">Post-Injection Syndrome (Olanzapine LAI-Specific)</th></tr>
<tr><td></td><td colspan="3">impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsion.</td></tr>
<tr><td></td><td colspan="3">Section 4.9 Overdose
If signs and symptoms of overdose consistent with post-injection syndrome are observed, appropriate supportive measures should be taken (see section 4.4).</td></tr>
<tr><td></td><td colspan="3">Comment
Wording regarding this risk has been included in the olanzapine SmPC since the initial approval in November 2008.</td></tr>
<tr><td></td><td colspan="3">Other routine risk minimisation measures
None</td></tr>
<tr><td>Additional risk minimisation measure(s)</td><td colspan="3">Healthcare Awareness Programme
Objective:
• Ensure that physicians and patients are aware of the risk of post-injection syndrome
• Inform, especially HCPs/prescribers, about the importance of adherence to labelling instructions
• Emphasize the importance of the recommended reconstitution and administration technique by trained HCPs

Proposed actions/component:
<table>
<tr><th>Educational Element</th><th>Description (Education Material)[a]</th><th>Status as of 30 September 2013</th></tr>
<tr><td>Sponsor-targeted internal activities</td><td>• Sales force and neuroscience medical function personnel education to convey warnings and information about potential post-injection syndrome events.
• Provide education to Lilly call centre and/or Medical Information service to prepare staff for answering questions and providing information with regard to post-injection syndrome.</td><td>• Training ongoing.</td></tr>
<tr><td>Sponsor-targeted external activities</td><td>• Convene external advisors (eg, Lilly regional Schizophrenia Advisory Board, Lilly regional Treatment Team Advisory Board) to explain how to best disseminate education to physicians, pharmacists, and patients, as regionally appropriate (medium: DVDs, slide presentations, lectures, letters, and/or web sites; delivery: direct mailings, internet, and/or in-person</td><td>• Ongoing in line with planned EU launch schedule</td></tr>
</table></td></tr>
</table>

Post-Injection Syndrome (Olanzapine LAI-Specific)				
		Educational Element	**Description (Education Material)[a]**	**Status as of 30 September 2013**
		Prescriber and physician-targeted activities	• Broad disclosure of product safety information to all psychiatrists and other depot prescribers through the Product Introduction Letter. • Education for targeted HCPs about the risk of accidental intravascular injection with intramuscularly injected drugs, as well as the clinical presentation of patients reporting post-injection syndrome events. In addition, targeted HCPs will be informed about other key safety concerns and available resources, such as the patient card.	• Letters have been distributed in the 22 launched countries in Europe[b] • Targeted prescribers have been trained (using various methods, eg, DVD or slide presentation) in the 22 launched countries in Europe.[b]
		Administrators of treatment-targeted activities (nurses, etc)	• Training for administration, including instructions for proper reconstitution and administration technique. • Provide education materials, including details on reconstitution and administration technique, as well as how to recognise post-injection syndrome events and other safety concerns.	• Administration and reconstitution training has been initiated and is ongoing in the 22 launched countries in Europe.[b] • Educational materials pertaining to reconstitution and administration of olanzapine LAI have been distributed as appropriate in the 22 launched countries in Europe.[b]
		Patient-targeted activities	• Provide patient card through the physician or administrator of treatment which will include information about post-injection syndrome risk, the need for monitoring signs and symptoms, as well as other safety information, and to help provide potential event management information (eg, HCPs' phone numbers, local emergency numbers, information on taking the product). • Disseminate patient materials to HCPs for use beginning at time of launch.	• Patient card distribution to healthcare professionals is ongoing as appropriate in each of the 22 launched countries in Europe.[b]
		Note: The Zypadhera product training slides and the patient information card are included in Annex 11 of this RMP. Abbreviations: DVD = digital video disk; EU = European Union; HCP = healthcare professional; LAI = long-acting injection; PIL = Patient Information Leaflet; SmPC = Summary of Product Characteristics.		

Post-Injection Syndrome (Olanzapine LAI-Specific)	
	[a] Educational material refers to: recommended reconstitution and administration techniques (not needed for patients); risk of post-injection syndrome; presentation of these events (signs and symptoms); need for a 3-hour, observational period post-injection; recommendation for patients to observe a 3-hour period post-injection, to avoid driving or using machinery, and to be vigilant for signs and symptoms of post-injection syndrome events, and to be able to obtain assistance, if needed. [b] As of 30 September 2013, olanzapine LAI has been launched in 22 European countries (Austria, Belgium, Bulgaria, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Romania, Slovakia, Spain, Sweden, and the United Kingdom).
Effectiveness of risk minimisation measures	
How effectiveness of risk minimization measures for the safety concern will be measured	**Healthcare Awareness Program:** Completed assessment (Post-Injection Syndrome survey) of the risk minimization training program for targeted prescribers (percent trained). In the EU, to evaluate the awareness and adherence to the SmPC by HCPs, the Post-Injection Syndrome Survey has been conducted 6 to 12 months post launch among HCPs who received training through the Healthcare Awareness Program. The results of the Wave 4, Post-Injection Syndrome survey of Healthcare Professionals (HCPs), were submitted as an Addendum to RMP (v10) in July 2012. Lilly's proposal to discontinue future surveys was endorsed by the CHMP on 20 September 2012 (Ref: Rapporteur Assessment Report for Post-Authorisation Commitments [PACs], RMP v10 and Addendum to the RMP v10, dated 10.9.2012).
Criteria for judging the success of the proposed risk minimisation measures	Healthcare Awareness Program evaluation is complete (see above).
Planned dates for assessments	Healthcare Awareness Program: Completed
Results of effectiveness measuremen t	Reported in previous RMPs
Impact of risk minimisation	Evaluation of the Healthcare Awareness Program has been completed and showed acceptable understanding and adherence to the label suggestive of the effectiveness of the risk minimization effort.
Comment	Additional or different risk minimization activities are not needed for post-injection syndrome.

V.2. Risk Minimisation Measure Failure

Table V.10. Risk Minimisation Measure Failure, All Formulations

Safety Concern	Risk Minimization Measure
Not applicable.	

V.2.1. Analysis of Risk Minimisation Measure(s) Failure

Table V.11. Root Cause Analysis of Risk Minimisation Measure Failures, All Formulations

Safety Concern	
Risk Minimisation Measure(s)	Not applicable.
Discussion	None

V.2.2. Revised Proposal for Risk Minimisation

No new or revised risk minimisation measures are proposed.

Table V.12. Proposed New or Revised Risk Minimisation Measures, All Formulations

Safety Concern:	
Objective(s) of the risk minimisation activities	Not applicable.
Routine risk minimisation activities	**Synopsis of (proposed) text in SmPC:** Not applicable.
	Comment: Not applicable.
	Other routine risk minimisation activities: Not applicable.
Additional risk minimisation measure(s)	Objective and justification of why needed: Not applicable.
	Proposed actions/components and rationale: Not applicable.
Comment on how revised proposals will address failings	
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.

V.3. Summary Table of EU Risk Minimisation Measures

Table V.13. Summary of Risk Minimisation Measures, All Formulations

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)	The SmPC indicates that weight should be monitored regularly after starting olanzapine and quarterly thereafter. Patients should be observed for signs and symptoms of hyperglycaemia, and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Patients should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines. In postmarketing reports with olanzapine, the event of sudden cardiac death has been reported in patients with olanzapine and was approximately twice the risk in patients not using antipsychotics in a retrospective observational cohort study.	Not applicable.
Specific safety concerns for patients <18 years of age: Sedation Hepatic-related adverse events Hyperprolactinaemia	The SmPC indicates that sedation and elevations of hepatic transaminases (ALT/AST), and elevated plasma prolactin levels were very common in patients <18 years of age.	Not applicable.
RAIM-specificsafety concern: Potential risk of mortality	The SmPC states that simultaneous injection of intramuscular olanzapine and parenteral benzodiazepine is not recommended due to the potential for excessive sedation, cardiorespiratory depression and in very rare cases, death.	Not applicable.

Summary of Risk Minimisation Measures, All Formulations

Safety Concern	Routine Risk Minimisation Measures[a]	Additional Risk Minimisation Measures
Olanzapine LAI specific safety concerns: post-injection syndrome	Section 4.4 of the SmPC indicates that during premarketing clinical studies, events that presented with signs and symptoms consistent with olanzapine overdose were reported in patients following an injection of olanzapine LAI. These events occurred in <0.1% of injections and in approximately 2% of patients. The potential for onset of an event is greatest within the first hour. Events occurred rarely (<1 in 1000 injections) between 1 and 3 hours, and very rarely (<1 in 10 000 injections) after 3 hours. HCPs are advised to discuss this risk with patients each time they prescribe and administer olanzapine LAI. After each injection, patients should be observed in a healthcare facility by appropriately qualified personnel for at least 3 hours for signs and symptoms consistent with olanzapine overdose. Immediately prior to leaving the health care facility, it should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose. For the remainder of the day after injection, patients should be advised to be vigilant for signs and symptoms of overdose secondary to post-injection adverse reactions, be able to obtain assistance if needed and should not drive or operate machinery.	• Provide education to Lilly personnel to convey warnings and information and answer questions about potential post- injection syndrome events • Distribute educational materials to hospitals and pharmacies • Product Introduction Letter to broadly disclose safety information to prescribers • Education for targeted HCPs about the risk of accidental intravascular injection and clinical presentation of patients reporting post-injection syndrome events • Provide patient card through the administrator of treatment which includes information about post-injection syndrome risk and signs and symptoms, HCP's and local emergency numbers, and information on taking the products • Training and educational materials for administration, including instructions for proper reconstitution and administration technique

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

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

Part VI. Summary of Activities in the Risk Management Plan by Product

VI.1. Elements for Summary Tables in the European Public Assessment Report (EPAR)

VI.1.1. Summary Table of Safety Concerns

Table VI.1. Summary of Safety Concerns

Summary of Safety Concerns for All Formulations of Olanzapine	
Important Identified Risks	• Weight gain • Glucose dysregulation • Dyslipidaemia
Important Potential Risks	• Increased risk of cardiac death (presumed sudden cardiac death)
Missing Information	• N/A
Summary of Safety Concerns Specific to Patients <18 Years of Age	
Important Identified Risks	• Sedation • Hepatic-related events • Hyperprolactinaemia
Important Potential Risks	• N/A
Missing Information	• N/A
Summary of Safety Concerns Specific to RAIM Formulation of Olanzapine	
Important Identified Risks	• N/A
Important Potential Risks	• Risk of mortality
Missing Information	• N/A
Summary of Safety Concerns Specific to LAI Formulation of Olanzapine	
Important Identified Risks	• Post-injection syndrome
Important Potential Risks	• N/A
Missing Information	• N/A

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

VI.1.2. Table of EU Ongoing and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

Table VI.2. EU Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan, Olanzapine Long-Acting Injection (LAI)

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
F1D-MC-B041 Zyprexa Relprevv[a] Patient Care Program Registry (US REMS)	To establish long-term safety and safe use of Zyprexa Relprevv through periodic monitoring for the risk of post-injection syndrome events and by enrolling all patients who receive Zyprexa Relprevv in the Zyprexa Relprevv Patient Care Program Registry	Post-injection syndrome	Ongoing	Not applicable (US Registry; annual assessment reports provided to FDA)

Abbreviations: FDA = Food and Drug Administration; LAI = long-acting injection; REMS = Risk Evaluation and Mitigation Strategy; US = United States.

[a] Zyprexa Relprevv is the trade name for olanzapine LAI in the US.

VI.1.3. Summary of Postauthorisation Efficacy Development Plan

Table VI.3. Summary of Postauthorisation Efficacy Development Plan

Study (Type and Study Number)	Objectives	Efficacy Uncertainties Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports
Not applicable				

VI.1.4. Summary Table of Risk Minimisation Measures

Table VI.4. Summary of Risk Minimisation Measures, All Formulations

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)	The SmPC indicates that weight should be monitored regularly after starting olanzapine and quarterly thereafter. Patients should be observed for signs and symptoms of hyperglycaemia, and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Patients should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines. In postmarketing reports with olanzapine, the event of sudden cardiac death has been reported in patients with olanzapine and was approximately twice the risk in patients not using antipsychotics in a retrospective observational cohort study.	Not applicable.
Specific safety concerns for patients <18 years of age: Sedation Hepatic-related adverse events Hyperprolactinaemia	The SmPC indicates that sedation and elevations of hepatic transaminases (ALT/AST), and elevated plasma prolactin levels were very common in patients <18 years of age.	Not applicable.
RAIM-specific safety concern: Potential risk of mortality	The SmPC states that simultaneous injection of intramuscular olanzapine and parenteral benzodiazepine is not recommended due to the potential for excessive sedation, cardiorespiratory depression and in very rare cases, death.	Not applicable.

Summary of Risk Minimisation Measures, All Formulations

Safety Concern	Routine Risk Minimisation Measures[a]	Additional Risk Minimisation Measures
Olanzapine LAI-specific safety concerns: post-injection syndrome	Section 4.4 of the SmPC indicates that during premarketing clinical studies, events that presented with signs and symptoms consistent with olanzapine overdose were reported in patients following an injection of olanzapine LAI. These events occurred in <0.1% of injections and in approximately 2% of patients. The potential for onset of an event is greatest within the first hour. Events occurred rarely (<1 in 1000 injections) between 1 and 3 hours, and very rarely (<1 in 10 000 injections) after 3 hours. HCPs are advised to discuss this risk with patients each time they prescribe and administer olanzapine LAI. After each injection, patients should be observed in a healthcare facility by appropriately qualified personnel for at least 3 hours for signs and symptoms consistent with olanzapine overdose. Immediately prior to leaving the health care facility, it should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose. For the remainder of the day after injection, patients should be advised to be vigilant for signs and symptoms of overdose secondary to post-injection adverse reactions, be able to obtain assistance if needed and should not drive or operate machinery.	• Provide education to Lilly personnel to convey warnings and information and answer questions about potential post-injection syndrome events • Distribute educational materials to hospitals and pharmacies • Product Introduction Letter to broadly disclose safety information to prescribers • Education for targeted HCPs about the risk of accidental intravascular injection and clinical presentation of patients reporting post-injection syndrome events • Provide patient card through the administrator of treatment which includes information about post-injection syndrome risk and signs and symptoms, HCP's and local emergency numbers, and information on taking the product • Training and educational materials for administration, including instructions for proper reconstitution and administration technique.

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

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

VI.2. Elements for a Public Summary

VI.2.1. Overview of Disease Epidemiology

Schizophrenia

Schizophrenia is a brain disorder with symptoms such as hearing, seeing, or sensing things which are not there, mistaken beliefs, unusual suspiciousness, and becoming withdrawn. People with this disease may also feel depressed, anxious or uneasy, or tense, and may not feel like doing

regular activities. People with schizophrenia can get better for a period of time and then worse again but will generally not be free of the symptoms of schizophrenia in their lifetime. Across the world, approximately 1% of the general population has schizophrenia (APA 2000; McGrath et al. 2004; Kirkbride et al. 2012).

Bipolar Disorder

Bipolar disorder is a condition with symptoms that affect mood and may include periods of feeling extremely excited or feelings of euphoria or feelings of being very sad. Having extreme feelings of excitement or euphoria is called mania, while feeling very sad is called depression. Across the world, approximately 2.8% to 6.5% of people have bipolar disorder (Bauer and Pfennig 2005).

VI.2.2. Summary of Treatment Benefits

Schizophrenia

For patients with schizophrenia, antipsychotic medicines are the main treatment option. Not every medicine works for every person with schizophrenia.

In studies, olanzapine has been shown to be one of the most effective medicines in patients with schizophrenia. In one study, over 1400 patients with schizophrenia took olanzapine, risperidone, quetiapine, or ziprasidone. Olanzapine was the most effective (American Psychiatric Association Practice Guidelines 2009). In another study, over 100 patients with schizophrenia took olanzapine, quetiapine, or risperidone. All 3 medicines helped with schizophrenia symptoms, but olanzapine and quetiapine were more effective than risperidone. In both studies, more people kept taking olanzapine (first study) and olanzapine and quetiapine (second study) and did not need to stop because of adverse effects or because these medicines were not effective (Stroup et al. 2007).

BipolarDisorder

For patients with bipolar disorder, medicines that help balance mood, called mood stabilizers, or antipsychotic medicines are the main treatment options. Not every medicine is effective for every patient with bipolar disorder.

For patients with bipolar disorder, the medicine the doctor chooses is based on how bad symptoms are and if the patient is feeling very excited or very sad at the time. Taking an antipsychotic medicine with lithium was more effective than taking one medicine alone. The antipsychotic medications olanzapine and aripiprazole helped to keep symptoms from coming back (Price and Marzani-Nissen 2012).

VI.2.3. Unknowns Relating to Treatment Benefits

There is no evidence to suggest that olanzapine works differently in different age groups or in patients of a different race. In the EU, olanzapine is not approved for use in children and adolescents. There is little information from clinical trials about olanzapine use in children who are younger than 10 years old or in patients who are older than 76 years.

VI.2.4. Summary of Safety Concerns

Important risks for all forms of olanzapine (given by injection or taken as a tablet).

Table VI.5. Important Identified Risks

Risk	What is Known	Preventability
Olanzapine		
Weight gain	Gaining weight may affect more than 1 in 10 patients who take olanzapine.	The instructions the doctor receives about prescribing olanzapine may lower this risk by recommending that patients and doctors check weight regularly. Patients and those who care for them should watch for weight gain. In some patients, weight gain is a reversible condition that can be managed with diet and exercise or with help from the doctor.
High blood sugar (glucose dysregulation)	High blood sugar may affect up to 1 in 10 patients who take olanzapine.	The instructions the doctor receives about prescribing olanzapine may lower this risk by recommending that he/she do blood tests to check the patient's blood sugar before olanzapine is started, and regularly while the patient is taking olanzapine. If patients have high blood sugar, the doctor should test blood sugar on a morning when the patient has not eaten anything. The doctor should be told if the patient has diabetes as soon as possible. Patients and those who care for them should watch for symptoms of high blood sugar such as urinating a lot more than usual, drinking a lot more than usual, and feeling weak.
High levels of fat in the blood (dyslipidaemia)	High levels of fat in the blood may affect up to 1 in 10 patients who take olanzapine.	The instructions the doctor receives about prescribing olanzapine may lower the risk by recommending that the doctor do blood tests to check certain fat levels in the blood before olanzapine is started and regularly while the patient is taking olanzapine.
Olanzapine Risks Specific to Patients <18 years of age		
Sleepiness (sedation)	Sleepiness may affect more than 1 in 10 patients who take olanzapine.	Feeling sleepy with olanzapine treatment is not preventable, but the instructions the doctor receives about prescribing olanzapine informs him or her that patients <18 years of age are more likely to feely sleepy during treatment with olanzapine than adults. Patients should talk to their doctor or pharmacist if they experience any events, including sleepiness.
Increases in chemicals in the blood made by the liver (hepatic-related events)	Increases in chemicals in the blood made by the liver may affect up to 1 in 10 patients who take olanzapine.	The instructions the doctor receives about prescribing olanzapine may lower the risk by informing him or her that patients <18 years of age may be more likely to have increases in chemicals in the blood made by the liver compared with adult patients. Patients and those who care for them should watch for signs of increases in chemicals in the blood made by the liver such as yellowing of the skin or eyes. If these are seen, notify the doctor immediately.
Increases in prolactin in the blood (hyperprolactinaemia)	Increases in prolactin in the blood may affect more than 1 in 10 patients who take olanzapine.	The instructions the doctor receives about prescribing olanzapine may lower the risk by informing him or her that patients <18 years of age may be more likely to have increases in prolactin compared with adult patients.

Important Identified Risks

Risk	What is Known	Preventability
Olanzapine Risk Specific to Long-Acting Injection (LAI)		
Overdose-like symptoms after olanzapine injection (such as sleepiness, confusion, feeling irritable, nervous, aggressive, dizzy, weak, stiff, or shaky, or having problems talking or walking) (Post-Injection Syndrome)	These signs and symptoms can sometimes occur in approximately 1 in 50 patients given the LAI form of olanzapine. Most of the time, this is usually with 1 hour of the injection. These symptoms usually get better within 24 to 72 hours. Patients need to be observed at the medical facility for 3 hours after the injection.	The instructions the doctor receives about prescribing olanzapine LAI is aimed to minimize any risk to patients by informing him or her of these signs and symptoms. Each patient receiving an injection of the long-acting form of olanzapine should be kept at the place where the injection was given and then observed for these signs and symptoms for at least 3 hours after each injection. Before leaving the health care facility where the injection was given, the doctor or nurse will make sure that the patient is alert, knows where they are, and does not have any signs and symptoms of overdose. Patients should talk to their doctor immediately if they get symptoms more than 3 hours after the injection. For the remainder of the day after injection, patients should watch for signs and symptoms of overdose and be able to obtain help if needed and should not drive or use machinery.

Table VI.6. Important Potential Risks

Risk	What is Known (including Reason Why it is Considered a Potential Risk)
Higher risk of death due to heart problems (increased risk of cardiac death; presumed sudden cardiac death) (olanzapine)	Outside of clinical trials, death due to heart problems was very rarely seen (<0.01% of patients taking olanzapine). This risk is considered a potential risk because some studies have reported that patients treated with antipsychotic medications like olanzapine have an increased risk of death, including sudden death due to heart problems (Ray et al. 2001; Enger et al. 2004; Schneeweiss et al. 2007; Ray et al. 2009). In one study, the risk of death for patients taking olanzapine was about twice the risk for patients not taking antipsychotics (Ray et al. 2009). However, a study conducted in American patients with schizophrenia from 1995 to 1999 found no association between antipsychotic medications like olanzapine and death or death due to heart problems (Enger et al. 2004). Clinical trials with olanzapine suggest that olanzapine does not increase the risk of heart problems that could lead to death.
Risk of death (risk of mortality) (rapid-acting olanzapine [RAIM])	No deaths occurred in clinical trials with injected olanzapine medication (RAIM). Outside of clinical trials, death was very rarely seen (<0.01% of patients taking olanzapine). This risk is considered a potential risk because of the increased number of deaths in patients treated with injected antipsychotic medications like olanzapine compared with patients who take medication orally. Injecting olanzapine and other sedating medications like benzodiazepines at the same time is not recommended.

Table VI.7. Missing Information

Risk	What is Known
None	There are no risks for olanzapine for which there is missing information.

VI.2.5. Summary of Risk Minimisation Measures by Safety Concern

These additional risk minimisation measures are for the following risks.

Table VI.8 Overdose-Like Symptoms after Long-Acting Olanzapine Injection (LAI) (Post-Injection Syndrome), Risk Minimisation Measures

Risk Minimisation Measure(s): Healthcare Awareness Programme
Objective and Rationale: The main programme for risk minimisation for long-acting injectable olanzapine is called the healthcare awareness programme. The aims of this programme are: • To make sure that doctors and patients know about the risk of overdose-like symptoms after olanzapine LAI injection • To make sure that doctors and patients understand the importance of following the instructions provided in the prescribing information and patient leaflet when using olanzapine LAI • To make sure that doctors understand how to manage the overdose like symptoms if a patient develops this post-injection syndrome risk • To make clear the importance of following the instructions for how olanzapine LAI is prepared for injection and given by trained HCPs
Main Additional Risk Minimisation Measures: • Education for Lilly staff such as people who answer medical information enquiries so that they are able to answer questions about overdose-like symptoms after olanzapine LAI injection if they receive an enquiry from a doctor or nurse • Give educational materials to hospitals and pharmacies • A Product Introduction Letter to give safety information to prescribers • Education for healthcare professionals about the risk of accidentally injecting olanzapine LAI into a vein and what symptoms of this looks like in patients who report overdose-like symptoms after olanzapine injection • A patient card given by the person who provides treatment which includes information about the risk of overdose-like symptoms after olanzapine injection and signs and symptoms, HCP's and local emergency numbers, and information on taking the product • Training and educational materials for giving olanzapine LAI, including instructions for on how to make olanzapine LAI ready for injections and how to correctly give olanzapine LAI.

VI.2.6. Planned Postauthorisation Development Plan

Table VI.9. List of Studies in Postauthorisation Development Plan, All Formulations

Study/Activity (including Study Number)	Objectives	Safety Concerns /Efficacy Issue Addressed	Status	Planned Date for Submission of Interim and Final Results
None				

VI.2.6.1. Studies that are a Condition of the Marketing Authorisation

None of the above studies are a condition of the marketing authorisation.

VI.2.7. Summary of Changes to the Risk Management Plan over Time

Important changes to the RMP are listed in Table VI.10. All revisions of the Risk Management Plan include typical updates to information that is new for safety or regulatory reasons. These updates may include:

- places where olanzapine can be sold
- number of patients taking olanzapine in clinical trials and outside of clinical trials
- frequency of adverse effects in clinical trials and what is seen or reported in an everyday medical setting
- important regulatory actions taken for safety reasons
- any significant changes in information on important risks for olanzapine and what actions are being taken to minimise the risk

Table VI.10. Major Changes to the Risk Management Plan over Time

Version	Date	Safety Concerns	Comments
Major Changes to the Oral/RAIM Risk Management Plan			
Initial RMP	17 April 2008	This was the first risk management plan.	None
Version 2	21 May 2009	Added language to watch weight, fat levels in the blood, and blood sugar and added ways to make sure prescribing information was being followed. Added increased risk of death from heart problems to the risk management plan.	None
Version 3	26 May 2010	Added that olanzapine can be used in adolescent patients (13 through 17 years of age) with bipolar I disorder or schizophrenia in the United States. Added a new warning about higher risk of death due to heart problems (sudden cardiac death).	None
Version 4	22 May 2011	Added risk that use of the rapid-acting injectable olanzapine solution at the same time as anti-anxiety medications may have serious consequences and may possibly result in death.	None
Major Changes to the Olanzapine LAI Risk Management Plan			
Version 10.1	08 February 2013	Added text about the 3-hour period that patients should be watched for overdose-like symptoms after olanzapine injection to make the RMP the same as prescribing information. Also stated that this time can be longer if the patient shows signs of olanzapine overdose. Statement that patients should not travel alone to their destination after the observation period was removed from the product training slides to be consistent with the product labelling.	None
Major Changes to the Olanzapine Risk Management Plan (All Formulations)			
Version 11	03 June 2014.	Combined information for all formulations of olanzapine into a single RMP. For olanzapine LAI, removed the important potential risks of "medication error" (confusion between RAIM vs LAI intramuscular injection) and "high concentrations of olanzapine or additive effects of concomitant medications." Since no one has reported these possible risks, they do not affect how safe it is to take olanzapine LAI. Based on the real world use, Lilly believes that these two safety issues are not important potential risks for olanzapine LAI anymore.	None
Version 12	See cover page of this document.	Data in this document are through 30 September 2013 unless otherwise noted. Results of Study B034 (Clinical Study Report approval date 29 June 2016) were added. Updated Action Taken by Regulatory Authorities and/or Marketing Authorisation Holders for Safety Reasons.	None

Annex 4. Synopsis of Ongoing and Completed Clinical Trial Programme

Main or Pivotal Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
Schizophrenia (oral olanzapine)						
F1D-MC-HGAD	Olanzapine vs Placebo/Haloperidol in the Treatment of Schizophrenia	CA, US	Double Blind	Planned: 385 Actual: 335		Actual: Jul-1995
F1D-MC-HGAP	Fixed-Dose Olanzapine vs Placebo in the Treatment of Schizophrenia	US	Double Blind	Planned: 165 Actual: 152		Actual: Apr-1995
F1D-MC-HGAJ	Olanzapine vs Haloperidol in Treatment of Schizophrenia and Other Psychotic Disorders	GB, US, IT, DK, FR, DE, SE, PL, ES, AT, French Antilles, NL, BE, FI, CA, CZ, PT, LU	Double Blind	Planned: 2225 Actual: 1996		Actual: 01-Feb-1998
F1D-MC-HGGI	Olanzapine Relapse Prevention vs Placebo in the Treatment of Schizophrenia	CZ, HR, RO, RU, US, YU	Double Blind	Planned: 720 Actual: 326		Actual: 10-Nov-1999
F1D-EW-E003	A Fixed-Dose Range Safety and Efficacy Study of Olanzapine versus Haloperidol in the Treatment of Schizophrenia	FI, ES, DK, SE, NO, FR, GB, IL, ZA, NL, AT, PT, DE, AU, BE	Double Blind	Planned: 620 Actual: 431		Actual: Jul-1995
Bipolar Disorder (oral olanzapine)						
F1D-MC-HGEH	Olanzapine vs Placebo in Treatment of Mania Associated with Bipolar I Disorder	US	Double Blind	Planned: 180 Actual: 139		Actual: 29-May-2002
F1D-MC-HGFU	Olanzapine Added to Mood Stabilizers in Treatment of Bipolar Disorder. Patients on mood stabilizers (depakote or lithium) are randomised to placebo or olanzapine + stabilizer	CA, US	Double Blind	Planned: 336 Actual: 344		Actual 22-Sep-2000

Main or Pivotal Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
Bipolar Disorder (oral olanzapine), continued						
F1D-MC-HGHD	Olanzapine vs Haloperidol in the Treatment of Acute Mania	AR, BR, ES, FR, MX, PE, PT, US, VE, YU, ZA	Double Blind	Planned: 472 Actual: 453		Actual: 30-Sep-2002
F1D-US-HGHQ	Olanzapine vs Divalproex in the Treatment of Acute Mania Acute double-blind treatment for 3 weeks, then double-blind maintenance for 11 months, then optional naturalistic follow-up period	US	Double Blind	Planned: 780 Actual: 251		Actual: 6-Jun-2001
F1D-MC-HGHL	Olanzapine vs Placebo in the Prevention of Relapse in Bipolar Disorder Patients Open label olanzapine for 6-12 weeks, then randomised to olanzapine or placebo for 1 year.	RO, US	Double Blind	Planned: 1300 Actual: 361		Actual: 17-Sep-2002
F1D-MC-HGHT	Olanzapine vs Lithium in Relapse Prevention in Bipolar Disorder Open label olanzapine + lithium for 6-12 weeks, then randomised to olanzapine or lithium for 1 year.	AT, AU, BE, BG, CA, CH, CZ, DE, DK, EE, FI, GB, HR, HU, IE, IL, IT, LT, NL, NO, NZ, PL, RO, RU, SA, SE, SI, SK, SL, TR	Double Blind	Planned: 850 Actual: 431		Actual 17-Oct-2002

Main or Pivotal Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
Bipolar Disorder (oral olanzapine), continued						
F1D-MC-HGGY	Placebo-controlled Olanzapine in Bipolar 1 Depression Eight week acute double blind followed by 6 month open label period. Olanzapine, placebo, and olanzapine/fluoxetine combination.	AU, BG, CO, ES, GR, HR, LB, MX, PT, RO, RU, SK, TR, US	Double Blind	Planned: 1024 Actual: 833		Actual: 26-Mar-2002
F1D-MC-HGMP	Randomized, double-blind comparison with placebo for up to 24 weeks to assess the efficacy and safety of olanzapine in the treatment of patients with bipolar I disorder	CN, JP, KR, TW, US	Double Blind	Planned: 600 Actual: 514		Actual: 09-Jul-2010
Adolescent Patients (oral olanzapine)						
F1D-MC-HGIN	Olanzapine versus Placebo in the Treatment of Adolescents with Schizophrenia 2-arm, placebo-controlled	RU, US	Double Blind	Planned 145 Actual: 107		Actual: 16-May-2006
F1D-MC-HGIU	Olanzapine in juvenile mania. Multicentre, randomised, double-blind, placebo-controlled, parallel trial in adolescent patients	PR, US	Double Blind	Planned: 152 Actual: 161		Actual: 09-May-2005

Main or Pivotal Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
Olanzapine RAIM						
F1D-MC-HGHB	A Double-Blind Randomized Comparison of the Efficacy and Safety of Short Acting Intramuscular Olanzapine, Short Acting Intramuscular Haloperidol and Intramuscular Placebo in Patients with Schizophrenia.	AU, AT, BE, CA, CZ, FR, HU, GR, IL, ZA, ES, RU, UK, US	Double Blind	Planned: 300 Actual: 311		Actual: 25-May-2000
F1D-MC-HGHV	A Double-Blind Dose Response Study Comparing Short-Acting Intramuscular Olanzapine, Short-Acting Intramuscular Haloperidol and Intramuscular Placebo in Patients with Schizophrenia	HR, ZA, IT, RO	Double Blind	Planned: 285 Actual: 270		Actual: 22 Mar-2000
F1D-MC-HGHW	A Double-Blind Randomized Comparison of the Efficacy and Safety of Short-Acting Intramuscular Olanzapine, Short-Acting Intramuscular Lorazepam, and Intramuscular Placebo in Acutely Agitated Patients Diagnosed with Mania Associated with Bipolar Disorder	RO, US	Double Blind	Planned: 200 Actual: 201		Actual: 05-Apr-2000

Main or Pivotal Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
Olanzapine LAI						
F1D-MC-HGJZ	A Double-Blind Randomized Study Comparing Olanzapine Pamoate Depot with Placebo in the Treatment of Patients with Schizophrenia	HR, RU, US	Double Blind	Planned: 400 Actual:404		Actual: 10-Jan-2006
F1D-MC-HGKA	A Double-Blind Randomized Study Comparing Intramuscular Olanzapine Depot to Oral Olanzapine and Low-Dose Intramuscular Olanzapine Depot in the Maintenance Therapy of Patients with Schizophrenia	AR, AT, AU, BE, BR, DE, ES, FI, FR, GR, HU, IL, IT, MX, NL, NO, PL, PR, PT, RO, RU, SE, TR, TW, US, ZA	Double Blind	Planned: 1050 Actual: 1065		Actual: 15 March 2007

Abbreviations: AR = Argentina; AT = Austria; AU = Australia; BE = Belgium; BG = Bulgaria; BR = Brazil; CA = Canada; CH = Switzerland; CN = China; CO = Columbia; CZ = Czech Republic; DK = Denmark; DE = Germany EE = Estonia; ES = Spain; FI = Finland; FR = France; GB = United Kingdom; GR = Greece; HR = Croatia; HU = Hungary; IE = Ireland; IL = Israel; IS = Iceland; IT = Italy; JP = Japan; KR = South Korea; LB = Lebanon; LT = Lithuania; LU = Luxembourg; MX = Mexico; NL = Netherlands; NO = Norway; NZ = New Zealand; PE = Peru; PK = Pakistan; PL = Poland; PR = Puerto Rico; PT = Portugal; RO = Romania; RU = Russia; SA = Saudi Arabia; SE = Sweden; SG = Singapore; SI = Slovenia; SK = Slovakia; SL = Sierra Leone; TR = Turkey; TW = Taiwan; US = United States; VE = Venezuela; YU = Yugoslavia; ZA = South Africa.

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-CR-HGNB	A Study to Assess the Short-Term Efficacy and Safety of Olanzapine and Fluoxetine Compared with Fluoxetine for Nonpsychotic Treatment-Resistant Depression. O + F and Placebo. Phase 3	China	Double Blind	Planned: 286 Actual: 54		Forecast: 10-Nov-2015 Actual: 30-Mar-2016
F1D-CR-HGNC	CN Zyprexa O+F Regional IMCT phase 3 BPD Phase 3	China	Double Blind	Planned: 308 Actual: 0		Forecast: 16-Jan-2016 Actual: N/A
F1D-FW-LOCA	BE Study to Support Zydis Local Registration in China Phase 1	China	Open Label	Planned: 50 Actual: 24		Actual: 27-Nov-2007
F1D-GH-LOBV	Olanzapine versus Lithium carbonate in the treatment of bipolar disorder, manic or mixed episodes Phase 3	China	Double Blind	Planned: 160 Actual: 140		Forecast: 15-Jan-2006 Actual: 05-Dec-2005
F1D-JE-BMAC	Placebo- and Haloperidol-Controlled Double-Blind Trial of Olanzapine in Patients with Manic or Mixed Episode of Bipolar I Disorder Phase 3	Japan	Double Blind	Planned: 280 Actual: 224		Forecast: 23-Jun-2009 Actual: 17-Jun-2009
F1D-JE-BMEX	Efficacy and Safety of Olanzapine in the Extended Treatment for Manic or Mixed Episode of Bipolar I Disorder Phase 3	Japan	Open Label	Planned: 143 Actual: 139		Forecast: 22-Oct-2009 Actual: 14-Oct-2009

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-JE-HGMS	Safety and Efficacy of Olanzapine (LY170053) in the Long-term Treatment for Patients with Bipolar I Disorder, Depressed. No comparator Phase 3	Japan	Open Label	Planned: 100 Actual: 102		Forecast: 25-Feb-2011 Actual: 25-Jan-2011
F1D-JE-LOBW	Olanzapine: A 5-mg Strength Bioequivalence of Tablet Formulations in Healthy Adult Male Japanese Subjects Phase 1	Japan	Open Label	Planned:16 Actual: 16		Forecast: 08-Jul-2005 Actual: 31-May-2005
F1D-JE-RA01	A Pilot Study Confirming Safety and Efficacy of Rapid Acting Intermuscular Olanzapine for Agitated Patients with Schizophrenia Phase 1B/2	Japan	Open Label	Planned: 43 Actual: 31		Forecast: 30-Oct-2005 Actual: 19-Oct-2005
F1D-JE-RA02	A Double-Blind Dose-Response Study Comparing Rapid Acting Intramuscular Olanzapine and Intramuscular Placebo in Agitated Patients with Schizophrenia Phase 2	Japan	Double Blind, Placebo	Planned: 176 Actual: 163		Forecast: 30-Nov-2007 Actual: 30-Oct-2007
F1D-JE-RA03	A Double-Blind Confirmatory Study Comparing Rapid Acting Intramuscular Olanzapine and Intramuscular Placebo in Agitated Patients with Schizophrenia Phase 3	Japan	Double Blind, Placebo	Planned: 31 Actual: 33		Forecast: 28-Jan-2009 Actual: 28-Jan-2009

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-JE-RACD	A Placebo-Controlled, Double-Blind Confirmatory Study of Rapid-Acting Intramuscular Olanzapine in Patients with an Exacerbation of Schizophrenia with Acute Psychotic Agitation Phase 3	Japan	Double Blind, Placebo	Planned: 30 Actual: 33		Forecast: 28-Jan-2009 Actual: 28-Jan-2009
F1D-JE-RAPK	A Study Examining Pharmacokinetics of Rapid Acting Intra-muscular Olanzapine In Japanese Agitated Patients with Schizophrenia Phase 1	Japan	Open Label	Planned: 10 Actual: 10		Forecast: 25-Jun-2007 Actual: 15-Jun-2007
F1D-MC-HGKK	Efficacy of Olanzapine in Subjects with Borderline Personality Disorder: A Randomized Fixed-Dose Double-Blind Comparison with Placebo Phase 3	Argentina, Australia, Chile, Italy, Peru, Poland, Romania, Russia, Turkey, United States, Venezuela, South Africa	Double Blind	Planned: 675 Actual: 450	12 weeks	Forecast: 15-September-2006 Actual: 15-September-2006
F1D-MC-HGKL	Efficacy of Olanzapine in Subjects with Borderline Personality Disorder: A Randomized Flexible-Dose Double-Blind Comparison with Placebo Phase 3	Belgium, Canada, Germany, Spain, France, United Kingdom, Norway, Puerto Rico, Portugal, Sweden, United States	Double Blind	Planned: 408 Actual: 318	12 weeks	Forecast: 15-Sep-2006 Actual: 1-Sep-2006
F1D-MC-HGKQ	Olanzapine vs Divalproex and Placebo in the Treatment of Mild to Moderate Mania Associated with Bipolar I Disorder Phase 4	Germany, France, Lithuania, Poland, Puerto Rico, Romania, Russia, United States	Double Blind	Planned: 600 Actual: 521	1 week	Forecast: 8-Jun-2007 Actual: 18-Jun-2007

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-MC-HGKR	Protocol F1D-MC-HGKR Olanzapine Plus Carbamazepine Versus Carbamazepine Alone in the Treatment of Manic or Mixed Episodes Associated with Bipolar I Disorder Phase 3B	Austria, Australia, Czech Republic, Greece, Hungary, Russia, Slovakia, Turkey	Double Blind	Planned: 140 Actual: 118	20 weeks	Forecast: 29-Sep-2006 Actual: 29-Sep-2006
F1D-MC-HGMF	Population Pharmacokinetic Study in Adolescent Patients with Schizophrenia or Bipolar I Disorder Treated with Olanzapine Phase 3/4	Spain, Russia, United States	Open Label	Planned: 125 Actual: 107		Forecast: 14-Aug-2006 Actual: 24-Jul-2006
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 Phase 4	Germany, Poland, Puerto Rico, Russia, United States	Open Label	Planned: 285 Actual: 206		Forecast: 28-Oct-2013 Actual: 05-Nov-2013
F1D-TW-S025	A Double-Blind Randomized Comparison of the Efficacy and Safety of Intramuscular Olanzapine and Intramuscular Haloperidol in Acutely Agitated Patients with Schizophrenia Phase 4	Taiwan	Double Blind	Planned: 60 Actual: 50		Forecast: 29-Jul-2005 Actual: 12-Jul-2005
F1D-FP-S057	Validation of Multidimensional Assessment of THYmic States (MATHYS): A study in a population of bipolar patients treated with olanzapine Phase 3/4	France	Open Label	Planned: 200 Actual: 141		Forecast: 31-Mar-2010 Actual: 15-Mar-2010

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-MC-HGLB	Protocol F1D-MC-HGLB A Randomized Double-Blind Study of Olanzapine Versus Aripiprazole in the Treatment of Schizophrenia Phase 4	Argentina, Australia, Brazil, Chile, Spain, Mexico, Puerto Rico, United States, Venezuela	Double Blind	Planned: 675 Actual: 566		Forecast: 12-Feb-2008 Actual: 27-Feb-2008
F1D-US-HGLF	Efficacy of High Dose Olanzapine in a Controlled Fixed Dose-Response Trial for the Treatment of Schizophrenia and Schizoaffective Disorder Phase 4	United States	Double Blind	Planned: 750 Actual: 593		Forecast: 03-Nov-2006 Actual: 19-Dec-2006
F1D-US-HGLS	Olanzapine Versus Aripiprazole in the Treatment of Acutely Ill Patients with Schizophrenia Phase 4	United states	Double Blind	Planned: 700 Actual: 586		Forecast: 09-Jul-2007 Actual: 16-Jul-2007
F1D-FR-HGMZ	A Randomized, Open-Label Study assessing the impact of a Structured Psychoeducational Program on Patient Attitude Toward Medication in Patients with Schizophrenia Phase 4	France	Open Label	Planned: 294 Actual: 319	24 weeks	Forecast: 15-Mar-2012 Actual: 23-Jun-2012
F1D-BX-LOAG	Olanzapine in Schizophrenic Patients Phase 4	Belgium	Open Label	Planned: 400 Actual: 308		Forecast: 13-Oct-1999 Actual: 13-Oct-1999

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-CA-S063	BMI Evaluation: Placebo and Active Comparator Trial of Olanzapine Zydis Pills Used Sublingually (PLATYPUS) Phase 4	Canada, Mexico, Netherlands, United States	Double Blind	Planned: 186 Actual: 151		Forecast: 30-Oct-2008 Actual: 12-Dec-2008
F1D-FP-S029	Double-Blind randomised study of the medium and long term effect of a switch from haloperidol to olanzapine Phase 4	France	Double Blind	Planned: 250 Actual: 274		Forecast: 31-Dec-2007 Actual: 14-Aug-2007
F1D-GW-S034	Cost Benefit study comparing Olanzapine versus Haloperidol Phase 4	Venezuela	Open Label	Planned: 100 Actual: 74		Forecast: 31-Jan-2006 Actual: 20-Apr-2006
F1D-IT-HGLE	A prospective/parallel study on induced weight gain during atypical antipsychotic treatment and its management with psychoeducational programme Phase 4	Italy	Open Label	Planned: 50 Actual: 47		Forecast: 15-Jun-2008 Actual: 15-Oct-2005
F1D-MC-S014	Insulin Sensitivity in Patients with Schizophrenia or Schizoaffective Disorder Treated with Olanzapine and Risperidone Phase 4	United States	Double Blind	Planned: 156 Actual: 132		Forecast: 06-Oct-2008 Actual: 13-Nov-2008

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-SU-HGMA	Bipolar Depression Assessment Study on Treatment Response (BiDAS-TR) Phase 4	Puerto Rico	Open Label	Planned: 150 Actual: 165		Forecast: 30-Jan-2007 Actual: 22-Nov-2006
F1D-US-HGLR	The Comparison of Efficacy and Safety of Continuing Olanzapine to Switching to Quetiapine in Overweight or Obese Patients with Schizophrenia or Schizoaffective Disorder Phase 4	United States	Double Blind	Planned: 172 Actual: 120	1 week	Forecast: 08-Mar-2007 Actual: 10-May-2007
F1D-US-HGMM	Assessment of the Safety, Efficacy, and Practicality of an Algorithm that includes Amantadine, Metformin and Zonisamide for the Prevention of Olanzapine-Associated Weight Gain in Outpatients with Schizophrenia Phase 3/4	Brazil, Israel, Korea, South, Mexico, Russia, United States	Open Label	Planned: 240 Actual: 203		Forecast: 15-Mar-2009 Actual: 09-Mar-2009
F1D-US-HGMN	Predicting Response to Risperidone Treatment Through Identification of Early-onset of Antipsychotic Drug Action in Schizophrenia Phase 4	Argentina, Russia, United States	Double Blind	Planned: 820 Actual: 524		Forecast: 15-Sep-2008 Actual: 21-Aug-2008
F1D-US-HGMO	A double-blind placebo controlled trial of divalproate and olanzapine in bipolar I disorder, mixed episode Phase 3/4	United States	Double Blind	Planned: 300 Actual: 199		Forecast: 13-Feb-2009 Actual: 13-Feb-2009

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-US-HGMU	A Randomized Comparison of Metabolic Changes Between Orally Dissolving Olanzapine and Oral Olanzapine in Health Volunteers Phase 1	United States	Single Blind	Planned: 86 Actual: 17		Forecast: 12-May-2009 Actual: 11-May-2009
F1D-VI-S067	12-Week Open Label Trial On Olanzapine Orodispersible Tablet Vs Oral Olanzapine Preference Study Phase 4	Brazil, Israel, Mexico, Netherlands, Romania, Turkey	Open Label	Planned: 284 Actual: 251		Forecast: 11-Sep-2008 Actual: 04-Aug-2008
F1D-XM-HGLW	Optimal length of continuation treatment with Olanzapine after maniac or mixed episode. Open, randomise study comparing 2 therapeutic strategics Phase 4	Spain	Open Label	Planned: 200 Actual: 15		Forecast: 30-Jul-2007 Actual: 16-Mar-2007
F1D-EW-S018	A prospective observational study of the safety and effectiveness of intramuscular psychotropic medication in patients who are acutely agitated Phase 4	Australia, Belgium, Bulgaria, Switzerland, Germany, Denmark, Spain, Finland, France, United Kingdom, Greece, Ireland, Iceland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Sweden	Prospective Cohort	Planned: 2080 Actual: 1948	Up 7 Days	Forecast: 30-Apr-2007 Actual: 25-Dec-2006

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-JE-CS07	Evaluate effectiveness of Zyprexa for bipolar mania Phase 4	Japan	Prospective Cohort	Planned: 500 Actual: 618		Forecast: 31-May-2015
F1D-JE-CS08	This study is conducted for the reexamination under the Pharmaceutical Affairs Act because olanzapine has an indication for the treatment of depression episodes in patients with bipolar disorder in Japan. Patients enrolled in this study are enrolling for the collection of their data on observations made during normal clinical practice Phase 4	Japan	Prospective Cohort	Planned: 500 Actual: 497		Forecast: 31-Mar-2016
F1D-JE-CS09	Post-marketing surveillance of olanzapine Rapid-Acting Intramuscular Injection treatment for the acute phase of schizophrenia in Japan Phase 4	Japan	Prospective Cohort	Planned: 1000 Actual: 85		Forecast: 27-Jan-2019
F1D-JE-CS11	Post-marketing surveillance of olanzapine treatment in acutely agitated patients initially treated with olanzapine IM and followed by oral olanzapine Phase 4	Japan	Prospective Cohort	Planned: 300 Actual: 35		Forecast: 27-Jan-2019

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-MC-B042	Risk of Cardiac Mortality (including Sudden Cardiac Death) in Atypical Antipsychotic Users Phase 4	United Kingdom	Retrospective Cohort	Actual: Adults aged 18 years or older from the General Practice Research Database Olanzapine: 20 954 Nonuser Psychiatric comparison group: 193 920 The matched general population comparison group 62 720 Cardiac Mortality Outcome – Olanzapine (current use): 26 765 PYs	The average duration of follow-up time was 4.0 years [SD 4.0] for antipsychotic users, 3.56 years [SD 2.86] years for olanzapine users, and 4.1 years [SD 3.5] for patients with psychiatric illness.	Forecast: 31-Jul-2011 Actual: 04-Aug-2011

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-TW-B006	Comparative Health Outcome of Schizophrenia Outpatients treated by Olanzapine and Risperidone Phase 4	Taiwan	Prospective Cohort	Planned: 200 Actual: 65		Forecast: 28-Jun-2007 Actual: 11-Jul-2007
F1D-AY-B004	Olanzapine verses mood stabilizers in the treatment and outcome of outpatients with Bipolar I Disorder - An observational study Phase 4	Australia	Prospective Cohort	Planned: 240 Actual: 240		Forecast: Actual: 20-Jul-2005
F1D-AY-B033	A 12-month, Prospective, Observational Study to Establish the Time to All-Cause Treatment Discontinuation in Outpatients with Schizophrenia at Risk of Medication Non-Adherence Phase 4	Australia, Italy, Mexico, Romania, Slovenia, Taiwan	Prospective cohort	Planned: 595 Actual: 439	Follow Up 9 Months	Forecast: 30-Jun-2010 Actual: 31-May-2010
F1D-BL-B013	A 3-year, prospective, observational study of health outcomes associated with antipsychotic medication therapy in outpatients treated for schizophrenia. (SOHO) Phase 4	Brazil	Prospective cohort	Planned: 500 Actual: 1100		Forecast: 20-Nov-2005 Actual: 18-Nov-2005
F1D-BL-B014	The Clinical Global Impression - Schizophrenia scale: translation to Portuguese and validation Phase 4	Brazil	Prospective cohort	Planned: 140 Actual: 140		Forecast: 15-Oct-2004 Actual: 10-Oct-2004

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-CA-B011	Mixed Bipolar Symptoms in Primary Care Settings: a Canadian 1-Month Descriptive Observational Study Phase 4	Canada	Open Label	Planned: 50 Actual: 53		Forecast: 28-Jun-2005 Actual: 08-Jul-2005
F1D-CA-HGKN	Health Outcomes of a Canadian Community-based Cohort treated for Schizophrenia and related psychotic disorders: a Naturalistic Study Phase 4	Canada	Open Label	Planned: 816 Actual: 924		Forecast: 15-Jul-2005 Actual: 02-Jul-2005
F1D-CA-HGKO	A Canadian Naturalistic Study of a community-based cohort treated for Bipolar disorder Phase 4	Canada	Open Label	Planned: 450 Actual: 499		Forecast: 09-Sep-2005 Actual: 09-Sep-2005
F1D-CP-B028	Evaluation of the effectiveness of the Solutions for Wellness program, in terms of quality of life and weight control Phase 4	Denmark, Norway, Sweden	Prospective cohort	Planned: 400 Actual: 427		Forecast: 30-Aug-2008 Actual: 28-Sep-2008
F1D-CY-B005	A Czech 24-months observational study to evaluate Olanzapine treatment of patients with manic episode of Bipolar Disorder Phase 4	Czech Republic	Prospective cohort	Planned: 170 Actual: 251	Follow Up 6 Months	Forecast: 30-Dec-2008 Actual: 16-Dec-2008

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-EW-HGJO	A 3-year, pan-European, prospective, observational study of health outcomes associated with antipsychotic medication therapy in outpatients treated for schizophrenia. (SOHO) Phase 4	Germany, Denmark, Spain, France, United Kingdom, Greece, Italy, Netherlands, Norway, Portugal	Prospective cohort	Planned: 10800 Actual: 11002		Forecast: 30-Apr-2006 Actual: 05-Feb-2006
F1D-EW-HGKV	A European Observation Study of Health Outcomes Associated with Treatment for Mania in Bipolar Disorder European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) Phase 4 Current version 16 Oct 2002	Belgium, Switzerland, Germany, Denmark, Spain, Finland, France, United Kingdom, Greece, Italy, Netherlands, Norway, Portugal, Sweden	Prospective cohort	Planned: 5000 Actual: 3683		Forecast: 30-Sep-2007 Actual: 29-Jun-2007
F1D-FP-B009	European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) Phase 4	France	Prospective cohort	Planned: 740 Actual: 528		Forecast: 30-Jun-2013 Actual: 22-Apr-2013
F1D-FR-B035	An observational study of olanzapine coated and orodispersible tablets effectiveness in schizophrenic and bipolar outpatients Phase 4	Germany, France, Greece	Prospective cohort	Planned: 1000 Actual: 1131		Forecast: 25-May-2010 Actual: 27-Apr-2010
F1D-IS-B001	Olanzapine Observational Study Phase 4	Turkey	Prospective cohort/open label	Planned: 560 Actual: 578		Forecast: 30-Dec-2005 Actual: 30-Dec-2005

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-IT-B023	Evaluation of Pharmacotherapy Adherence in Bipolar Disorder Phase 4	Italy	Open Label	Planned: 625 Actual: 684		Forecast: 24-Feb-2009 Actual: 24-Feb-2009
F1D-JE-CS04	Investigate health outcome of Zyprexa in schizophrenia (Social Functioning, Clinical status, Tolerability, Health-related QOL) Phase 4	Japan	Prospective cohort	Planned: 1100 Actual: 1949		Forecast: 21-Mar-2007 Actual: 20-Mar-2007
F1D-JE-CS05	Safety and effectiveness of Zyprexa in Japanese patients with acute Phase 4	Japan	Prospective cohort	Planned: 1000 Actual: 1142		Forecast: 31-Dec-2007 Actual: 17-Dec-2007
F1D-JE-CS10	The assessment of the clinical course of patients with bipolar disorder experiencing an acute episode, who are initiated with olanzapine treatment in the naturalistic clinical setting in Japan Phase 4	Japan	Prospective cohort	Planned: 500 Actual: 386		Forecast: 06-Apr-2015 Actual: 16-Dec-2015
F1D-JE-CSOS	Post-marketing non safety observational study of effectiveness in Japanese acute schizophrenic patients treated with olanzapine and other antipsychotics by mono-therapy Phase 4	Japan	Prospective cohort	Planned: 1050 Actual: 1115	Follow Up 12 Months	Forecast: 18-Jun-2013 Actual: 31-May-2013

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-MC-B043	Retrospective database analysis on resource use of patients initiating Olanzapine long-acting treatment in Sweden No Phase	United Kingdom, Sweden	Retrospective cohort	Planned: 300 Actual: 0		Forecast: 28-Jun-2013 Actual: 17-Feb-2014
F1D-ML-B003	An Observational Study to Evaluate the Effectiveness of Olanzapine in the Treatment of Acute Mania in Malaysia Phase 4	Malaysia	Prospective cohort	Planned: 120 Actual: 102		Forecast: 30-Mar-2008 Actual: 09-Sep-2008
F1D-OE-B015	An Observational Study of Compliance Associated with Olanzapine-Treatment in Bipolar Disorder Phase 4	Austria, Hungary, Korea, South, Mexico, Romania, Taiwan	Prospective cohort	Planned: 960 Actual: 960		Forecast: 26-Jul-2011 Actual: 25-Dec-2010
F1D-PL-O204	Observational study of efficacy and safety of olanzapine in treatment of the first episode of schizophrenia Phase 4	Poland	Prospective cohort	Planned: 250 Actual: 251		Forecast: 15-Nov-2005 Actual: 28-Jun-2006
F1D-RO-B010	Clinical Response of Olanzapine in the Treatment of Patients with Schizophrenia and Relation with Length of Treatment Phase 4	Romania	Prospective cohort	Planned: 360 Actual: 419		Forecast: 01-Jun-2006 Actual: 01-Jun-2006

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-SB-B018	Prevention Of Bipolar Relapse With Olanzapine And Other Mood-Stabilizers. A Prospective Observational Study (PROTECT) Phase 4	Germany	Prospective cohort	Planned: 600 Actual: 761		Forecast: 30-Sep-2008 Actual: 06-Oct-2008
F1D-SB-B020	Predisposing factors for early retirement in patients with schizophrenia Phase 4	Germany	Prospective cohort	Planned: 620 Actual: 627		Forecast: 31-Jan-2006 Actual: 30-Nov-2005
F1D-SB-B027	Prevalence of metabolic changes and exposure to neuroleptics in schizophrenic patients Phase 4	Germany	Prospective cohort	Planned: 1900 Actual: 718		Forecast: 30-Nov-2008 Actual: 10-Nov-2008
F1D-SB-HGJE	Health Economic Survey of Olanzapine in the Treatment of Schizophrenia in Germany (GEO) Phase 4	Germany	Prospective cohort	Planned: 600 Actual: 655		Forecast: 18-Oct-2004 Actual: 17-Sep-2004
F1D-SB-S051	External Assessment of Quality of Life in Outpatients with Schizophrenia Phase 4	Germany	Prospective cohort	Planned: 1500 Actual: 1538		Forecast: 31-Jan-2006 Actual: 30-Nov-2005
F1D-SB-S052	IMPULSE Immediate Aggression Control, Antipsychotics and Tranquilization: An Observational Study Phase 4	Germany	Prospective cohort	Planned: 500 Actual: 558		Forecast: 13-Jun-2005 Actual: 18-Mar-2005

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-SR-B032	A 6 months observational study of the effectiveness of the Greek lifestyle program Solutions for Wellness for psychiatric patients - focusing on quality of life Phase 4	Greece	Prospective cohort	Planned: 355 Actual: 365		Forecast: 28-Nov-2008 Actual: 10-Dec-2008
F1D-TW-S024	Effectiveness and Safety of Olanzapine in the Treatment of Taiwanese Patients with Schizophrenia Phase 4	Taiwan	Prospective cohort	Planned: 400 Actual: 650	Follow Up 1 Hours	Forecast: 30-Jun-2005 Actual: 11-Nov-2004
F1D-US-HGKH	An Observational Study of the Effectiveness and Safety of Intramuscular Olanzapine in the Treatment of Agitation in Patients with Schizophrenia or Bipolar Mania Phase 4	United States	Prospective cohort	Planned: 75 Actual: 75		Forecast: 05-Jun-2006 Actual: 19-Sep-2006
F1D-VI-B007	aSTORM: Study of Treatment Outcomes Relating to Mania. An observational study of the clinical and functional outcomes associated with pharmacological treatment of mania in Bipolar Disorder Phase 4	Bosnia And Herzegovina, Bulgaria, Cyprus, Egypt, Jordan, Lebanon, Saudi Arabia, Slovenia, Slovakia, Turkey	Prospective cohort	Planned: 900 Actual: 860		Forecast: 08-Nov-2006 Actual: 15-May-2006

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-VI-B019	Six month multinational, prospective, observational study on factors influencing weight change in patients with schizophrenia or bipolar mania initiating or changing to olanzapine treatment Phase 4	China, Mexico, Romania, Taiwan	Prospective cohort	Planned: 550 Actual: 629		Forecast: 19-Dec-2008 Actual: 18-Dec-2008
F1D-VI-B031	Factors Affecting Clinical Treatment Outcome and Recovery: Multinational Observational Study on Factors Affecting Recovery from Mania in Bipolar Disorder in Patients Treated with Atypical Antipsychotics Phase 4	United Arab Emirates, Bosnia And Herzegovina, China, Algeria, Egypt, Greece, Hungary, Mexico, Romania, Saudi Arabia, Slovenia, Tunisia	Prospective cohort	Planned: 875 Actual: 927		Forecast: 16-Feb-2009 Actual: 23-Mar-2009
F1D-VI-S046	Observational Study Description F1D-VI-S046. A Prospective Observational Study of Intramuscular Antipsychotic Medications Phase 4	Australia, Bulgaria, Brazil, Canada, Czech Republic, Algeria, Egypt, Croatia, Hungary, Israel, Korea, South, Lithuania, Mexico, Poland, Romania, Russia, Saudi Arabia, Slovenia, Slovakia, Thailand, Turkey, Taiwan, South Africa	Prospective cohort	Planned: 2700 Actual: 2046		Forecast: 27-Oct-2006 Actual: 29-Nov-2006

Other Non-Pivotal Oral Olanzapine and RAIM Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-XM-B024	Cross Sectional Epidemiological Study Evaluating Symptomatic Remission and Adequate Socio Vocational Functioning in Outpatients with Schizophrenia Phase 4	Spain	Prospective cohort	Planned: 1000 Actual: 1014		Forecast: 19-Nov-2007 Actual: 18-Jul-2007
F1D-XM-B026	Epidemiological Study to Evaluate Functional Remission in Patients Diagnosed with Bipolar I Disorder in Syndromic Remission Phase 4	Spain	Prospective cohort	Planned: 400 Actual: 460		Forecast: 30-Jun-2008 Actual: 10-Apr-2008
F1D-XM-B040	A 1-year, Prospective, Observational Study to Identify The Clinical Factors Associated to the Time to Relapse in Outpatients with Schizophrenia at Risk of Medication Non-Adherence Phase 4	Spain	Prospective cohort	Planned: 607 Actual: 628		Forecast: 30-Nov-2009 Actual: 28-Sep-2009
F1D-XM-HGLK	Observational Descriptive Study of Patterns of Use of pharmacological Treatment of Patients with Acute Psychotic Decompensation and Conduct Disorders in the Emergency room Setting Phase 4	Spain	Prospective cohort	Planned: 240 Actual: 280		Forecast: 31-Mar-2005 Actual: 31-Mar-2005

Other Non-Pivotal Olanzapine LAI Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-EW-HGJW	An Open-Label Study Assessing the In Vivo D2 Receptor Occupancy of Intramuscular Olanzapine Depot (Pamoate) Using Positron Emission Tomography in Patients with Schizophrenia Phase 1B	CA, US	Open Label	Planned: 18 Actual: 14		Actual: 10-Oct-2003
F1D-EW-LOBE	A Study to Assess the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of an Intramuscular Formulation of Depot Olanzapine (Pamoate Salt) in Stable Schizophrenic Subjects Phase 1B	BE, ES, HR, US	Open Label	Planned: 350 Actual: 281		Actual: 19-Jan-2004
F1D-EW-LOBS	Pharmacokinetic Characterization of Intramuscular Olanzapine Depot as a Function of Particle Size Distribution Phase 1B	AU, BE, BR, HR, CZ, DE, MX, SG, SK, ES, US	Open Label	Planned: 175 Actual: 134		Actual: 30-Oct-2006
F1D-MC-HGKB	An Open-Label Study of Intramuscular Olanzapine Depot in Patients with Schizophrenia or Schizoaffective Disorder Phase 3	AR, AT, AU, BE, BR, CZ, DE, ES, FR, GR, HR, HU, IL, IT, MX, NL, PL, PR, PT, RO, RU, SE, SK, TW, US, ZA	Open Label	Planned: 700-1500 Actual: 931		Actual: 10-Oct-2011
F1D-MC-HGLQ	Olanzapine LAI versus oral olanzapine in treatment outcomes in patients with schizophrenia Phase 3B	AR, BR, CA, ES, FR, GR, PT, RO, SK, TW, PR, US	Open Label	Planned: 520 Actual: 524		Actual: 31 August 2010

Other Non-Pivotal Olanzapine LAI Studies

Study	Description	Countries	Study Design	Number of Patients	Duration of Follow Up	Estimated/Actual Completion Date
F1D-EW-LOBO	A Study to Investigate the Metabolites of Olanzapine Following Administration of Oral Olanzapine and the Pamoate Formulation of Intramuscular Olanzapine Depot in Stable Patients With Schizophrenia or Schizoaffective Disorder Phase 1B	United States	Open Label	9		Forecast: 09-Jan-2004 Actual: 09-Jan-2004

Annex 6. Protocols for Proposed and Ongoing Studies in Categories 1-3 of the Section "Summary Table of Additional Pharmacovigilance Activities" in RMP Part III

Overview of Included Protocols

Study Title	Protocol Status	Version of Protocol	Date of Protocol Version
Not applicable.			