Zyprexa

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
T/0135	Transfer of Marketing Authorisation	04/01/2024	08/02/2024	SmPC, Labelling and PL	
IG/1620	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished	01/08/2023	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	product formulation - Change that does not affect the product information				
PSUSA/10540 /202203	Periodic Safety Update EU Single assessment - olanzapine	01/12/2022	n/a		PRAC Recommendation - maintenance
N/0131	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/12/2021	08/02/2024	PL	
WS/1956	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/11/2020	09/12/2021	SmPC, Annex II and PL	
IA/0129	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	26/03/2020	n/a		
PSUSA/10540 /201903	Periodic Safety Update EU Single assessment - olanzapine	12/12/2019	21/02/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10540/201903.
WS/1454	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update section 4.8 of the SmPC to add stuttering as adverse drug reaction based on data from clinical trials and spontaneous reporting. PL is updated	22/11/2018	18/02/2019	SmPC and PL	Based on post-marketing cases and frequency of stuttering reported during clinical trials, plausible mechanism and causality linked with olanzapine use, the adverse event ' stuttering' is added to section 4.8 of the SmPC. The PL has been updated accordingly. In addition, the text in section 5.2 regarding the pharmacokinetics of olanzapine in hepatically impaired

	accordingly. In addition, the MAH took this opportunity to revised wording of section 5.2 on pharmacokinetics of olanzapine in hepatically impaired patients to improve clarity. In addition, the list of local representatives in the PL is being revised. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				patients has be revised to reflect correctly data from the related study.
IB/0126	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	15/06/2018	n/a		
IG/0898	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	12/02/2018	18/02/2019	Annex II	
IB/0124/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	28/04/2017	n/a		
IB/0123	B.II.b.1.e - Replacement or addition of a	28/04/2017	n/a		

	manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products				
WS/1127	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	23/02/2017	11/09/2017	SmPC and PL	
IA/0121/G	This was an application for a group of variations. B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	05/01/2017	n/a		
PSUSA/2205/201603	Periodic Safety Update EU Single assessment - olanzapine	01/12/2016	n/a		PRAC Recommendation - maintenance
WS/0987	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	15/09/2016	11/09/2017	SmPC, Annex II, Labelling and PL	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
N/0117	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/04/2016	11/09/2017	PL	
IA/0118	A.7 - Administrative change - Deletion of manufacturing sites	23/03/2016	n/a		
IG/0662	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2016	08/04/2016	SmPC, Labelling and PL	
N/0115	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/10/2015	08/04/2016	PL	
IA/0114	A.7 - Administrative change - Deletion of manufacturing sites	23/04/2015	08/04/2016	Annex II and PL	
IB/0113/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished	16/03/2015	n/a		

	product - Addition of a new test(s) and limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.c.3.a.1 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents NOT used in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product				
IB/0112/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	30/07/2014	n/a		
IG/0455	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	08/07/2014	13/04/2015	Annex II and PL	

WS/0485	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 5.1 of the SmPC in order to reflect the level of data available in adolescents with bipolar I disorder (manic or mixed episodes) or schizophrenia following the completion of a long-term safety study, in fulfilment of the requirement laid down in Article 46 of the paediatric regulation. The MAH took also the opportunity to align the Product Information with the Quality Review of Documents (QRD) template (Version 9), to update the list of local representatives in the Package Leaflet and to correct an editorial mistake concerning the ATC code. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	13/04/2015	SmPC, Annex II and PL	Please refer to the scientific discussion Zyprexa-H-000287-WS-0485-AR.
IG/0337	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	09/08/2013	n/a		
IG/0321	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/07/2013	n/a		
WS/0337	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	25/04/2013	27/05/2013	SmPC and PL	Lilly has recently completed the process of integration of 42 controlled olanzapine clinical studies into a single Olanzapine Integrated Database of patients exposed to

	Update of section 4.8 of the SmPC and relevant section of the PL to include "amnesia, epistaxis, abdominal distension, arthralgia, GGT high, uric acid high, pyrexia and dysarthria", as new undesirable effects for Zyprexa, Zyprexa Velotab and Zypadhera and "injection site abscess and injection site pain" as new undesirable effects for Zypadhera. The frequencies of currently labelled undesirable effects have also been revised throughout sections 4.4 and 4.8 of the SmPC and relevant sections of the PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				olanzapine across multiple indications and formulations. The Olanzapine Integrated Database aimed at creating a sufficiently large database with maximum olanzapine exposure numbers in adults as possible, while maintaining the characteristics that would make the results of the studies consistent enough to be rationally combined for a robust analysis of safety. Following an analysis of safety data from the Olanzapine Integrated Database, the MAH proposed an update the Product information to include amnesia, epistaxis, abdominal distension, arthralgia, GGT high, uric acid high, pyrexia and dysarthria", as new undesirable effects for Zyprexa, Zyprexa Velotab and Zypadhera and "injection site abscess and injection site pain" as new undesirable effects for Zypadhera. The frequencies of currently labelled undesirable effects have also been revised throughout sections 4.4 and 4.8 of the SmPC and relevant sections of the PL.
WS/0215	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update to section 4.8 of the olanzapine SmPCs to add urinary retention as an undesirable effect and to reflect this change in the section 4 of the PLS further to a cumulative review of "urinary retention" in temporal association with olanzapine treatment as requested by the CHMP following assessment of PSUR 25. C.I.4 - Variations related to significant modifications	24/05/2012	27/06/2012	SmPC, Annex II, Labelling and PL	Further to the assessment of safety data, the Product Information (section 4.8 of the SmPC and section 4 of the PL) has been updated to add loss of ability to urinate as an uncommon side-effect in patients taking olanzapine.

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IG/0155	B.III.2.a.1 - Change of specification('s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS	07/03/2012	n/a		
IB/0105	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	13/02/2012	n/a		
WS/0127	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of SmPC section 4.4 to include metabolic monitoring frequency examples following the assessment of the latest PSURs and RMP. The Package Leaflet is updated accordingly. Update of the frequency of Venous thromboembolism (VTE) in SmPC section 4.4 and 4.8 following PhVWP recommendation to include warnings about the risk of venous thromboembolism. The Package Leaflet is updated accordingly. The Package Leaflet is brought in line with the SmPC wording to include the use of tranquillisers and benzodiazepines for Zyprexa IM rapid-acting injection (RAIM). Correction to the annexes for Zyprexa coated tablets, specifically the excipient constituents of the edible blue ink of the 2.5-, 5-, 7.5-, and 10-mg tablet	20/10/2011	24/11/2011	SmPC and PL	Further to the assessment of safety data, the Product Information (section 4.4 of the SmPC and section 2 of the PL) has been updated to add examples of monitoring of blood glucose, lipids, weight in patients taking olanzapine. In addition warning on the risk of blood clotting (venous thromboembolism) was made consistent throughout Zyprexa products. The frequency of VTE was also recalculated and as a result assessed as uncommon in SmPC sections 4.4 and 4.8 and PL section 4. Last, the PL of Zyprexa IM rapid-acting injection (RAIM Zyprexa) was updated to provide information on the use of tranquillisers and benzodiazepines which is in line with the SmPC.

	coating in the respective SmPCs and PL is aligned with information in Module 3 of the dossier. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				
WS/0152/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change in the analytical procedure used to test an intermediate of the active substance, for residual tin. Tightening of the associated acceptance limit for tin in an intermediate of the active substance. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	17/11/2011	17/11/2011		
WS/0182	This was an application for a variation following a worksharing procedure according to Article 20 of	22/09/2011	20/10/2011	SmPC and PL	There is evidence to suggest that the newborn babies of mothers treated with antipsychotics during the third

	Commission Regulation (EC) No 1234/2008. Following PhVWP/CHMP conclusions of June 2011, update of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) regarding the use of antipsychotics during the third trimester of pregnancy and risk of abnormal muscle movements and/or withdrawal symptoms in newborns in accordance with the PhVWP/CHMP class labelling recommended wording. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				trimester of pregnancy may suffer adverse effects (primarily extrapyramidal side effects and/or withdrawal effects). Whilst there is limited data available for some antipsychotics, this is likely to be a class effect. In addition to the inclusion of neonatal drug withdrawal syndrome as listed adverse reaction, section 4.6 of the SmPC and section 2 of the PL were updated in accordance with the PhVWP/CHMP class labelling recommended wording, as follows: SmpC: Neonates exposed to antipsychotics (including [olanzapine]) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. PL: The following symptoms may occur in newborn babies, of mothers that have used [olanzapine] in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.
II/0102	Update of sections 4.4 and 4.9 for Zyprexa solution for injection related to the warning on the concomitant use of benzodiazepines and the management of oral overdose, respectively. Package Leaflet and Instructions for Health Care Professionals were amended accordingly. C.I.4 - Variations related to significant modifications	20/01/2011	21/02/2011	SmPC and PL	Following review of the latest safety information for olanzapine provided by the MAH on concomitant use of benzodiazepines with intramuscular olanzapine (58% of cases) and the number of related adverse events including deaths, the CHMP recommended the following update in section 4.4: - Simultaneous injection of intramuscular olanzapine and parenteral benzodiazepine is not recommended due to

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				the potential for excessive sedation, cardiorespiratory depression and in very rare cases, death (see sections 4.5 and 6.2). If the patient is considered to need parenteral benzodiazepine treatment, this should not be given until at least one hour after IM olanzapine administration. If the patient has received parenteral benzodiazepine, IM olanzapine administration should only be considered after careful evaluation of clinical status and the patient should be closely monitored for excessive sedation and cardiorespiratory depression. In addition, the CHMP recommended the deletion of the information in section 4.9 related to the management of oral overdose.
WS/0065/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Addition of a 98 tablets pack size for the 5, 10, 15 and 20mg strengths. B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g.	18/11/2010	20/12/2010	SmPC, Labelling and PL	

	tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes				
IG/0030	A.7 - Administrative change - Deletion of manufacturing sites	17/12/2010	n/a		
IB/0103/G	This was an application for a group of variations. B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	17/11/2010	17/11/2010	SmPC, Labelling and PL	
WS/0021	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008, update of sections 4.4 (deletion of a sentence in the warning related to hepatic function) and 4.8 (modification of the prolactin information in the footnote) of the Summary of Product	22/07/2010	06/09/2010	SmPC, Annex II and PL	Based on updated analyses concerning liver enzymes elevations and prolactin levels provided by the Marketing Authorisation Holder, the CHMP considered that the recommendation regarding dose reduction in patients with elevated liver enzymes and the reference to a decrease of prolactin levels over time related to diagnosis were no longer appropriate and recommended to delete this information. Subsequently, section 4.4 and footnote of section 4.8 were updated accordingly.

	Characteristics resulting of a review of the company core data sheet. Additional changes were made to the Product Information and Annex II in accordance with the QRD templates (version 7.3.1) and contact details of the local representatives (France, United Kingdom) were also updated in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0100	Update of the section 4.4 of the Summary of Product Characteristics to include a warning on sudden cardiac death. In addition, section 4.8 is also updated to include urinary incontinence as an uncommon adverse drug reaction and to revise the information on elevated plasma prolactin concentrations and related clinical manifestations. Section 4 of the Package Leaflet has been amended accordingly. Details of the local representative in Spain were updated in the Package Leaflet. Additionally, editorial changes were made in the relevant sections of the Product Information. Update of Summary of Product Characteristics and Package Leaflet	19/11/2009	21/12/2009	SmPC and PL	Following review of the latest safety information for olanzapine provided by the MAH on sudden cardiac death, urinary incontinence and elevated plasma prolactin concentrations and related clinical manifestations, the CHMP considered that: - In postmarketing reports with olanzapine, the events of sudden cardiac death have 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. Subsequently, this information was reflected as a warning in section 4.4. - Two apparently unconfounded serious case reports, and 13 serious case reports of urinary incontinence with a positive dechallenge were reported in PSUR 23. According to the current SPC, olanzapine exhibits a range of receptor affinities (Ki; < 100 nM) including ?1-adrenergic receptors.

					Furthermore; in the clinical trial data (from adult placebo-controlled database) the frequency of urinary incontinence with olanzapine was 0.3% (i.e., uncommon). Subsequently, urinary incontinence was added in section 4.8 as uncommon ADR. - In clinical trials of up to 12 weeks, plasma prolactin concentrations exceeded the upper limit of normal range in approximately 30% of olanzapine treated patients with normal baseline prolactin value. In the majority of these patients the elevations were generally mild, and remained below two times the upper limit of normal range. In patients with schizophrenia, mean prolactin level changes decreased with continued treatment, whereas mean increases were seen in patients with other diagnoses. The mean changes were modest. Generally in olanzapine-treated patients potentially associated breast- and menstrual related clinical manifestations (e.g. amenorrhoea, breast enlargement, galactorrhea in females,
IA/0101	IA_47_c_Deletion of a pack size(s)	25/09/2009	n/a	SmPC, Labelling and PL	
II/0099	Update of the section 4.8 of the Summary of Product Characteristics (SPC) to provide further detailed information on the risk of weight gain following CHMP conclusions on additional analyses performed by the MAH. Safety information on glucose levels observed during long term exposure was also updated. Editorial change was made in section 4.4 of the SPC.	29/05/2009	03/07/2009	SmPC	Following further analyses related to weight, lipids, and glucose for two populations (elderly patients with Alzheimer's disease, other types of dementia, or Parkinson's disease; and patients who were naïve to antipsychotic treatment when they entered the relevant clinical trials) and additional weight analyses from 2 clinical studies (F1D-US- HGJU and F1D-HGGF) performed by the MAH, the CHMP recommended that an update of the SPC should be made in relation to the wording on weight gain in

	Update of Summary of Product Characteristics				section 4.8 to provide better information for prescribers. The CHMP recommended that the frequency of potentially clinically significant weight gain should be clarified as proportions of patients in each class (over 7%, over 15% and over 25% weight gain) in short term use (under 24 weeks) and long term use (over 24 weeks), separately. In line with the CHMP's recommendations, the MAH updated footnotes 1 and 9 as follows: Adults 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). Adolescents 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.
II/0096	Update of sections 4.4 and 4.9 of the Summary of Product Characteristics (SPC) in line with the Product Information of a recently approved olanzapine	19/02/2009	25/03/2009	SmPC	Recommendations on monitoring for signs and symptoms of hyperglycaemia, weight gain, and new information on acute overdoses were added to sections 4.4 and 4.9 of the

	related product. Section 5.1 of the SPC was also updated with regard to details of the ATC code. Update of Summary of Product Characteristics				SPC.
IA/0098	IA_09_Deletion of manufacturing site	08/12/2008	n/a		
IA/0097	IA_09_Deletion of manufacturing site	08/12/2008	n/a		
IA/0095	IA_09_Deletion of manufacturing site	03/12/2008	n/a	Annex II and PL	
IA/0094	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	17/10/2008	n/a		
IA/0093	IA_05_Change in the name and/or address of a manufacturer of the finished product	27/08/2008	n/a		
II/0092	Update of section 4.8 of the Summary of Product Characteristics (SPC) to reflect new data regarding changes in bodyweight, glucose and lipid levels over time in adults and adolescents. The Marketing Authorisation Holder has also taken the opportunity to introduce a minor linguistic correction in all languages and some corrections in the SPC of the Spanish version. Update of Summary of Product Characteristics	26/06/2008	28/07/2008	SmPC	Based on the long -term results from studies conducted in the adolescent and adult population, the section 4.8 of the SPC has been updated to reflect new data regarding the increase of proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HCL cholesterol or triglycerides over time. In addition, the magnitude of weight gain and the propotion of adolescent patients who had clinically significant weight gain were greater with long-term exposure (at least 24 weeks) than with short-term exposure.
II/0091	Update of or change(s) to the pharmaceutical documentation	26/06/2008	30/06/2008		

II/0083	Update of the Summary of Product Characteristics (SPC) to include data from studies conducted in adolescent population with schizophrenia and bipolar I disorder (manic or mixed episodes). In addition, section 4.8 of the SPC was updated in accordance with the SPC guideline. The Product Information was updated in accordance with the latest QRD templates and the Labelling was combined. Details of the local representative in Iceland were updated in the Package Leaflet. Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/03/2008	22/04/2008	SmPC, Annex II, Labelling and PL	Based on the results from studies conducted in the adolescent population, the CHMP concluded that these data are insufficient to recommend the use of olanzapine in patients less than 18 years of age, in the treatments of schizophrenia and bipolar I disorder. The CHMP considered that there is a lack of data on efficacy and safety in these indications for the paediatric population. Nevertheless, the CHMP considered acceptable to reflect these available short -term results in section 5.1 of the SPC. With respect to safety, further concerns were raised in the paediatric population concerning weight gain, lipid and prolactin alterations, which have been reported with a greater magnitude as compared to the adult population. Sedation (including hypersomnia; lethargy, somnolence), increased appetite, dry mouth, elevated hepatic transaminases, GGT and decreased total bilirubin were also of concerns in this population. The CHMP considered acceptable to update sections 4.4 and 4.8 of the SPC to reflect this new safety information. Furthermore, to emphasize on the safety concerns in this population, section 4.2 of the SPC has been updated accordingly.
II/0090	Change(s) to the manufacturing process for the active substance	21/02/2008	26/02/2008		
II/0088	Update of sections 4.4 and 4.8 of the Summary Products Characteristics (SPC) to include further information on changes to lipid levels and body weight as well as updated information on changes to glucose levels (change in the frequency of hyperglycaemia and addition of 'glycosuria'). Section 4 of the Package Leaflet has been amended	13/12/2007	17/01/2008	SmPC and PL	The MAH performed an analysis from the clinical trials databases in relation to changes to glucose lipid levels and body weight. The CHMP concluded that olanzapine was associated with a greater mean change in both fasting and non-fasting (random) glucose levels relative to placebo in the adult population. Furthermore, the incidence of treatment-emergent glycosuria was statistically

	accordingly. Update of Summary of Product Characteristics and Package Leaflet				significantly higher for olanzapine-treated patients compared with placebo-treated patients. Analysis including data from clinical trials and post-marketing experience showed an increased frequency of reported hyperglycemia (from very rare to rare). Concerning lipids levels, mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in olanzapine treated patients without evidence of lipid dysregulation at baseline. Concerning weight gain, clinically significant treatment-emergent weight gain is observed across all baseline Body Mass Index (BMI) categories. Consequently, update of sections 4.4 and 4.8 of the SPC were made to reflect this further detailed information.
II/0086	Update of the SPC to include "fatigue" to section 4.8. In addition, a correction was made in the dose table in Section 6.6 for the 10 mg powder for solution for injection formulation only. This correction is consistent with the currently recommended lower dose for elderly. The section of Instructions to Health Care Professionals in the PL is consequently updated. Update of Summary of Product Characteristics and Package Leaflet	18/10/2007	21/11/2007	SmPC and PL	Update of section 4.8 of the SPC to include "fatigue" as adverse event of clinical trials following the safety information of the study report looking into the Efficacy of High Dose Olanzapine in a Controlled Fixed Dose-Response Trial for the Treatment of Schizophrenia and Schizoaffective Disorder LY170053 (Study F1D-US-HGLF).
IA/0089	IA_05_Change in the name and/or address of a manufacturer of the finished product	16/10/2007	n/a		
II/0084	This variation refers to an update of sections 4.4 and 4.8 of the Summary Product Characteristics (SPC) to include information on elevated lipid levels based on an analysis from placebo controlled studies in adult	19/07/2007	30/08/2007	SmPC and PL	Based on the submitted data, observed frequencies in adults of increased fasting total cholesterol (normal to high), fasting LDL cholesterol (borderline to high), and fasting triglyceride levels in patients treated with

	and adolescent populations. In addition, inclusion of 'alopecia' and 'oculogyration' in section 4.8 of the SPC as recommended by CHMP. Section 4 of the Package Leaflet (PL) has been amended accordingly. Update of Summary of Product Characteristics and Package Leaflet				olanzapine were more than 1 percentage points greater (but less than 10 percentage points greater) than in patients receiving placebo. The CHMP concluded that this observation supported the inclusion in section 4.8 of the SPC of "elevated cholesterol levels" as a common (1-10%) adverse event. Additionally a general warning relating to clinical management of lipid alterations was included in section 4.4 of the SPC. 'Alopecia' and 'oculogyration' were also included in section 4.8 of the SPC as recommended by CHMP.
IA/0087	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	23/08/2007	n/a		
IA/0085	IA_13_a_Change in test proc. for active substance - minor change	08/05/2007	n/a		
N/0081	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/02/2007	n/a	PL	
IB/0080	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	18/12/2006	18/12/2006	SmPC, Labelling and PL	
IB/0079	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	18/12/2006	18/12/2006	SmPC, Labelling and PL	
IB/0078	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	18/12/2006	18/12/2006	SmPC, Labelling and PL	
IB/0077	IB_41_a_02_Change in pack size - change in no. of	18/12/2006	18/12/2006	SmPC,	

	units outside range of appr. pack size			Labelling and PL	
IB/0076	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	18/12/2006	18/12/2006	SmPC, Labelling and PL	
IB/0075	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	18/12/2006	18/12/2006	SmPC, Labelling and PL	
IA/0082	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	18/12/2006	n/a		
IA/0074	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	07/12/2006	07/12/2006	SmPC, Labelling and PL	
IA/0073	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	07/12/2006	07/12/2006	SmPC, Labelling and PL	
IA/0072	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	07/12/2006	07/12/2006	SmPC, Labelling and PL	
IA/0071	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	07/12/2006	07/12/2006	SmPC, Labelling and PL	
IA/0070	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	07/12/2006	07/12/2006	SmPC, Labelling and PL	
IA/0069	IA_41_a_01_Change in pack size - change in no. of	07/12/2006	07/12/2006	SmPC,	

	units within range of appr. pack size			Labelling and PL	
II/0065	This variation refers to an update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) to include information on hepatitis (including hepatocellular, cholestatic or mixed liver injury), increased alkaline phosphatase, increased total bilirubin and increased transaminases based on a cumulative review of post-marketing hepatobiliary adverse events reported in temporal association with olanzapine treatment. Section 4 of the Package Leaflet (PL) was amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	28/06/2006	13/09/2006	SmPC and PL	The MAH carried out a post-marketing analysis to identify and describe reports of potential hepatobiliary adverse events in temporal association with olanzapine treatment. Data was analyzed with an original data lock point of 30 November 2004, followed by an update with a data lock point of 30 November 2005. Global post-marketing patient exposure to olanzapine was estimated to be approximately 18,000,000 million. The MAH had received more than 35,000 olanzapine post-marketing case reports with approximately 2,500 being considered hepatobiliary events after medical review. Cases were medically categorized and assessed with respect to several factors including medical history, concomitant medications, presence of risk factors or potential confounders and clinical outcome. Based on the review of these data, the CHMP considered the change of frequency for hepatitis (including hepatocellular, cholestatic or mixed liver injury) from 'very rare' to 'rare' undesirable effects to be acceptable. In addition, since hepatocellular reactions and increased transaminases have also been reported, the CHMP recommended inclusion of these terms in the SPC. The CHMP concluded that the update of sections 4.4 and 4.8 of the SPC to include information on hepatitis (including hepatocellular, cholestatic or mixed liver injury), increased alkaline phosphatase, increased total bilirubin and increased transaminases to be acceptable and agreed on the change in section 4 of the PL.
R/0064	Renewal of the marketing authorisation.	01/06/2006	12/09/2006	SmPC, Annex II, Labelling	

				and PL	
IA/0066	The marketing authorisation holder applied for the deletion of the marketing authorisation of the product from the range. IA_09_Deletion of manufacturing site IA_47_a_Deletion of a pharmaceutical form	15/05/2006	n/a	SmPC, Labelling and PL	
IB/0062	IB_10_Minor change in the manufacturing process of the active substance	08/11/2005	n/a		
II/0059	This variation relates to an update of sections 4.4 and 4.8 of the SPC and corresponding changes to the PL with safety data following a safety review on QT prolongation submitted subsequent to the assessment of Periodic Safety Update Report 12. Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	31/08/2005	SmPC and PL	The section 4.4 (Special warnings and special precautions for use) of the SPC was updated to state that in clinical trials, clinically meaningful QTc prolongations were uncommon (0.1% to 1%) in patients with olanzapine with no significant differences compared to placebo. In section 4.8 (Undesirable effects), hypercholesterolaemia was added as a very rare undesirable effect based on post-marketing spontaneous reports.
IB/0061	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	24/08/2005	n/a	SmPC	
IA/0060	IA_13_a_Change in test proc. for active substance - minor change	31/03/2005	n/a		
II/0053	Update of sections 4.2, 4.4, 4.5 and 4.8 of the SPC and corresponding sections of the PL. Update of Summary of Product Characteristics and Package Leaflet	15/12/2004	09/02/2005	SmPC and PL	Information was added to the Product Information 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. In addition the section 4.8 was updated following PSUR 13 to include hypothermia as a very rare adverse event for all formulations of Zyprexa. The Package Leaflet (PL) was updated accordingly.
II/0052	Update of section 6.2 of the SPC for Zyprexa 10 mg Powder for Solution for Injection and Zyprexa 10 mg Powder and Solvent for Solution for Injection based on compatibility studies between olanzapine and other drugs administered to patients with schizophrenia and acute agitation. Quality changes	15/12/2004	09/02/2005	SmPC and PL	As a result of physical compatibility studies, the section 6.2 of the SPC for the intramuscular formulations was amended with information that Zyprexa powder for solution for injection must not be combined in the syringe with any commercially available drugs. Moreover, intramuscular olanzapine should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed. In addition, lorazepam injection should not be used to reconstitute olanzapine for injection as this combination results in a delayed reconstitution time. Furthermore, olanzapine for injection should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.
IA/0058	IA_32_a_Change in batch size of the finished product - up to 10-fold	04/02/2005	n/a		
II/0051	Change(s) to the manufacturing process for the active substance	15/12/2004	20/12/2004		
IA/0057	IA_32_a_Change in batch size of the finished product - up to 10-fold	14/12/2004	n/a		
IB/0055	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	13/12/2004	n/a		

IB/0054	IB_33_Minor change in the manufacture of the finished product	13/12/2004	n/a		
II/0049	Update of section 4.4 of the SPC to include information on venous thromboembolism and section 4.8 to include the terms rhabdomyolysis, pulmonary embolism and deep vein thrombosis, as well as increased body temperature, lethargy, erythema and visual hallucinations following PSUR 12. In addition, changes were made to section 4.8 of the SPC and section 4 of the PL following a safety review of olanzapine in clinical trials conducted in elderly patients with dementia. Update of Summary of Product Characteristics and Package Leaflet	29/07/2004	04/11/2004	SmPC and PL	Information on a temporal association of olanzapine treatment and venous thromboembolism that has been reported very rarely (<0.01%) was added to the Product Information. A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism, all possible risk factors for VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken. Moreover, thromboembolism (including pulmonary embolism and deep vein thrombosis) and rhabdomyolysis was added as very rare (<0.01%) undesirable effects. Furthermore, increased body temperature, lethargy, erythema, and visual hallucinations were added as undesirable effects observed commonly (1-10%) in clinical trials in elderly patients with dementia.
IA/0050	IA_09_Deletion of manufacturing site	26/07/2004	n/a		
II/0044	Update of sections 4.4 and 4.8 of the SPC with corresponding update of the PL based on a review of olanzapine clinical trials conducted in elderly patients with dementia. The SPC and PL were amended through an Urgent Safety Restriction (USR) procedure on 2 March 2004.	24/03/2004	13/07/2004	SmPC and PL	The section 4.4 of the SPC was updated to state that 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

	Update of Summary of Product Characteristics and Package Leaflet				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 of treatment. Risk factors that may predispose this patient population to increased mortality include age >65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors. Further, in the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient ischemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in patients treated with olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All olanzapine- and placebo-treated patients who experienced a cerebrovascular event had pre-existing risk factors. Age >75 years and vascular/mixed type dementia were identified as risk factors for CVAE in association with olanzapine treatment. The efficacy of olanzapine was not established in these trials. In section 4.8 of the SPC, it was inserted that in clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse events compared to placebo (see also section 4.4

IA/0048	IA_34_a_01_Change in colour/flavour - Reduction or deletion: colouring system	25/05/2004	n/a		
IA/0047	IA_05_Change in the name and/or address of a manufacturer of the finished product	30/04/2004	n/a		
IA/0046	IA_09_Deletion of manufacturing site	29/04/2004	n/a		
IA/0045	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	27/02/2004	n/a		
IA/0043	IA_47_a_Deletion of a pharmaceutical form	26/02/2004	n/a	SmPC, Labelling and PL	
IA/0042	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	26/02/2004	26/02/2004	SmPC, Labelling and PL	
II/0036	Extension of Indication	24/07/2003	24/10/2003	SmPC and PL	
II/0037	This variation refers to an update of section 4.6 of the Summary of Product Characteristics (SPC) regarding the levels of olanzapine found in breast milk, as well as section 4.8 regarding EPS and hyperprolactinaemia, following the review of the 9th Periodic Safety Updated Report (PSUR). The corresponding sections of the Package Leaflet (PL) were amended. Update of Summary of Product Characteristics and Package Leaflet	26/06/2003	08/10/2003	SmPC and PL	

I/0041	16_Change in the batch size of finished product 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	02/10/2003	06/10/2003		
I/0040	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	02/10/2003	06/10/2003		
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/09/2003	n/a	Labelling	
I/0038	08_Change in the qualitative composition of immediate packaging material	07/04/2003	10/04/2003		
N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/10/2002	20/11/2002	PL	
II/0034	Extension of Indication Update of Summary of Product Characteristics and Package Leaflet	25/07/2002	18/10/2002	SmPC and PL	
II/0032	Update of Summary of Product Characteristics and Package Leaflet	30/05/2002	09/09/2002	SmPC, Labelling and PL	
II/0028	Extension of Indication	21/02/2002	04/06/2002	SmPC and PL	
I/0033	01_Change in the name of a manufacturer of the medicinal product 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	15/04/2002	19/04/2002		

I/0031	07_Change in coating weight of tablets or change in weight of capsule shells	29/01/2002	04/02/2002		
R/0029	Renewal of the marketing authorisation.	26/07/2001	20/11/2001	SmPC, Annex II, Labelling and PL	
I/0030	01_Change following modification(s) of the manufacturing authorisation(s)	24/08/2001	19/10/2001	Annex II and PL	
X/0021	X-3-iv_Change or addition of a new pharmaceutical form	29/03/2001	02/07/2001	SmPC, Annex II, Labelling and PL	
II/0024	Update of Summary of Product Characteristics and Package Leaflet	01/03/2001	14/06/2001	SmPC and PL	
I/0027	03_Change in the name and/or address of the marketing authorisation holder	01/03/2001	14/06/2001	SmPC, Labelling and PL	
I/0026	16_Change in the batch size of finished product	20/02/2001	08/03/2001		
I/0025	32_Change of imprints/bossing/marking on tablets/printing on capsules, incl. addition/change of inks	13/02/2001	13/02/2001		
X/0016	X-3-iii_Addition of new strength	21/09/2000	27/12/2000	SmPC, Annex II, Labelling and PL	
I/0014	01_Withdrawal of the manufacturing authorisation for a site of manufacture	24/09/1999	05/10/1999		

I/0013	16_Change in the batch size of finished product	21/07/1999	03/08/1999		
II/0011	Update of Summary of Product Characteristics and Package Leaflet	21/04/1999	19/07/1999	SmPC and PL	
I/0012	13_Batch size of active substance	09/06/1999	10/06/1999		
I/0010	16_Change in the batch size of finished product	17/02/1999	25/02/1999		
I/0008	20_Extension of shelf-life as foreseen at time of authorisation	03/11/1998	17/12/1998	SmPC	
II/0007	Update of Summary of Product Characteristics	25/06/1998	22/10/1998	SmPC and PL	
I/0009	20a_Extension of shelf-life or retest period of the active substance	01/10/1998	n/a		
II/0001	Update of Summary of Product Characteristics	19/11/1997	26/03/1998	SmPC and PL	
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/01/1998	03/03/1998	PL	
I/0004	12_Minor change of manufacturing process of the active substance	18/12/1997	n/a		
I/0003	01_Change following modification(s) of the manufacturing authorisation(s)	18/12/1997	n/a		
I/0002	01_Change following modification(s) of the manufacturing authorisation(s)	31/10/1997	n/a		
