EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Sonata

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
PSUSA/03140	Periodic Safety Update EU Single assessment - ZALEPLON	26/03/2015	27/05/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/03140.
II/0033	Update of sections 4.5, 4.9 and 5.3 of the SmPC in order to update the safety information related to drug-drug interactions with diphenhydramine, fertility and overdose. The Package Leaflet is updated accordingly.	23/10/2014	27/05/2015	SmPC, Annex II, Labelling and PL	Diphenhydramine is reported to be a weak inhibitor of aldehyde oxidase in rat liver, but its inhibitory effects in human liver are not known. There is no pharmacokinetic interaction between zaleplon and diphenhydramine following the administration of a single dose (10 mg and 50

[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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

	In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 9.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				mg, respectively) of each drug. However, because both of these compounds have CNS effects, an additive pharmacodynamic effect is possible. In a fertility and reproductive performance study in rats, mortality and decreased fertility were observed in males and females at an oral zaleplon dose of 100 mg/kg/day (equivalent to 49-times the maximum recommended human dose (MRHD) of 20 mg on a mg/m2 basis). Follow-up studies indicated that impaired fertility was due to an effect on the female. In embryofetal development studies, oral administration of zaleplon up to 100 mg/kg/day and 50 mg/kg/day to pregnant rats and rabbits, respectively, produced no evidence of teratogenicity (equivalent to 49- (rat) and 48- (rabbit) times the MRHD on a mg/m2 basis). Pre-and postnatal growth of rats was reduced at the maternally toxic dose of 100 mg/kg/day. The no-effect dose for growth of rat offspring was 10 mg/kg (equivalent to 5-times the MRHD on a mg/m2 basis). No adverse effects on embryofetal development were observed in rabbits. In a pre- and postnatal development study in rats, increased stillbirth and postnatal mortality, and decreased growth and physical development, were observed in the offspring of females treated with doses of ≥7 mg/kg/day that did not elicit maternal toxicity. The no-effect dose for postnatal development was 1 mg/kg/day (equivalent to 0.5-times the MRHD on a mg/m2 basis). In a subsequent cross-fostering study, adverse effects on offspring viability and growth appeared to result from both in utero and lactational exposure to zaleplon.
IG/0277	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/03/2013	n/a		

II/0030	Update version of the ASMF by the current active substance manufacturer to replace the site for micronizacion operation and testing for particle size of the micronized active susbstance and related changes. B.I.a.z - Change in manufacture of the AS - Other variation	15/03/2012	15/03/2012		
II/0031/G	This was an application for a group of variations. to replace the current manufacturing site of the finished product by the new manufacturing site and related changes in the manufacturing process. B.II.b.1.e - Replacement or addition of 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 B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for	15/12/2011	06/02/2012	SmPC, Annex II, Labelling and PL	

	a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer				
IA/0027	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	29/06/2009	n/a	Annex II and PL	
IA/0028	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	24/06/2009	n/a		
R/0026	Renewal of the marketing authorisation.	18/12/2008	19/02/2009	SmPC, Annex II, Labelling and PL	Based on their review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP was of the opinion that the quality, safety and efficacy continue to be adequately and sufficiently demonstrated. Therefore, the benefit/risk profile of Sonata continues to be favourable. The Marketing Authorisation for Sonata is renewed with unlimited validity.
IA/0025	IA_09_Deletion of manufacturing site	01/09/2008	n/a	Annex II and PL	
IA/0024	IA_47_c_Deletion of a pack size(s)	21/08/2008	n/a	SmPC, Annex II, Labelling and PL	
T/0023	Transfer of Marketing Authorisation	15/11/2007	12/12/2007	SmPC, Labelling and PL	
II/0020	Update of the section 4.4 (Special warnings and precautions for use) of the Summary of Product Characteristics (SPC) to include warnings regarding complex sleep-related behaviours and anaphylactic/anaphylactoid reactions (specifically	18/10/2007	21/11/2007	SmPC, Labelling and PL	The MAH performed a cumulative review of the post-marketing safety surveillance database up to March 2007. In this review, 12 reports suggestive of complex sleep behaviour were identified. They include cases of sleep-walking, sleep-driving and other complex behaviours such

	angioedema). Additionally, section 4.8 (Undesirable effects) of the SPC and relevant sections of the Package Leaflet (PL) have been updated accordingly. Furthermore, changes to the labelling and Package Leaflet have been introduced, in accordance with the QRD template and the contact details for the local representative of Bulgaria and Romania has been included. Update of Summary of Product Characteristics, Labelling and Package Leaflet				as preparing and eating food. On the basis of this review, the MAH proposed to include a warning in section 4.4 of the SPC. Furthermore, due to the risk to the patients in the community, it is also recommended that zaleplon should be discontinued for patients who report sleep-driving episodes. From the cumulative review, 8 reports of angioedema were also identified. On this basis, the MAH proposed a warning to inform that cases of anaphylactic/anaphylactoid reactions (specifically angioedema) have been reported. The MAH also proposed to update section 4.8 of the SPC (Undesirable effects) to add sleep-walking and angioedema. Section 2 (Before you take Sonata) and section 4 (Possible side- effects) of the PL have also been updated to reflect the above SPC changes. Additionally, the MAH is proposing to update the PL in accordance with QRD Template version 7.2, and to update the address list of local representatives in section 6 (Further Information) with the inclusion of contact details for representatives in Bulgaria and Romania.
IA/0022	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	13/09/2007	n/a		
IA/0021	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	10/09/2007	n/a		

II/0019	Update of Summary of Product Characteristics (section 4.4 Special Warnings and Special Precautions for Use) to include a specific warning on the potential for dependence with zaleplon. Corresponding changes have been introduced in section 2 of the Package Leaflet. Update of Summary of Product Characteristics, Labelling and Package Leaflet	27/04/2006	12/06/2006	SmPC, Annex II, Labelling and PL	In the 9th Periodic Safety Update Report (PSUR) for Sonata, 4 case reports of dependence were included. In view of this the CHMP requested the MAH to update the Product Information accordingly. Subsequently, the MAH identified in its database 14 reports consistent with dependence on zaleplon. Most of the patients were taking other psychotropic medications. Therefore, the following information has been included in the Summary of Product Characteristics: "There have been post-marketing reports of dependence associated with zaleplon predominantly in combination with other psychotropic agents." The Package Leaflet was updated accordingly. In addition, in this Type II variation, the MAH updated the list of local representatives and updated the Product Information in accordance to the latest template.
II/0018	Update of sections 4.8 and 4.9 of the SPC and consequent changes of the PL following CHMP assessment of the PSUR 8. Update of Summary of Product Characteristics and Package Leaflet	26/05/2005	14/07/2005	SmPC and PL	Section 4.8 (Undesirable effects) of the SPC was updated to reflect the available info on hepatotoxicity (mostly described as increased transaminase levels). In section 4.9 (Overdose), information was added that chromaturia (blue-green urine discolouration) has been reported in connection with zaleplon overdose.
N/0017	The Marketing Authorisation Holder (MAH) applied for the inclusion of additional local representatives of the MAH for all new Member States. Minor change in labelling or package leaflet, not connected with the SPC (Art. 61.3 Notification)	09/06/2004	n/a	PL	
R/0016	Renewal of the marketing authorisation.	21/01/2004	31/03/2004	SmPC, Annex II, Labelling	The CHMP was of the opinion that the quality, safety and efficacy of Sonata continues to be adequately

				and PL	demonstrated and therefore that the benefit/risk profile of Sonata remains favourable in the approved indication.
IA/0015	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	20/10/2003	n/a		
II/0014	Update of Summary of Product Characteristics and Package Leaflet	22/05/2003	16/09/2003	SmPC and PL	
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/02/2003	17/03/2003	PL	
II/0012	Update of Summary of Product Characteristics and Package Leaflet	27/06/2002	10/09/2002	SmPC and PL	
I/0010	20_Extension of shelf-life as foreseen at time of authorisation	28/09/2001	21/11/2001	SmPC	
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/11/2001	28/01/2002	PL	
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/04/2001	14/06/2001	PL	
II/0008	Update of or change(s) to the pharmaceutical documentation	29/03/2001	05/04/2001		
II/0007	Update of Summary of Product Characteristics and Package Leaflet	14/12/2000	20/03/2001	SmPC and PL	
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/04/2000	31/05/2000	Labelling and PL	

I/0005	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	20/12/1999	09/03/2000	SmPC	
I/0004	30_Change in pack size for a medicinal product	20/12/1999	09/03/2000	SmPC, Labelling and PL	
I/0003	30_Change in pack size for a medicinal product	20/12/1999	09/03/2000	SmPC, Labelling and PL	
I/0002	25_Change in test procedures of the medicinal product	29/04/1999	10/05/1999		
I/0001	01_Change in the name of a manufacturer of the medicinal product	23/04/1999	06/05/1999		