Circadin

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
N/0073	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2024		PL	
II/0071/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a	06/06/2024	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).

	starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier				
PSUSA/1963/ 202309	Periodic Safety Update EU Single assessment - melatonin	16/05/2024	n/a		PRAC Recommendation - maintenance
WS/2499	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	29/06/2023	n/a		
IAIN/0070	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	16/05/2023	06/05/2024	Annex II and PL	
N/0068	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/03/2023	06/05/2024	PL	
IA/0067	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP -	09/09/2022	n/a		

	Replacement/addition of a site where batch control/testing takes place				
PSUSA/1963/ 202009	Periodic Safety Update EU Single assessment - melatonin	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0064	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	09/03/2021	n/a		
II/0061	Risk Management Plan update to remove the following risks from the list of potential risks: "Drug interaction with levothyroxine" "Panic Attacks", "Potential interaction with warfarin", "Sperm motility decreased/Spermatozoa morphology abnormal" and "Withdrawal". C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	11/02/2021	n/a		
IA/0066	A.7 - Administrative change - Deletion of manufacturing sites	18/01/2021	24/01/2022	Annex II and PL	
IB/0063	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	12/01/2021	n/a		
N/0062	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/12/2020	24/01/2022	PL	

IAIN/0060	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	29/05/2020	17/08/2020	Annex II and PL	
IB/0059	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	23/08/2019	17/08/2020	SmPC, Labelling and PL	
T/0058	Transfer of Marketing Authorisation	04/01/2019	07/02/2019	SmPC, Labelling and PL	
IA/0057/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	21/11/2018	n/a		
IA/0056	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	29/10/2018	n/a		
IAIN/0055	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	26/07/2018	07/02/2019	Annex II and PL	

II/0053/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	05/07/2018	07/02/2019	Annex II and PL	
IAIN/0054/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	31/05/2018	07/02/2019	SmPC, Labelling and PL	

	B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test				
PSUSA/1963/ 201709	Periodic Safety Update EU Single assessment - melatonin	17/05/2018	n/a		PRAC Recommendation - maintenance
IA/0051	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	15/10/2017	n/a		
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/03/2017	07/02/2019	PL	
IB/0049/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/11/2015	n/a		
PSUSA/1963/ 201409	Periodic Safety Update EU Single assessment - melatonin	21/05/2015	17/07/2015		Please refer to Circadin PSUSA-00001963/201409 EPAR: Scientific conclusions and grounds recommending the variation ot the terms of the marketing authorisation.
IAIN/0048	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	30/04/2015	n/a		

PSUSA/1963/ 201309	Periodic Safety Update EU Single assessment - melatonin	08/05/2014	n/a		PRAC Recommendation - maintenance
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/02/2014	27/06/2014	PL	
IB/0044	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	19/02/2014	n/a		
IB/0043/G	This was an application for a group of variations. 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.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	18/02/2014	n/a		
IAIN/0041/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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	13/09/2013	27/06/2014	Annex II and PL	

	responsible for importation and/or batch release - Not including batch control/testing				
IB/0040/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/09/2013	n/a		
IB/0038	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	04/07/2013	27/06/2014	SmPC, Labelling and PL	
IAIN/0039	C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	20/06/2013	n/a		

IAIN/0037/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	21/05/2013	12/08/2013	Annex II and PL	
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/03/2013	12/08/2013	PL	
IAIN/0035/G	This was an application for a group of variations. B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing A.7 - Administrative change - Deletion of manufacturing sites A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	18/01/2013	12/08/2013	Annex II and PL	

N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/09/2012	12/08/2013	PL	
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/08/2012	12/08/2013	PL	
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/06/2012	12/08/2013	PL	
R/0031	Renewal of the marketing authorisation.	16/02/2012	20/04/2012	SmPC, Annex II, Labelling and PL	Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considered that the risk-benefit balance of Circadin in the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over remained favourable and therefore recommended the renewal of the marketing authorisation. The CHMP recommended that the renewal be granted with unlimited validity.
IA/0029	A.7 - Administrative change - Deletion of manufacturing sites	18/10/2011	n/a		
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/10/2011	n/a	PL	
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/09/2011	n/a	PL	
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/08/2011	n/a	PL	

IA/0026	B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale	05/08/2011	n/a	SmPC	
IB/0025	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	11/01/2011	11/01/2011	SmPC, Labelling and PL	
II/0023	Update of Section 5.1 of the Summary of Product Characteristics with wording relating to Study 112006 (to bring the SPC in line with the recently approved posology of Circadin). Section 4 of Package Leaflet (Possible Side Effects) was also updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/10/2010	26/11/2010	SmPC and PL	With this variation, wording relating to Study 112006 (which constituted the scientific data bulk for Variation II/19) has been introduced in section 5.1 (Pharmacodynamic Properties), to bring it in line with recently approved changes in the posology section of the Circadin 2 mg tablets SPC. Section 4 of Package Leaflet (Possible Side Effects) was also updated to make it reader-friendly. Layman terms were introduced to the section to replace scientific terms, bringing the section in line with the latest Guideline on Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use.
IA/0024/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons	01/09/2010	n/a	Annex II	

	or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities				
N/0022	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/07/2010	n/a	PL	
II/0019	Change in the possible duration of treatment (section 4.2 of the SPC and section 3 of the PL) of Circadin based on data emerging from clinical Study 112006. Section 4.8 of the SPC and section 4 of the PL were also amended to reflect safety data from Study 112006 and from a post-authorisation surveillance study carried out in the context of follow-up measure 012 (12545A). The details of the MAH's representative for Romania have also been updated in section 6 of the PL. Update of Summary of Product Characteristics and Package Leaflet	22/04/2010	02/06/2010	SmPC, Annex II and PL	Study 112006 was a large Randomised Clinical Trial with a complex design. It analysed more than 600 patients, over 400 of whom where on Circadin treatment for 6 months. The safety and efficacy data provided in Study 112006 and 12545A support the proposed changes. In particular, the analysis of data from Study 112006 showed that the benefit observed after 3 weeks is maintained for up to 3 months. At 3 months, about an extra 10% of responders were seen in the Circadin treated group. Therefore, melatonin treatment for longer than 3 weeks may be beneficial for a subgroup of patients.
IA/0021/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.h - Changes to an existing pharmacovigilance	22/04/2010	n/a	Annex II	

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD				
II/0020	Update of DDPS (Pharmacovigilance) Update of DDPS (Pharmacovigilance)	22/10/2009	20/11/2009	Annex II	The Detailed Description of the Pharmacovigilance System (DDPS) has been updated (version 2.2) in order to reflect various organisational changes. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
IB/0018	IB_17_a_Change in re-test period of the active substance	16/07/2009	n/a		
II/0014	Change to the manufacturing process of the finished product, analytical methods and specifications. Quality changes	19/03/2009	26/03/2009		
IA/0017	IA_01_Change in the name and/or address of the marketing authorisation holder	19/03/2009	n/a	SmPC, Labelling and PL	
II/0016	The Marketing Authorisation Holder applied for a change in the composition of the finished product Change in formulation	19/02/2009	27/02/2009		

II/0015	Change in test procedure of active substance Change(s) to the test method(s) and/or specifications for the active substance	19/02/2009	27/02/2009	Annex II	
IB/0013	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	22/10/2008	n/a		
II/0011	Change of section 5.3 the SPC, as recommended by the CHMP further to the assessment of data previously submitted in the context of FUM 002. Additionally, the ATC code for melatonin was amended to reflect its recent update by the WHO. Update of Summary of Product Characteristics	26/06/2008	29/07/2008	SmPC	An increased incidence of benign thyroid tumours had been observed at high doses (equivalent to an AUC x 1,500,000 than the human exposure after ingestion of Circadin) in a rat carcinogenicity study presented within the initial Marketing Authorisation Application of October 2005. The MAH has now submitted further data on this regards. This variation application was submitted to update the SPC to reflect the above data. Section 5.3 was updated to include the following sentence: "The carcinogenicity study in the rat did not reveal any effect which may be relevant for humans". Additionally, the ATC code for melatonin has been amended to reflect its recent update by the WHO.
IB/0007	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	04/03/2008	n/a		
IB/0008	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	27/02/2008	n/a		
IA/0010	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	18/02/2008	n/a	Annex II and PL	

IA/0006	IA_01_Change in the name and/or address of the marketing authorisation holder	16/01/2008	n/a	SmPC, Labelling and PL	
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/01/2008	n/a	PL	
IA/0005	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	05/12/2007	05/12/2007	SmPC, Labelling and PL	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/10/2007	n/a	Labelling and PL	
IB/0002	IB_33_Minor change in the manufacture of the finished product	27/09/2007	n/a		