EMA/24189/2021

Thymanax

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
IA/0046	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	06/01/2021	n/a		
WS/1849	This was an application for a variation following a worksharing procedure according to Article 20 of	29/10/2020	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).

	Commission Regulation (EC) No 1234/2008. Submission of an updated RMP version 24.0 in order to revise the safety concerns, important identified and potential risks in line with the new GVP module V. In addition, the completed studies have been deleted and, as agreed in LEG 031, the frequency of the educational material distribution is updated to once a year. 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				
WS/1779	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC to add 'Myalgia' with a frequency 'uncommon' following routine pharmacovigilance review. The Package Leaflet section 4 is updated accordingly. In addition, the WorkShare Applicant takes the opportunity to bring the Product Information of Valdoxan and Thymanax in line with the latest QRD template version 10.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	07/05/2020		SmPC, Annex II, Labelling and PL	The MAH performed a safety review analysis based on two Targeted Medical Events (TME) list: the TME Rhabdomyolysis focusing on events related to muscular lysis (blood CPK increased with or without muscular symptoms) and the TME Myalgia/Muscle fatigue/Muscle spasms on muscular symptoms. The analysis has been based on clinical review of case reports, as well as data from clinical trials. Based on a review of these, the CHMP was of the opinion that SMQ Rhabdomyolysis/myopathy should remain to be under close monitoring during the PSUR period and agreed that evidence is sufficient to include myalgia as an Adverse Drug Reaction in section 4.8 of the SmPC (frequency uncommon). For more information, please refer to the Summary of

	data				Product Characteristics.
WS/1622/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. B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	14/06/2019	n/a		
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/06/2019		PL	
IA/0041	B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold	10/01/2019	n/a		
R/0040	Renewal of the marketing authorisation.	18/10/2018	07/01/2019	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Valdoxan in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/71/20	Periodic Safety Update EU Single assessment -	06/09/2018	n/a		PRAC Recommendation - maintenance

1802	agomelatine				
II/0038	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/09/2018	n/a		
II/0037	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	08/03/2018	n/a		
IA/0036	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	11/09/2017	01/12/2017	SmPC, Annex II, Labelling and PL	
PSUSA/71/20 1702	Periodic Safety Update EU Single assessment - agomelatine	01/09/2017	n/a		PRAC Recommendation - maintenance
N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/06/2017	01/12/2017	PL	
IB/0033	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/04/2017	n/a		
II/0031	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/12/2016	n/a		
IAIN/0032	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/11/2016	01/12/2017	SmPC and PL	
PSUSA/71/20	Periodic Safety Update EU Single assessment -	15/09/2016	18/11/2016	SmPC, Annex	Refer to Scientific conclusions and grounds recommending

1602	agomelatine			II and PL	the variation to terms of the Marketing Authorisation(s)' for PSUSA/71/201602.
IB/0030	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	29/06/2016	n/a		
II/0028	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/02/2016	n/a		
PSUSA/71/201502	Periodic Safety Update EU Single assessment - agomelatine	24/09/2015	19/11/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/71/201502.
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/06/2015	19/11/2015	PL	
IA/0025	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	08/05/2015	n/a		
IB/0023/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.1.a - Replacement or addition of a	06/05/2015	19/11/2015	Annex II and PL	

	manufacturing site for the FP - Secondary packaging site 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.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.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold				
IAIN/0024	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	09/02/2015	n/a		
IA/0022	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	20/01/2015	n/a		
PSUV/0021	Periodic Safety Update	25/09/2014	19/11/2014	SmPC, Annex II and PL	Please refer to Thymanax PSUV-0021 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0019	Update of sections 4.2 and 5.1 of the SmPC to incorporate treatment recommendations when switching to agomelatine from another antidepressant (SNRI/SSRI) based on results of the study CL3-20098-073. The Package Leaflet is	22/05/2014	23/06/2014	SmPC and PL	The current change to the agomelatine product information includes advice related to the discontinuation of previous antidepressant medicine when switching to Thymanax and makes prescribers and patients aware that discontinuation symptoms related to stopping of previous medicine may

	updated accordingly. 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				occur for a few weeks, even if the dose of the previous antidepressant medicine is decreased gradually.
II/0018	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	22/05/2014	n/a		
II/0020	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	20/03/2014	n/a		
PSUV/0017	Periodic Safety Update	19/09/2013	13/11/2013	SmPC and PL	Please refer to Thymanax EMEA/H/C/000915/PSUV/0017 EPAR Assessment Report – Periodic safety update report, as well as: Thymanax EMEA/H/C/000915/PSUV/0017 EPAR - Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
R/0015	Renewal of the marketing authorisation.	19/09/2013	13/11/2013	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Thymanax remains positive, but that there are outstanding safety concerns with agomelatine THYMANAX in the treatment of major depressive episodes which require an additional five year renewal on the basis of the following pharmacovigilance grounds:

					• Uncertainty concerning the risk of liver toxicity and the effectiveness of the risk minimisation measures introduced which are as follows: The observed reactions of serious liver toxicity indicated a lack of compliance with treatment recommendations. Consequently, updated treatment recommendations, a DHPC and updated educational materials had been distributed to potential prescribers to inform of the risk of liver toxicity and remind prescribers of the necessity to comply with the treatment recommendations. Due to the short period of time since these risk minimisation measures were set out in practice, the effectiveness of these measures could not be properly evaluated. • Uncertainty regarding the potential association between agomelatine and QT prolongation (on-going signal evaluation on potential effect on the heart).
IB/0016	C.I.3.a - 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 - Implementation of wording agreed by the competent authority	16/10/2013	23/06/2014	SmPC	
II/0014	The MAH proposed the update of section 4.8 of the SmPC in order to add a warning following the review and assessment of a signal for urticaria, face oedema and angioedema. The Package Leaflet was updated accordingly. 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	25/04/2013	13/11/2013	SmPC and PL	With this variation the company updated the Product information for agomelatine, adding three new adverse events: urticaria, face oedema and angioedema to the SPC and the package leaflet. The change was made following the analysis of the data from the performed cumulative review on these events from the time of marketing authorisation.

	45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				
II/0013	Update of sections 4.2, 4.4, 5.1 and 5.2 of the SmPC in order to add information on the safety and efficacy of agomelatine in patients < 75 years of age, and to add a new warning to prevent its use in patients ≥75 years, as requested by the CHMP further to the assessment of Study CL3-20098-070 (follow up measure 002 and 002.1). The package leaflet is updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 8.3. C.I.3.z - 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 - Other variation	21/02/2013	13/11/2013	SmPC, Annex II, Labelling and PL	Results from study CL3-20098-070, a phase III, double-blind, placebo-controlled randomised study of the efficacy and safety of agomelatine oral administration (25 to 50 mg/day) in elderly patients suffering from Major Depressive Disorder, confirmed the safety and efficacy of agomelatine in patients < 75 year old. Section 4.2, 5.1 and 5.2 of the SmPC are being further substantiated with results from this study. However no effect was shown in patients aged ≥ 75 years, therefore a warning is being added section 4.4 of the SmPC to recommend against the use of agomelatine in this age group.
IA/0012	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	11/12/2012	n/a		
IAIN/0011	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/12/2012	n/a		
II/0010	Update of the following SmPC sections following the PSUR 5 and RMP version 11 assessment: - section 4.2 with the advice to prescribers to	20/09/2012	24/10/2012	SmPC, Annex II and PL	This variation updated sections 4.2, 4.4 and 4.8 of the SmPC to include information on cases of liver injury, hepatitis and jaundice as well as recommendation to

	monitor liver enzymes when increasing the dosage; - section 4.4 with the information on cases of liver injury, hepatitis and jaundice and the time of their occurrence; recommendation to monitor liver enzymes when increasing the dosage, and discontinue treatment in case of symptoms and signs of potential liver injury; information on new risk for hepatic injury, i.e. diabetes; - section 4.5 to include interactions between agomelatine and rifampicin and smoking; - section 4.6 to update the statement on limited amount of data in pregnant women; - section 4.8 to update the frequency of increased liver enzymes and include jaundice, hepatic failure, vomiting and weight changes as adverse events. The Package Leaflet is updated accordingly 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				monitor liver enzymes with the dose increase, and discontinue treatment in case of symptoms and signs of potential liver injury occur. Furthermore, three new adverse events, i.e. vomiting, weight increased, weight decreased were included in the section 4.8 of the SmPC, and updates to sections 4.5 to reflect newly observed drug-drug interactions and 4.6 to reflect limited data on pregnancy outcomes were added. The Package Leaflet has been updated accordingly.
II/0008	Following the assessment of the PSUR 4 sections 4.2, 4.4, and 4.8 of the SmPC were updated in order to: - include new treatment recommendations for liver function monitoring (additional blood sampling after 3 weeks of treatment); - update the frequency of increased ASAT and/or ALAT and other adverse reactions based on post-marketing experience;	16/02/2012	21/03/2012	SmPC, Annex II and PL	With this variation the company updated the Product information for agomelatine following the assessment of the safety data in the Periodic Safety Update Report 4 to reflect the new recommendations on frequency of the liver function monitoring (additional blood sampling after 3 weeks of treatment). Moreover, new side effects have been added: increased gamma-glutamyl transferase (GGT), increased alkaline phosphatase (ALP), hallucinations; while

	- add new safety information pertinent to increased gamma-glutamyl transferase (GGT), increased alkaline phosphatase (ALP), and hallucinations. The Package leaflet has been updated accordingly. Additional minor linguistic changes have also been introduced. 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				the frequency of other side effects has been updated based on the information that became available after agomelatine had been put on the market.
IB/0009	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	07/02/2012	n/a		
II/0006	Submission of a new description of the pharmacovigilance system and the addendum dedicated to the agomelatine specificities of the pharmacovigilance system. C.I.8.a - Introduction of a new Pharmacovigilance system - which has not been assessed by the relevant NCA/EMA for another product of the same MAH	15/12/2011	15/12/2011		With this variation the MAH submitted a new description of the pharmacovigilance system in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.
II/0007	Update of section 4.4 to include the warning about agomelatine use in patients with a history of bipolar disorder and pre-treatment elevation of transaminases as a risk factor for increase in	23/06/2011	27/07/2011	SmPC, Annex II and PL	This variation updates the product information for Thymanax to include precautions related to the use of the product in patients with increased levels of liver enzymes (transaminases) and in those who have had a history of

	transaminases; update of section 4.8 to include new adverse reactions 'nightmare' and 'abnormal dreams' following the assessment of the PSUR #3. Furthermore, based on the analysis of signal detection data covering the period between February 2009 and February 2011 terms 'aggression' and 'abdominal pain' were added to the section 4.8 of the SmPC. The Package Leaflet has been updated accordingly. The MAH also took the opportunity to reflect the up-to-date version identifier of the RMP in Annex II. Furthermore, minor editorial changes were made to the product information. 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				bipolar disorder before starting the treatment. Additionally, new side effects were added including aggressive behaviour, nightmares, abnormal dreams and abdominal pain.
II/0005	This type II variation concerns the update of the following sections of the SmPC: - section 4.4 to include obesity/overweight and non-alcoholic fatty liver disease as risk factors for increases in transaminases, - section 4.8 to include new adverse events (mania/hypomania, irritability, restlessness, pruritus), - and section 4.9 to include symptoms of overdose as requested by the CHMP further to the assessment of PSUR 2. The sections 2, 3 and 4 of the package leaflet have	16/12/2010	21/01/2011	SmPC, Annex II and PL	With this variation the following sections of the SmPC were updated: - section 4.4 to include obesity/overweight and non-alcoholic fatty liver disease as risk factors for increases in liver enzymes (transaminases), - section 4.8 to include new adverse events (mania/hypomania, irritability, restlessness, pruritus), - and section 4.9 to include symptoms of overdose. These updates were requested by the CHMP further to the assessment of the PSUR 2.

	been updated accordingly. Furthermore, minor editorial changes were introduced to the Product Information (PI). 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				
II/0004	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 - Change(s) with new additional data submitted by the MAH. 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	22/07/2010	26/08/2010	SmPC, Annex II, Labelling and PL	The MAH updated the section 4.8 of the SmPC to include a new adverse event (agitation) observed in the post-marketing setting and the section 4.9 to reflect post-marketing experience with overdose of agomelatine, as requested by the CHMP further to the assessment of the PSUR 1. Section 4 of the Package Leaflet has been updated accordingly. Additionally the MAH has taken the opportunity to implement the new QRD template and introduce minor editorial and administrative changes to the Product Information.
IA/0003	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	17/12/2009	n/a		
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/12/2009	n/a	PL	

IA/0002	To add an alternative site for secondary packaging IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	18/11/2009	n/a		