Wakix

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/10490 /202209	Periodic Safety Update EU Single assessment - pitolisant	14/04/2023	n/a		PRAC Recommendation - maintenance
II/0030	Extension of indication to include treatment of narcolepsy with or without cataplexy in adolescents and children from the age of 6 years, based on	26/01/2023	24/02/2023	SmPC and PL	Please refer to Scientific Discussion 'Wakix-H-C-2616-II-30.

[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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

	results from Study P11-06; an ongoing phase III, double-blind, multicentre, randomized, placebo-controlled trial undertaken to evaluate safety and efficacy of pitolisant in children from 6 to less than 18 years with narcolepsy with/without cataplexy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7.0 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10490 /202109	Periodic Safety Update EU Single assessment - pitolisant	05/05/2022	n/a		PRAC Recommendation - maintenance
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/05/2022	24/02/2023	PL	
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/10/2021	10/02/2022	PL	
II/0023/G	This was an application for a group of variations. Update of the SmPC section 5.1 to reflect the information of the new clinical data from the open-label, long-term treatment of EDS (with or without cataplexy) in narcolepsy P09-10 HARMONY III study, and update of SmPC section 4.4 based on the randomised, double-blind, placebo-controlled, drug	10/06/2021	10/02/2022	SmPC, Labelling and PL	

	abuse potential study (P16-02). Risk Management Plan version 6.0 has been updated to remove abuse potential from the list of potential risks of and to bring it in line with GVP V rev 2. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10490 /202009	Periodic Safety Update EU Single assessment - pitolisant	06/05/2021	n/a		PRAC Recommendation - maintenance
IB/0027	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/02/2021	10/02/2022	Annex II	
R/0024	Renewal of the marketing authorisation.	15/10/2020	17/12/2020	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Wakix in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IA/0025	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	10/09/2020	n/a		

	an obsolete parameter)				
PSUSA/10490 /201909	Periodic Safety Update EU Single assessment - pitolisant	30/04/2020	25/06/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10490/201909.
IA/0022	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)	10/04/2020	n/a		
IAIN/0020	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	19/08/2019	25/06/2020	Annex II and PL	
PSUSA/10490 /201809	Periodic Safety Update EU Single assessment - pitolisant	11/04/2019	n/a		PRAC Recommendation - maintenance
PSUSA/10490 /201803	Periodic Safety Update EU Single assessment - pitolisant	31/10/2018	n/a		PRAC Recommendation - maintenance
IB/0016	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	01/08/2018	22/11/2018	SmPC, Labelling and PL	
IA/0014	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)	24/05/2018	n/a		

PSUSA/10490 /201709	Periodic Safety Update EU Single assessment - pitolisant	12/04/2018	n/a		PRAC Recommendation - maintenance
II/0011	Update of section 5.2 of the SmPC in order to include information on newly identified metabolites as requested in variation EMEA/H/C/002616/II/0004/G. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/02/2018	22/11/2018	SmPC	The metabolism of pitolisant in humans is fully characterized. The major non-conjugated metabolites are hydroxylated derivatives in several positions and cleaved forms of pitolisant leading to inactive major carboxylic acid metabolite found in urine and serum. They are formed under the action of CYP3A4 and CYP2D6. Several conjugated metabolites were identified, the major ones (inactive) being two glycine conjugates of the acid metabolite of pitolisant and a glucuronide of a ketone metabolite of monohydroxy desaturated pitolisant. On liver microsomes, pitolisant and its major metabolites do not significantly inhibit the activities of the cytochromes CYP1A2, CYP2C9, CYP2C19, CYP2C8, CYP2B6, CYP2E1 or CYP3A4 and of uridine diphosphate glucuronosyl transferases isoforms UGT1A1, UGT1A4, UGT1A6, UGT1A9 and UGT2B7 up to the concentration of 13.3 µM, a level considerably higher than the levels achieved with therapeutic dose.
IA/0013	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	21/12/2017	n/a		
IB/0010	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	19/12/2017	22/11/2018	SmPC, Labelling and	

				PL	
PSUSA/10490 /201703	Periodic Safety Update EU Single assessment - pitolisant	26/10/2017	n/a		PRAC Recommendation - maintenance
II/0004/G	This was an application for a group of variations. Update of sections 4.2, 4.5 and 5.2 of the SmPC based on the final CSR of study P15-02 (to assess the mass balance recovery, metabolite profile and metabolite identification of 14C-pitolisant at steady state conditions, in healthy CYP2D6 phenotyped subjects), P14-07 (to evaluate pharmacokinetic interaction of pitolisant with sodium oxybate and modafinil in healthy male volunteers) and P15-15 (to evaluate pharmacokinetic interaction of pitolisant with CYP3A4 substrates (midazolam), CYP2B6 substrates (bupropion), UGT2B7 inhibotors (probenecide)) in fulfilment of PAM (MEA 02, 03 and 04). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial change in section 4.6 and 4.8 of the SmPC. Moreover, updated RMP version 5.2 has been agreed as part of this procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2017	13/10/2017	SmPC and PL	By comparison to CYP2D6 extensive metabolisers, higher systemic exposure (up to 3 fold) to pitolisant is observed in CYP2D6 poor metabolisers. In the up-titration scheme, dose increment should take into account this higher exposure. The exposure to pitolisant was higher in the CYP2D6 poor metabolisers after a single dose and at steady state; Cmax and AUC(0-tau) was approximately 2.7 fold and 3.2-fold greater on Day 1 and 2.1-fold and 2.4-fold on Day 7. The serum pitolisant half-life was longer in CYP2D6 poor metabolisers compared to the extensive metabolisers. In a clinical multiple dose study, the combination of pitolisant with probenecid decreases the AUC of pitolisant by about 34%. The combination of pitolisant with modafinil or sodium oxybate, usual treatments of narcolepsy was evaluated in healthy volunteers, at therapeutic doses. No clinically relevant pharmacokinetic drug-drug interaction was evidenced either with modafinil or with sodium oxybate.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0008	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	20/07/2017	14/09/2017	SmPC, Labelling and PL	
II/0007	Submission of the final CSR for Study P11-11, a multi-centre, single dose trial to evaluate the pharmacokinetics of pitolisant in children from 6 to less than 18 years with narcolepsy (Measure 3 of the agreed PIP). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/06/2017	n/a		
PSUSA/10490 /201609	Periodic Safety Update EU Single assessment - pitolisant	05/05/2017	n/a		PRAC Recommendation - maintenance
IB/0006	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	09/02/2017	14/09/2017	SmPC	
IB/0002/G	This was an application for a group of variations. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	17/10/2016	14/09/2017	SmPC	

	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation				
IB/0001/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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	28/09/2016	n/a		