Xyrem

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
II/0067/G	This was an application for a group of variations. Update of section 4.6 of the SmPC in order to amend the information about breast-feeding. The Package Leaflet is updated accordingly. Update of section 4.8 of the SmPC in order to add the adverse reactions "increased libido" and "seborrhea" with an unknown frequency.	14/09/2017		SmPC and PL	Sodium oxybate and/or its metabolites are excreted into breast milk. Changes in sleep patterns have been observed in breastfed infants from exposed mothers, which may be consistent with the effects of sodium oxybate on the nervous system. Sodium oxybate should not be used during breastfeeding. In addition, the adverse reactions 'increase libido' and 'seborrhoea' are added to the product information with a frequency unknown, based on post-marketing reporting.

[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).

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	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				
II/0066	Submission of the final report from study (C00302) listed as a category 3 study in the RMP. This is a post marketing non-interventional surveillance pharmacoepidemiology study (PMSS) to evaluate long-term safety, tolerability and compliance in administration of Xyrem (sodium oxybate) oral solution in patients who receive treatment with this medication in regular clinical practice. In addition, the MAH submitted a revised risk management plan version 8.0. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	01/09/2017	n/a		The PASS study C00302 is a post-marketing non interventional pharmacoepidemiology study to evaluate long-term safety, tolerability and compliance in administration of sodium oxybate (sodium oxybate) oral solution in patients who receive treatment with this medication in regular clinical practice. The objective of this study is to capture information about the potential for dependence, abuse, withdrawal, overdose, misuse, and compliance with the instructions for using sodium oxybate. This study includes a specific checklist to be completed by the study physician, to identify potential misuse, overconsumption, abuse, and inappropriate use of sodium oxybate. Furthermore to broaden the knowledge of known/not known adverse drug reactions when treated with sodium oxybate in regular clinical practice and to broaden the knowledge about the safety profile in special patient populations. As of 12 October 2016, a total of 41 sites had been initiated in 9 countries. In total 749 patients were screened, with 730 patients included in the intention-to-treat set. Overall, the results from the PASS study C00302 were consistent with the known safety profile of sodium oxybate, supported the information contained in the SmPC, and did not reveal any new safety signal. No change to the benefit profile could be observed from this

					study.
IA/0069	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	31/08/2017	n/a		
PSUSA/2757/ 201610	Periodic Safety Update EU Single assessment - sodium oxybate	09/06/2017	n/a		PRAC Recommendation - maintenance
II/0063/G	This was an application for a group of variations. 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	19/01/2017	29/06/2017	SmPC, Labelling and PL	
N/0064	Update of the package leaflet with revised contact details of local representative for Finland, Lithuania, Latvia and Estonia. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/12/2016	29/06/2017	PL	
IB/0062	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate	16/08/2016	n/a		

	for AS - Other variation				
II/0061	Update of section 4.8 of the SmPC in order to add the adverse events dehydration, sleep-related eating disorder, panic attack, mania/bipolar disorder, delusion, bruxism, loss of consciousness, tinnitus, pollakiuria/ micturition urgency with a frequency not known. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	04/08/2016	29/06/2017	SmPC and PL	Based on the review of available safety information from literature, the Marketing Authorisation Holder Global safety database, clinical and pharmaco-epidemiological studies and disproportionality analyses, the signals of sleep-related eating disorder; loss of consciousness; pollakiuria/ micturition urgency; dehydration; panic attacks; delusion; tinnitus; bruxism; and mania/bipolar disorder were confirmed as identified risks. Consequently, the section 4.8 of the summary of product characteristics was updated to include these new adverse drug reactions. The package leaflet was updated accordingly.
PSUSA/2757/ 201510	Periodic Safety Update EU Single assessment - sodium oxybate	13/05/2016	n/a		PRAC Recommendation - maintenance
IB/0059/G	This was an application for a group of variations. B.II.e.1.b.1 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Solid, semi-solid and non-sterile liquid pharmaceutical forms B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.IV.1.a.1 - Change of a measuring or administration device - Addition or	19/11/2015	n/a		

	replacement of a device which is not an integrated part of the primary packaging - Device with CE marking				
R/0054	Renewal of the marketing authorisation.	25/06/2015	08/09/2015	SmPC, Labelling and PL	Based on the review of available information, the CHMP is of the opinion that the quality, safety and efficacy of Xyrem continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of this medicinal product continues to be favourable. The product information has been updated to include “dehydration” as adverse event with frequency “not known” and to bring it in line with new QRD template. The CHMP recommends that the renewal be granted with unlimited validity.
PSUSA/2757/ 201410	Periodic Safety Update EU Single assessment - sodium oxybate	25/06/2015	28/08/2015	SmPC and PL	Please refer to Xyrem PSUSA/00002757/201410 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IA/0058	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	12/08/2015	n/a		
IB/0056	B.II.e.1.a.2 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Semi-solid and non-sterile liquid pharmaceutical forms	12/08/2015	n/a		
IA/0057	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	23/07/2015	n/a		

II/0052	Update of the Annex II to reflect the existing additional risk minimisation measures in the form of educational materials and controlled distribution system 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	20/11/2014	08/09/2015	Annex II	Possible pharmacodynamic and pharmacokinetic interactions when sodium oxybate is used concomitantly with topiramate cannot be excluded as clinical observation(s) of coma, and increased plasma GHB concentration were reported in a patient(s) under concomitant use of sodium oxybate and topiramate. Therefore, patients should be warned against the use of topiramate in conjunction with sodium oxybate.
II/0051	Update of sections 4.4 and 4.5 of the SmPC with regards to the concomitant use of sodium oxybate with topiramate. The package leaflet has been updated accordingly. In addition the MAH took the opportunity to introduce format and/or editorial changes throughout the SmPC and to bring the product information 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	20/11/2014	08/09/2015	SmPC, Labelling and PL	In this variation the MAH provided new warning against the concomitant use of sodium oxybate with an antiepileptic agent, topiramate.
II/0050	Update of sections 4.2, 4.4, 4.5, and 4.8 of the SmPC in order to include the results of drug interaction studies. The Package Leaflet and Labelling were proposed to be updated accordingly.	22/05/2014	27/06/2014	SmPC, Annex II, Labelling and PL	The SmPC was updated to reflect the results of three new clinical studies, which evaluated the pharmacokinetics and pharmacodynamics of Xyrem when co-administered with ibuprofen, diclofenac and valproate. Instructions on dose adjustment with co-administration of

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				valproate and new warnings for concomitant use with valproate, highlighting potential respiratory depression induction and/or CNS-depressant effects when combined with alcohol or any other CNS depressant were included. Additionally, information on interactions with ibuprofen, diclofenac and valproate was added, together with “Euphoric mood” as a new Adverse Drug Reaction.
PSUV/0049	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
IA/0048/G	This was an application for a group of variations. 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.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	04/09/2013	n/a		
IA/0047	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	18/04/2013	n/a		
IA/0046	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	05/04/2013	n/a		

	changes to an approved test procedure				
IB/0044	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size	08/01/2013	n/a		
IB/0041	B.IV.1.z - Change of a measuring or administration device - Other variation	20/11/2012	n/a		
IG/0222	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/11/2012	n/a		
IB/0039/G	This was an application for a group of variations. B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation 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	05/10/2012	n/a		
IAIN/0040/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	24/08/2012	n/a		

	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
IB/0038/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.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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.c.z - Container closure system of the AS - Other variation	12/01/2012	n/a		
IB/0036	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	10/11/2011	n/a		
IG/0121	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that	03/11/2011	n/a		

	does not impact on the operation of the pharmacovigilance system				
IA/0035	A.7 - Administrative change - Deletion of manufacturing sites	27/10/2011	31/01/2012	Annex II and PL	
IA/0033	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	19/08/2011	n/a		
IB/0032	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	27/05/2011	n/a		
II/0026	Update of relevant sections of the SmPC to include the following information relevant to the authorised indication: contraindication in patients with major depression (4.3), information on drug-drug interactions with duloxetine, lorazepam and tramadol (4.5), pharmacokinetic results in elderly population (5.2) and safety information in relation to the clinical trials conducted in fibromyalgia patients (4.2, 4.4, 4.6 and 4.8). Information on absolute bioavailability and preclinical data were also updated in section 5.2, and 5.3, respectively. The Package Leaflet has been amended accordingly. Finally, annex II has been updated in order to delete the reference to the versions of the RMP and Pharmacovigilance system and to reflect the previously agreed yearly PSUR	17/03/2011	18/04/2011	SmPC, Annex II and PL	Please refer to the scientific discussion H-593-II-26-AR

	cycle. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0031	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	06/04/2011	n/a		
IB/0030/G	This was an application for a group of variations. B.II.e.1.a.2 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Semi-solid and non-sterile liquid pharmaceutical forms B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	14/01/2011	n/a	SmPC, Labelling and PL	

IB/0029	Minor changes to SPC in order to put sections 4.2 and 6.5 in line with measuring device's graduations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	29/10/2010	n/a	SmPC	
IB/0028/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	05/10/2010	n/a		
R/0027	Renewal of the marketing authorisation.	22/07/2010	17/09/2010	SmPC, Annex II, Labelling and PL	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 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. This application was submitted following a worksharing procedure according to Article 20 of Commission Regulation

					(EC) No 1234/2008.
IA/0025	A.7 - Administrative change - Deletion of manufacturing sites	25/03/2010	n/a	Annex II and PL	
N/0024	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2009	n/a	PL	
IA/0023	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	21/05/2009	n/a		
IB/0022	IB_10_Minor change in the manufacturing process of the active substance	05/03/2009	n/a		
IB/0021	IB_33_Minor change in the manufacture of the finished product	04/03/2009	n/a		
IB/0020	IB_30_b_Change in supplier of packaging components - replacement/addition	13/02/2009	n/a		
N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/11/2008	n/a	PL	
IA/0018	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	22/07/2008	n/a	SmPC and PL	
IB/0017	IB_07_b_02_Replacement/add. of manufacturing site: Primary packaging site -	13/06/2008	n/a		

	Semi-solid ph. forms				
IB/0016	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	13/06/2008	n/a		
IA/0015	IA_32_a_Change in batch size of the finished product - up to 10-fold	28/05/2008	n/a		
IA/0014	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	28/05/2008	n/a	Annex II and PL	
IA/0013	IA_05_Change in the name and/or address of a manufacturer of the finished product	26/03/2008	n/a	Annex II and PL	
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/02/2008	n/a	PL	
IA/0012	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	27/11/2007	n/a		
II/0007	Update of Summary of Product Characteristics (SPC) and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	31/10/2007	SmPC and PL	Following assessment of PSUR 2 (Periodic Safety Update Report, reporting period: 13 April 2006 to 12 October 2006), the CHMP requested addition of three adverse events to section 4.8 "Undesirable effects "of the SPC (weight decrease, suicidal ideation and suicidal attempt). UCB, the MAH (Marketing Authorisation Holder) for Xyrem also performed a safety assessment as part of PSUR 03 (reporting period: 13 October 2006 to 12 April 2007). As a

					result of their review, the MAH included three additional terms to section 4.8 of the SPC: "insomnia", "initial insomnia" and "restless legs syndrome".
IA/0010	IA_05_Change in the name and/or address of a manufacturer of the finished product	31/10/2007	n/a		
IA/0009	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	26/09/2007	n/a	Annex II and PL	
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/06/2007	n/a	PL	
II/0001	Extension of the indication for Xyrem to "Treatment of narcolepsy with cataplexy in adult patients". Amendments have been introduced to sections 4.1, 4.2, 4.8 and 5.1 of the Summary of Product Characteristics (SPC) and sections 1 and 4 of the Package Leaflet (PL). The Bulgarian and Romanian Local Representatives were added to section 6 of the PL. Changes to the SPC, Annex II, Labelling and Package Leaflet have also been made in accordance with the latest QRD template. Extension of Indication	24/01/2007	01/03/2007	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion H-593-II-01-AR.
IA/0005	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition	21/02/2007	n/a	SmPC	

	or replacement				
IA/0004	IA_36_ b_Change in shape or dimensions of the container/closure - other pharm. forms	10/10/2006	n/a		
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/08/2006	n/a	PL	
IA/0002	IA_05_Change in the name and/or address of a manufacturer of the finished product	19/06/2006	n/a	Annex II and PL	