PASS INFORMATION

Title	XYREM EU-RMP: Effectiveness Assessment Protocol of Educational Materials
Protocol version identifier	4.0
Date of last version of protocol	13 Nov 2017
EU PAS register number	EUPAS15024
Active substance	Sodium oxybate
Medicinal product	XYREM
Pharmacotherapeutic group	N07XX04
Product reference	EMEA/H/C/000593 number
Procedure number	EMEA/H/C/000593/MEA/PRO 019
Marketing authorization holder(s)	UCB Pharma Ltd 208 Bath Road Slough, SL1 3WE UNITED KINGDOM
Joint PASS	No
Research question and objectives	The overall research question is to evaluate the effectiveness of the risk minimization measures being implemented in the EU to mitigate the important identified risks of respiratory and CNS depression, depression and suicidality, abuse and misuse of XYREM, diversion and criminal use, overdose, dependency/withdrawal, and interactions of XYREM with alcohol, the important potential risks associated with sodium overload, in patients prescribed XYREM. Specifically, the objectives of the survey are to: 1. Assess Prescribers' awareness of the educational materials (i.e., Health Care Professional (HCP) Checklist, Frequently Asked Questions (FAQ) Patient Information Sheet, How to Take XYREM brochure, and, Patient Alert Card) by estimating the proportion of targeted Prescribers who were sent the materials. 2. Assess whether Prescribers' self-reported behaviour/practices with

	respect to minimizing the important identified risks of respiratory and CNS depression, depression and suicidality, abuse and misuse of XYREM, diversion and criminal use, overdose, dependency/withdrawal, and interactions of XYREM with alcohol the important potential risks associated with sodium overload, are in accordance with the XYREM SmPC. This will be evaluated by estimating the proportion of targeted Prescribers whose responses to the practice -related questions are consistent with the SmPC's prescribing information. 3. Assess Prescribers' knowledge of the posology of XYREM by estimating the proportion of targeted Prescribers whose responses to the dosing-related questions are consistent with the SmPC's prescribing information.
Countries of survey	Belgium, Germany, Italy, Spain, Sweden, United Kingdom
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MARKETING AUTHORIZATION HOLDER

Marketing authorization holder	UCB Pharma Ltd 208 Bath Road Slough, SL1 3WE UNITED KINGDOM
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2 LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
CNS	central nervous system
CRO	contract research organisation
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAQ	frequently asked questions
HCP	health care professional
Luto	Luto Research Ltd.
MAH	marketing authorisation holder
N/A	not assigned
RMM	risk minimization measure
RMP	risk management plan
SADR	serious adverse drug reaction
SAE	serious adverse event
SmPC	summary of product characteristics
UBC	United Biosource Corporation
UK	United Kingdom

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Italy	
Spain	
Sweden	
United Kingdom	

4 ABSTRACT

Title

XYREM EU-RMP: Effectiveness Assessment Protocol of Educational Materials

Protocol amendment version 4.0, 13 Nov 2017

Rationale and background

UCB, the Marketing Authorisation Holder (MAH) of XYREM (sodium oxybate), a prescription treatment for adult patients diagnosed with narcolepsy with cataplexy, will conduct a survey of healthcare professionals (HCP)s. The purpose of this survey is to evaluate the effectiveness of the risk minimization measures (RMM)s as part of the updated XYREM European Union (EU) Risk Management Plan (RMP) being implemented to mitigate the important identified risks of respiratory and central nervous system (CNS) depression, depression and suicidality, abuse and misuse of XYREM, diversion and criminal use, overdose, dependency/withdrawal, interactions of XYREM with alcohol, the important potential risks associated with sodium overload, and how to manage these important identified risks in patients prescribed XYREM.

To ensure that the risks are adequately managed by HCPs and patients, new routine and additional RMMs are being implemented in the EU. These include an updated XYREM Summary of Product Characteristics (SmPC) and a comprehensive program at the point of patient care that will educate/remind HCPs about the posology of XYREM and the important serious risks. The details of the risk minimization materials for the program and how these materials will be implemented in the EU are described in Part V and Annex 10 and 11 of the RMP. The four educational components of the RMP are (1) HCP Checklist, (2) FAQ Patient Information Sheet, (3) How to Take XYREM brochure, and (4) Patient Alert Card.

According to the European legislation of Good Vigilance Practice UCB assesses the effectiveness of the XYREM RMP educational materials. To that end, a survey of Prescribers' awareness and understanding of the posology and important identified risks of XYREM will be conducted to ensure its safe use. Results of this survey will be used to assess the effectiveness of the educational materials about the appropriate and safe use of XYREM, and to make adjustments if necessary.

Research question and objectives

The overall research question is to evaluate the effectiveness of the RMMs being implemented in the EU to mitigate the important identified risks of respiratory and CNS depression, depression and suicidality, abuse and misuse of XYREM, diversion and criminal use, overdose, dependency/withdrawal, and interactions of XYREM with alcohol, the important potential risks associated with sodium overload, in patients prescribed XYREM. Specifically, the objectives of the survey are to:

1. Assess Prescribers' awareness of the educational materials (i.e., HCP Checklist, FAQ Patient Information Sheet, How to Take XYREM brochure, and Patient Alert Card) by estimating the proportion of targeted Prescribers who got sent the materials
2. Assess whether Prescribers' self-reported behaviour/practices with respect to minimizing the important identified risks of respiratory and CNS depression, depression and suicidality, abuse and misuse of XYREM, diversion and criminal use, overdose, dependency/withdrawal, and interactions of XYREM with alcohol the important potential risks associated with sodium overload, are in accordance with the XYREM SmPC. This will be evaluated by estimating the proportion of targeted Prescribers whose responses to the practice -related questions are consistent with the SmPC's prescribing information.
3. Assess Prescribers' knowledge of the posology of XYREM by estimating the proportion of targeted Prescribers whose responses to the dosing-related questions are consistent with the SmPC's prescribing information.

Study Design

The survey objectives will be accomplished by means of a cross-sectional survey of a sample of Prescribers in Belgium, Germany, Italy, Spain, Sweden and the United Kingdom who were sent the educational materials. The target sample is 200 prescribers total from all participating countries. These countries were selected for conducting the effectiveness assessment as they had the highest number of XYREM prescriptions. The data from the Prescribers will be collected using a structured, self-administered questionnaire. The Prescribers will be invited to take the survey online using a secure URL that requires a unique identifier to access the survey.

Population

This survey aims to recruit a random sample of XYREM prescribers from Belgium, Germany, Italy, Spain, Sweden, and the UK. The sampling frame will be from the lists of HCPs in each of the countries to whom the XYREM educational materials were sent, which includes HCPs with possibility to prescribe XYREM, current prescribing HCPs as well as sleep disorder specialists with available contact information.

Variables

Prescribers' awareness of the appropriate dosing and risks of XYREM, as described in the XYREM SmPC and the educational materials, will be assessed using a standardized questionnaire.

The primary outcome of the survey is the proportion of Prescribers providing a correct response for each individual survey question consistent with the XYREM SmPC.

The proportion responding correctly will be tabulated separately for each item in the survey instrument.

HCP demographic information will be collected at the end of the survey in order to further characterize the respondent population and, if possible, those who eventually choose not to fully participate. This will include gender, medical specialty, and type of medical practice, country and years in medical practice.

Data sources

Responses to the prescriber survey will be analysed in order to calculate the percentage of correct responses to the individual questions.

Study size

There is no target comprehension rate specified *a priori*. It is aimed to reach sample size of 200 completed surveys. If this sample size cannot be reached, descriptive statistics of lower sample sizes will be presented, regardless of number of respondents.

Data analysis

The primary outcome of the survey is the proportion of prescribers providing a correct response for each individual question in the key risk messages consistent with the XYREM EU SmPC.

Point estimates for the proportion with correct responses, and associated 95% confidence intervals, will be calculated for each question. In the case of multiple choice questions, the number and proportion of prescribers reporting each response will also be provided.

Information obtained from the survey will be reported as descriptive statistics for the survey administration, survey population, and the survey questions. The following will be reported as part of this analysis:

- The number of invitations issued
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who completed the survey
- Description of survey participants including:
  - Country
  - Medical specialty
  - Type of medical practice (public/private activity)
  - Years in medical practice
  - Gender

- Frequency distribution of responses to each question (the number of respondents who give each answer to each question)
- Primary outcome: For each key risk message question, the percent of respondents selecting desired response for the question and 95% confidence interval
- Responses will be stratified by country and prescriber medical specialty where applicable. Additional analyses may be performed as needed.

Milestones

The distribution of the surveys is started in begin in January 2016 and will continue until December 2017. The results of this PASS will be included in the next RMP update.

5 AMENDMENTS AND UPDATES

Number	Date	Section of survey protocol	Amendment or update	Reason
1	29 Aug 2016	PASS INFORMATION, 9.2.1, APPENDIX 5	Change from country France to countries Belgium, Italy, and Sweden	France has country-specific RMP in which the educational materials of the EU RMP are not used. Change to countries where educational material for EU RMP has been provided.
1	29 Aug 2016	9.1, 9.2.1.2, 9.2.1.3, 9.3, 9.3.2, APPENDIX 5	Change from UBC to Luto Research Ltd. to execute the survey.	Selected CRO for survey execution was Luto.
1	29 Aug 2016	Whole protocol	Editorial update to ENCePP PASS protocol format.	On 15 Jun 2016 classification as PASS by UCB EEA QPPV.
2	12 Jun 2017	PASS INFORMATION, 3, 6, 9.4.1.3	Update of study personnel, study timelines and deletion of absolute payment amount	Request by EMA after protocol review
3	30 Aug 2017	14	Add signature pages only for local Spanish Amendment	Request by Spanish Ethics Committee and therefore local Spanish amendment
4	13 Nov 2017	9.5	Add percentage of correct responses	Request by EMA
4	13 Nov 2017	9.5	Add estimation for lower sample size and percentage of country responses	Request by EMA

6 MILESTONES

Milestone	Planned date
Start of data collection	Jan 2016
End of data collection	Dec 2017
Registration in the EU PAS register	Sep 2016
Final report of survey results	Jul 2018

7 RATIONALE AND BACKGROUND

UCB will conduct a survey of Prescribers who were provided with the XYREM RMP educational materials. The survey will evaluate Prescribers' awareness of the posology and the important identified risks of respiratory and CNS depression, depression and suicidality, abuse and misuse of XYREM, diversion and criminal use, overdose, dependency/withdrawal, interactions of XYREM with alcohol the important potential risks associated with sodium overload, and how to manage these important identified risks as described in the EU SmPC.

The design for this survey is based on UCB's previous experience designing risk management programs for UCB product(s), and on the prior experience of United BioSource Corporation (UBC) in conducting similar surveys in the EU as well as in a number of countries outside of the EU and US.

8 RESEARCH QUESTION AND OBJECTIVES

The overall research question is to evaluate the effectiveness of the RMMs being implemented in the EU to mitigate the important identified risks of respiratory and CNS depression, depression and suicidality, abuse and misuse of XYREM, diversion and criminal use, overdose, dependency/withdrawal, and interactions of XYREM with alcohol, the important potential risks associated with sodium overload in patients prescribed XYREM. Specifically, the objectives of the survey are to:

1. Assess Prescribers' awareness of the educational materials (i.e., HCP Checklist, FAQ Patient Information Sheet, How to Take XYREM brochure, and Patient Alert Card) by estimating the proportion of targeted Prescribers who got sent the materials.
2. Assess whether Prescribers' self-reported behaviour/practices with respect to posology of XYREM and minimizing the important identified risks of respiratory and CNS depression, depression and suicidality, abuse and misuse of XYREM, diversion and criminal use, overdose, dependency/withdrawal, and interactions of XYREM with alcohol, the important potential risks associated with sodium overload are in accordance with the XYREM SmPC. This will be evaluated by estimating the proportion of targeted Prescribers whose responses

to the practice-related questions are consistent with the SmPC's prescribing information.
3. Assess Prescribers' knowledge of posology of XYREM by estimating the proportion of targeted Prescribers whose responses to the dosing-related questions are consistent with the SmPC's prescribing information.

9 RESEARCH METHODS

9.1 Study design

The final survey design is based on experience from risk management evaluation studies previously completed by UCB and UBC, who has designed the assessment surveys to evaluate prescribers' understanding of risk messages. Recruitment and analytic strategies included in this protocol are similar to those programs.

This survey is being offered only online. Experience in conducting similar surveys has shown that physicians prefer to complete the surveys online rather than by telephone or in-person. Online surveys allow flexibility of completing the survey at a time convenient to the physician, any time of the day or night and any day of the week. This flexibility is much harder to achieve in a telephone or in-person survey.

9.2 Setting

This survey is sponsored by UCB, and will be conducted by Luto Research Ltd. (Luto), a global health communications and testing company. This is a cross-sectional survey of physicians' understanding of the appropriate use and significant risks of XYREM.

Physicians will be recruited by selecting a random sample of prescribers in each of the selected countries from lists of those health care professionals with contact information available who were sent the XYREM educational materials (physicians known to UCB personnel to prescribe Xyrem, sleep medicine specialists, and physicians working in sleep medicine centers). The prescribers will be XYREM prescribers and sleep disorder specialists. Following recruitment, prescribers' understanding of posology and the important identified risks of XYREM will be evaluated using an online survey. Each invitation will include information on how to access the survey online, and will include a unique code for each prescriber to ensure that the invitation is used only once.

To ensure comprehension of the invitation and survey, all of the physician outreach will be conducted in the local country language. The survey and invitation as well as any reminder letters will all be translated by a certified translation company.

9.3 Variables

Prescribers' awareness of the appropriate dosing and risks of XYREM, as described in the XYREM SmPC and the educational materials, will be assessed using a standardized questionnaire.

The primary outcome of the survey is the proportion of respondents providing a correct response for each individual question consistent with the XYREM SmPC. The proportion responding correctly will be tabulated separately for each item in the survey instrument.

HCP demographic information will be collected at the end of the survey in order to further characterize the respondent population and, if possible, those who eventually choose not to fully participate. This will include gender, medical specialty, and type of medical practice, country and years in medical practice.

9.4 Data sources

9.4.1 Prescribers

This survey aims to recruit a random sample of 200 XYREM prescribers from Belgium, Germany, Italy, Spain, Sweden, and the UK. The sampling frame will be from the lists of HCPs in each of the countries to whom the XYREM educational materials were sent, which includes HCPs with possibility to prescribe XYREM, current prescribing HCPs as well as sleep disorder specialists with available contact information. After removing duplicate names from the lists, the names will be assigned a random number and the list re-ordered based on random number assignment. Then a sample of names on the randomized list in each country will be selected for recruitment. If necessary, an additional random sample will be selected and additional HCPs will be contacted through the period of recruitment and data collection, aiming to reach the target sample of 200 XYREM prescribers across all six countries combined.

9.4.1.1 Inclusion criteria for prescriber survey

Physicians will be required to meet the following inclusion criterion:

- Must have been included on the XYREM RMP educational materials mailing list

9.4.1.2 Exclusion criteria for prescriber survey

Physicians meeting the following criterion will not be eligible to take the survey:

- Currently an employee, or their immediate family member is an employee, of UCB, UnitedBiosourceCorporation (UBC), Luto, the EMA, or a National Competent Authority

9.4.1.3 Methods of Recruitment

The physicians will be recruited through a combination of phone calls and emailed invitation, translated into the local country language. The invitation will direct the physician to the online

agreement form, followed by the online survey to be completed. If there is no response after the first invitation, then a reminder invitation will be sent via email within 3 weeks after the first invitation or a follow-up call by Luto personnel.

Physicians will be paid the equivalent of the documentation time for completing the survey, which will be calculated for fair market value for a survey estimated to take 30 minutes to complete.

9.4.2 Questionnaire Structure

Each survey will be composed of multiple choice and close-ended questions. There will be no open-ended questions included. For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for key risk messages is generally "true" or "yes" indicating knowledge of, or behaviour in accordance with, the objectives of the program. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses. Multiple choice questions will include distractor or intentionally incorrect response options.

9.5 Study Size

There is no target comprehension rate specified *a priori*. Nevertheless, a rate of correct responses of less than 50% will be considered as unsatisfactory comprehension, one between 50% and less than 70% will considered satisfactory, and on of 70% or more will be considered excellent. Table 1 summarizes the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 200 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI. Subgroups of the total sample will have smaller numbers of prescribers, resulting in larger margins of error and therefore provide estimates with lower precision.

Table 1. Precision of Estimated Rates with a Sample Size of 200 (2-sided 95% Confidence Interval)

Estimated Rate of Understanding	95% Confidence Interval
50%	42.9%, 57.1%
55%	47.8%, 62.0%
60%	52.9%, 66.8%
65%	58.0%, 71.6%
70%	63.1%, 76.3%
75%	68.4%, 80.8%

80%	73.8%, 85.3%
85%	79.3%, 89.6%
90%	85.0%, 93.8%
95%	91.0%, 97.6%

If this sample size cannot be reached, descriptive statistics of lower sample sizes will be presented, regardless of the number of respondents. Tables 2 and 3 summarize the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 100 and 50 completed surveys, respectively.

Table 2. Precision of Estimated Rates with a Sample Size of 100 (2-sided 95% Confidence Interval)

Estimated Rate of Understanding	95% Confidence Interval
50%	40.2%, 59.8%
55%	45.2%, 64.8%
60%	50.4%, 69.6%
65%	55.7%, 74.3%
70%	61.0%, 79.0%
75%	66.5%, 83.5%
80%	72.1%, 87.8%
85%	78.0%, 92.0%
90%	84.1%, 95.9%
95%	90.7%, 99.3%

Table 3. Precision of Estimated Rates with a Sample Size of 50 (2-sided 95% Confidence Interval)

Estimated Rate of Understanding	95% Confidence Interval
50%	36.1%, 63.9%
55%	42.2%, 69.8%
60%	46.4%, 73.6%
65%	50.7%, 77.3%
70%	57.3%, 82.7%
75%	64.2%, 87.8%
80%	68.9%, 91.1%

85%	76.4%, 95.6%
90%	81.7%, 98.3%
95%	90.6%, 101.4%

It is assumed that the response rate per country is proportional to population size, which is assumed to be Germany 30%, United Kingdom 23%, Italy 22%, Spain 17%, Belgium 4%, and Sweden 4% of total responded surveys.

9.6 Data management

All data collected during the survey will be held confidential. The electronic data capture (EDC) system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses. .

9.7 Data Analysis

9.7.1 Analysis Population

9.7.1.1 Survey population

The population for analysis will comprise all physicians recruited into the survey, meeting eligibility criteria as assessed in the survey screener, and completing the survey.

The outcomes will be summarized for all specified countries combined and for each country separately.

9.7.2 Analyses

9.7.2.1 Survey analysis

The primary outcome of the survey is the proportion of prescribers providing a correct response for each individual question in the key risk messages consistent with the XYREM EU SmPC. This is computed as the proportion of prescribers who correctly respond to the individual survey questions concerning the appropriate dosing and important identified risks of XYREM as described in the XYREM SmPC. The proportion responding correctly will be tabulated separately for each item in the survey instrument.

Point estimates for the proportion with correct responses, and associated 95% confidence intervals, will be calculated for each question. In the case of multiple choice questions, the number and proportion of prescribers reporting each response will also be provided.

Information obtained from the survey will be reported as descriptive statistics for the survey administration, survey population, and the survey questions. The following will be reported as part of this analysis:

- The number of invitations issued

- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who completed the survey
- Description of survey participants including:
  - Country
  - Medical specialty
  - Type of medical practice (public/private activity)
  - Years in medical practice
  - Gender
- Frequency distribution of responses to each question (the number of respondents who give each answer to each question)
- Primary outcome: For each key risk message question, the percent of respondents selecting desired response for the question and 95% confidence interval

Responses will be stratified by country and prescriber medical specialty where applicable. Additional analyses may be performed as needed.

9.7.3 Measures to minimize bias

The following are measures to minimize bias in the sample:

- A random sample of physicians will be selected from each country using lists of HCPs who were sent the XYREM RMP educational materials. Based on participation out of the initial selection the sample can be enlarged up to the complete list per country in order to reach significant participation.
- The sample of participating HCPs will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of HCPs for participation.
- Respondents who work for, or have immediate family members who work for, UCB (survey sponsor) or UBC (adviser on survey design) and Luto (survey administrator), EMA or a National Competent Authority are excluded.
- Respondents will be provided with a unique code in the invitation letter and will be asked to provide the unique code to gain access to the online survey. The code will be deactivated after use to minimize the possibility for fraud.

The following are measures to minimize bias in the survey:

- All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated in the survey documentation and the computer system will automatically direct the respondent to the next appropriate question based on their previous response.
- Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey.
- Response options presented in a list will be randomized to minimize positional bias (despite responses in which an option like 'none of the above' or 'all of the above' or 'I do not know' is contained).
- All relevant programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to launch.

9.7.4 Survey Assessments and Procedures

9.7.4.1 Screening and Assessment

The survey introductory information is outlined in Appendix 4, and the survey instrument is in Appendix 5. The questionnaire will begin with a screening module with questions to confirm eligibility. Depending on the answers to the screening questions, survey participation will either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message in their local language that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The screening questions included in the survey are:

- Agreement to take the survey
- No employment, or immediate family member employed at UCB, UBC, Luto, EMA, or a National Competent Authority

9.8 Quality control

Luto will ensure the research in this survey covers steps to ensure data quality / integrity and data protection.

Quality control checks begin ahead of fully starting the survey to confirm if answers are being recorded for all questions as expected and the online survey is working correctly. On study completion, quality checks on the raw data will be completed and any unsuitable respondents will be removed from the data.

Data tables will be checked twice. All data (questionnaires, raw data, tabulations) will be stored on a secure server by Luto and UCB.

9.9 Limitations of research methods

Limitations inherent in the survey design include that although the sample of physicians who are invited to participate will be a random sample of all XYREM prescribers (as indicated by UCB data (lists) regarding HCPs who were provided the RMP educational materials in each country), the sample of participating physicians will be self-selected since respondents will voluntarily respond to the invitation to participate. The results will likely have a positive bias, i.e. the participants will appear more educated than the population of all potential prescribers of XYREM. Also, some questions of the questionnaire are related. If any prescriber would report more than 15 prescriptions he would not easily answer that he does not know the recommended starting dose etc. Conversely, if one had never prescribed XYREM it seems more likely that he would rather not participate in the survey instead of admitting ignorance of dosing recommendations.

However, the survey recruitment strategies are intended to recruit a heterogeneous sample of prescribers for participation.

10 PROTECTION OF HUMAN SUBJECTS

10.1 Ethical approval

Survey participation is voluntary. The survey will begin with a question indicating the physician's agreement to participate in the survey. If the individual does not agree, the survey will be ended.

Ethics approval will be sought as required by individual countries.

10.2 Feedback to survey participants

Respondents who complete the survey will receive a Thank You Note which includes the payment. In addition, each respondent will receive a table summarizing all the correct answers to each risk message question.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Assessment of Safety

This survey will not investigate adverse events (AE) associated with the use of XYREM. Responses to survey questions do not constitute adverse events, and there are no open-ended questions in the survey where a respondent could make a notation about an AE. While it is not the intention of the survey to solicit adverse events, any reported adverse events will be entered into the UCB safety database and processed according to the appropriate local and national regulations.

While it is not the intention of the surveys to solicit AEs, if an adverse event, or any other safety relevant information related to UCB's own products is mentioned by a prescriber during completion of the survey, Luto will report this to UCB.

Should the prescriber want to report spontaneously any AE in association with XYREM treatment, he/she will be directed by the Luto in-country associate to contact UCB. At the beginning of the online recruitment agreement, there will be a survey support link. In this scenario, the respondent may click on that link to email Luto staff about reporting an AE. The Luto point of contact will direct the respondent to contact UCB's Patient Safety department via email at the dedicated e-mail address reported in section 3 (Responsible Parties) of this protocol to report any previously unreported adverse events encountered with XYREM.

Luto shall notify UCB of any adverse event or other safety relevant information as soon as possible and at the latest within one (1) calendar day from the Receipt Date (as defined below). In the event that a calendar day falls on a weekend or a holiday, the information shall be sent on the next business day.

Reporting of Adverse Events (AEs), and other safety relevant information

The safety relevant information to be reported by Luto to UCB, if mentioned by a survey respondent, includes (see also the detailed definitions below):

- reports of AEs
- reports of pregnancy/lactation exposure
- reports of medication errors, overdose, abuse, misuse or occupational exposure
- reports of lack of therapeutic efficacy
- reports of drug interactions
- reports of suspected transmission of an infectious agent via a UCB product
- reports of suspected AEs associated with a suspected or confirmed falsified medicinal product or quality defect (combined complaint) of a UCB product
- reports of off-label use of UCB products
- reports of unexpected therapeutic benefit
- product quality complaints.

"Receipt Date" (Date of Awareness)

Receipt date means the date on which Luto receives notification of an AE or other safety relevant information. For reports received electronically, the Receipt Date shall mean the date the AE or other safety relevant information arrives on a server, the date on a facsimile transmission, or the

date a voicemail is recorded; and not the date the report is actually retrieved from a server, fax machine, or from voicemail. For avoidance of doubt, the Receipt Date shall be counted as day 0 for reporting purposes. The time clock starts again at day 0 when follow-up information is received by Luto. The Receipt Date of any safety related information shall be clearly mentioned on documents sent to UCB.

All documentation related to the AE or other safety relevant information to be reported by Luto shall be made in English using the applicable UCB reporting form (see APPENDIX 1 List of stand-alone documents) and sent by electronic mail to UCB (see SECTION 3 Responsible parties).

Luto shall indicate that the information provided is in the frame of survey NA0001, to enable categorization of the information in UCB database.

Luto is required to report any pregnancy of a patient taking XYREM or any patient taking XYREM and giving breastfeading of which they become aware, using the "Pregnancy Report and Outcome Form" (see APPENDIX 1 List of stand-alone documents). The procedure for reporting a pregnancy or breastfeeding is identical to the procedure for reporting safety relevant information.

When feasible, upon receiving AE or other safety relevant information, or upon receipt of follow-up information on a previously received AE or other safety relevant information from Luto, UCB shall send an acknowledgment of receipt by electronic mail. If Luto does not receive such acknowledgment within two (2) working days from the date on which the initial or follow-up report was sent, Luto should resend the information and mark it as "re-sent." When the sending of acknowledgments by UCB is not feasible, compliance with the transmitting and receipt of AE or other safety relevant information must be managed via the agreed reconciliation process (see Section Reconciliation).

Follow-up

UCB shall follow up on the AE or other safety relevant information received from Luto. Luto shall provide reasonable assistance to UCB to obtain additional information on AE or other safety relevant information.

Attempts should be made by UCB to obtain missing or incomplete information.

The causal relationship between the UCB Compound and an AE must be asked to the reporter for each AE.

The progression of a pregnancy and the eventual birth (if applicable) must be followed-up. Every reasonable attempt should be made to follow the development and health of the child for at least 30 days after birth for any significant medical issues or development delay.

If the patient is lost to follow up and/or refuses to give information, written documentation of attempts to contact the patient needs to be provided by the treating physician and filed at the site.

Reconciliation

During the conduct of NA0001, Luto shall keep accurate and detailed records of each AE and other safety information it becomes aware of. Each case report must be assigned a unique identifier to support the reconciliation of AEs and other safety relevant information,

Luto shall send to UCB (see SECTION 3 Responsible parties) an inventory of all AE and other safety relevant information reported, at the end of the program. The following information should be provided to enable reconciliation: Luto case number, the Product, the country where the report originated, date report received by Luto, and the date report was submitted to UCB.

In the event a discrepancy is found, Luto shall immediately provide a copy of any missing AE or other safety relevant information to UCB. In addition, Luto shall provide detailed explanations for the discrepancy, indicate the corrective action that was taken or is planned, and justify that such corrective action is appropriate to avoid a similar discrepancy in the future.

Drug Safety Training

UCB will provide initial Pharmacovigilance and Product Quality Complaint recording and reporting training to Luto and will train identified individuals who will be involved in the UCB-specific project within Luto organization.

It is the responsibility of Luto to ensure that all relevant personnel working on a UCB project are trained on Pharmacovigilance reporting requirements prior to conducting the program for UCB.

In addition to providing Pharmacovigilance training, Luto will ensure continuous training of all employees working on the UCB-specific project and are trained on the management of the documentation according to the sop-016162.

Luto shall ensure that training of its personnel is adequately recorded and shall provide the corresponding documentation to UCB.

Safety contact details

Safety contact information for Luto and UCB is provided in SECTION 3 Responsible parties.

Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal

laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Adverse Drug Reaction (ADR)

An ADR is a response to a medicinal product which is noxious and unintended. 'Response' in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

This includes adverse reactions that arise from:

- The use of a medicinal product within the terms of the marketing authorization
- The use of a medicinal product outside the terms of the marketing authorization, including overdose, off-label use, misuse, abuse, and medication errors
- Occupational exposure (this refers to the exposure to a prescribed treatment as a result of one's professional or non-professional occupation)

Serious Adverse Event (SAE)/Serious Adverse Drug Reaction (SADR)

An adverse event or adverse drug reaction is Serious if 1 or more of the following criteria are met:

- Death
- Life threatening: an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Inpatient hospitalisation or prolongation of existing hospitalisation: If a hospitalisation is planned, prior to the patient receiving the first dose of medicinal product it is not classified as serious. However, if a hospitalisation is unplanned and is a result of an adverse experience, this is considered an SAE
- Persistent or significant disability/incapacity
- Congenital anomaly or birth defect
- An important medical event or an event requiring significant intervention: Medical and scientific judgment must be exercised in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the above definition. These are usually considered serious.

Other safety relevant information

Other safety relevant information includes the following:

- Off-label use

  This relates to situations where the UCB product is intentionally used for a medical purpose not in accordance with the authorised product information.

- Misuse

  This refers to situations where the UCB product is intentionally and inappropriately used not in accordance with the authorised product information.

- Abuse

  This corresponds to the persistent or sporadic, intentional excessive use of the UCB product, which is accompanied by harmful physical or psychological effects

- Medication error

  Medication error refers to any unintentional error in the prescribing, dispensing, or administration of the UCB product while in the control of the healthcare professional, patient, or consumer.

- Occupational exposure

  This refers to the exposure to the UCB product, as a result of one's professional or non-professional occupation.

- Lack of therapeutic efficacy
- Overdose

  Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information. Clinical judgment should always be applied.

- Suspected transmission of an infectious agent via a UCB product
- Suspected adverse reaction associated with a suspected or confirmed falsified medicinal product or quality defect (combined complaint) of the UCB product
- Unexpected therapeutic effect
- Product quality complaint

  Any verbal, written or electronic expression of dissatisfaction with the product's identity, quality, stability, reliability, effectiveness, performance or usage. The report could be made by a patient, pharmacist, health care professional, or health authority.

This information is to be reported to UCB regardless if associated or not with an AE.

12 PLANS FOR DISSEMINATING AND COMMUNICATING SURVEY RESULTS

Prescriber recruitment will begin at least one year following the launch of the RMP educational materials (version 1) in each country. The survey recruitment period per country and data collection is estimated to be four months. Data analysis and report writing will take approximately six weeks after the database is locked.

The Final Report will be prepared independently by Luto and submitted to UCB for review and approval. Once approved, the Final Report will be submitted to the European Health Authorities in accordance with regulations and good pharmacovigilance practice.

13 REFERENCES

None.

APPENDICES

APPENDIX 1 LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	SOP-af-007439	29 Aug 2016	Adverse Event Report Form for NA0001
2	SOP-af-004176	29 Aug 2016	Pregnancy Report and Outcome Form for NA0001
3	N/A	29 Aug 2016	ENCePP Checklist for Study Protocol NA0001
4	N/A	29 Aug 2016	NA0001 PASS Amendment 1 Appendix Online Recruitment Agreement
5	N/A	29 Aug 2016	NA0001 PASS Amendment 1 Appendix Prescriber online survey

APPENDIX 2 ENCEPP CHECKLIST FOR STUDY PROTOCOLS

See APPENDIX 1 List of stand-alone documents.

APPENDIX 3 ADDITIONAL INFORMATION

None.