EU-RISK MANAGEMENT PLAN FOR

XYREM®

SODIUM OXYBATE

500MG/ML ORAL SOLUTION

Version 10.1

Confidentiality Statement

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Date: 25 May 2021

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ADMINISTRATIVE INFORMATION ON THE RISK MANAGEMENT PLAN

Risk Management Plan (RMP) Version number: 10.1

Data Lock Point (DLP) for this RMP: 17 Dec 2020

Date of final sign off: 25 May 2021

Rationale for submitting an updated RMP: Based on the recommendations from the Pharmacovigilance Risk Assessment Committee (PRAC), dated 05 May 2021, this RMP is being submitted to reincorporate the French monitoring program (FMP) as an additional pharmacovigilance activity for Xyrem® in the document. Further, as per the feedback from the PRAC, the safety concerns that were removed from the RMP in line with Good Pharmacovigilance Practices module V rev2 (considering FMP termination), have been reincorporated in the respective sections of the RMP.

Summary of significant changes in the RMP compared to the last submitted version 10.0:

- Reincorporation of the details of the FMP in Part III, Part V, Part VI, and Part VII Annexes of the RMP
- Updating the milestone of the FMP to reflect its termination date and addition of details regarding submission of the final report
- Reincorporation of the details regarding the following safety concerns (that were removed in RMP v10.0) in Part II Modules SVII and SVIII, Part V, and Part VI of the RMP: important potential risks (aggravation of cardiac failure due to additional sodium load, fluid retention in patients with compromised renal function due to additional sodium load) and missing information (use in pregnancy, use in elderly patients, and use in patients with body mass index $\geq 40 kg/m^2$)

Summary of significant changes in the RMP compared to the previous approved version 9.5:

- Treatment with narcolepsy with cataplexy in children from the age of 7 years reflected as current indication and the recommended posology in pediatric patients reflected as current dosage in Part I
- Clinical trial exposure and postmarketing exposure updated in Part II Module SIII and SV, respectively
- Update to the characterization of the safety concerns to align with the DLP of 17 Dec 2020 and include data from the completed Jazz pediatric study 13-005 and other sources
- Update to the Controlled Distribution System process in Part V and Part VII Annex 6

Details of the currently approved RMP:

Version number: 9.5

Approved with procedure: EMEA/H/C/000593/II/0076

Date of approval (opinion date): 12 Nov 2020

Qualified Person for Pharmacovigilance (QPPV) name: Henri Jacoby

Please see the electronic signature of the European Economic Area QPPV or his deputy on the last page of this module.

Approval Signatures

Name: eu-rmp-rev2-administrative

Version: 13.0

Document Number: PVG-000014741

Title: EU-RMP Rev 2: Administrative

Approved Date: 25 May 2021

Document Approvals	
[redacted]	[redacted]

Table of Contents

Table of Contents

LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AOR	adjusted odds ratio
ARIC	Atherosclerosis Risk in Communities
aRMM	additional risk minimization measure
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CEIP	Committee of Evaluation and Information centers on Pharmacodependence
CI	confidence interval
CKD	chronic kidney disease
CMO	contract manufacturing organization
CNS	central nervous system
DDD	defined daily dose
EDS	excessive daytime sleepiness
EMA	European Medicines Agency
FDA	Food and Drug Administration
FMP	French monitoring program
GABA	gamma-aminobutyric acid
GHB	gamma-hydroxybutyrate
HCP	healthcare professional
HF	heart failure
HLA	human leukocyte antigen
MAH	marketing authorization holder
NIH	National Institute of Health
OR	odds ratio
PASS	postauthorization safety study
RMP	risk management plan
SMFQ	standard medical follow-up questionnaire
SmPC	summary of product characteristics
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Table 1: Product overview

Active substance(s)	Sodium oxybate
Pharmacotherapeutic group(s)	N07XX04
Marketing Authorization Holder or Applicant	UCB Pharma SA Allée de la Recherche 60 B-1070 Brussels Belgium
Medicinal products to which this Risk Management Plan refers	1 medicinal product
Invented name(s) in the European Economic Area (EEA)	Xyrem
Marketing authorization procedure	Centralized
Brief description of the product	Sodium oxybate is the sodium salt of γ-hydroxybutyrate, which is an analog of the neurotransmitter γ-aminobutyric acid. γ-Hydroxybutyrate is present in the human central nervous system (CNS) as well as in peripheral tissues. It has CNS depressant properties, but the exact physiological function and mode of action is not yet fully elucidated.
Hyperlink to the Product Information (PI)	Link to proposed PI.
Indication(s) in the EEA	**Current:** Treatment of narcolepsy with cataplexy in adult patients, adolescents, and children from the age of 7 years.
	Proposed: Not applicable

Table 1: Product overview

<table>
<tr><td>Dosage in the EEA</td><td>Current: For adults, the recommended starting dose is 4.5g/day sodium oxybate divided into 2 equal doses of 2.25g/dose. The dose should be titrated to effect based on efficacy and tolerability up to a maximum of 9g/day divided into 2 equal doses of 4.5g/dose by adjusting up or down in dose increments of 1.5g/day (ie, 0.75g/dose). A minimum of 1 to 2 weeks is recommended between dosage increments.
Adolescents and children from 7 years of age with a minimum body weight of 15kg: Sodium oxybate is administered orally twice nightly. The dosing recommendations are provided in the below table.
<table>
<tr><td>Patient weight</td><td>Initial total daily dose[a]</td><td>Titration regimen (to clinical effect)</td><td>Recommended maximum total daily dose</td></tr>
<tr><td>15kg-<20kg</td><td>≤1g/day</td><td>≤0.5g/day/week</td><td rowspan="3">0.2g/kg/day</td></tr>
<tr><td>20kg-<30kg</td><td>≤2g/day</td><td>≤1g/day/week</td></tr>
<tr><td>30kg-<45kg</td><td>≤3g/day</td><td>≤1g/day/week</td></tr>
<tr><td>≥45kg</td><td>≤4.5g/day</td><td>≤1.5g/day/week</td><td>9g/day</td></tr>
</table>
The dose should be gradually titrated to effect based on efficacy and tolerability. A minimum of 1 to 2 weeks is recommended between dosage increments. Sodium oxybate dose recommendations (initial dose, titration regimen, and maximum dose) for pediatric patients are based on body weight. Therefore, patients should have their body weight checked at regular intervals especially during titration to ensure that the appropriate dose of sodium oxybate is administered.
The recommended maximum total daily dose is 0.2g/kg/day in pediatric patients weighing less than 45kg. For pediatric patients weighing 45kg or more, the maximum total daily dose is 9g/day.</td></tr>
<tr><td></td><td>Proposed: Not applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strength(s)</td><td>Current: Oral solution, 500mg/mL supplied in 240mL bottles containing 180mL of oral solution.</td></tr>
<tr><td></td><td>Proposed: Not applicable</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

CNS=central nervous system; EEA=European Economic Area; PI=product information

[a] Taken in 2 divided doses at bedtime and 2.5 to 4 hours later. For children who sleep more than 8 hours per night, sodium oxybate may be given after bedtime, while the child is in bed, in 2 equally divided doses 2.5 to 4 hours apart.

PART II: SAFETY SPECIFICATION

PART II: MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

1 NARCOLEPSY WITH CATAPLEXY

Narcolepsy is a neurological condition characterized by excessive daytime sleepiness (EDS), cataplexy ('a sudden, temporary, often unpredictable loss of muscle tone, which leads frequently to complete collapse'), hypnagogic hallucinations, and sleep paralysis (Khan et al, 2009; Wolkove et al, 2007). There are 3 narcolepsy subtypes, including narcolepsy with cataplexy, narcolepsy without cataplexy, and narcolepsy due to medical conditions (Longstreth et al, 2007). According to the most recent publication of the third edition of the International Classification of Sleep Disorders, new categorization has been rendered. The narcolepsy is categorized into two subtypes, narcolepsy type 1 resulted from hypocretin deficiency (ie, narcolepsy with cataplexy) and narcolepsy type 2 (Sateia, 2014).

1.1 Incidence and prevalence

The incidence of narcolepsy is rarely reported. One study conducted in the US found the incidence of narcolepsy with or without cataplexy is 1.37 per 100,000 person-years while the incidence of narcolepsy with cataplexy is 0.74 per 100,000 person-years among all age population in Olmsted County, Minnesota between 1960 and 1989 (Silber et al, 2002). The global prevalence of narcolepsy is reported between 20 and 50 cases per 100,000 people with a mean of 30 per 100,000 (Partinen et al, 2014). Prevalence varies between nationalities and ethnicities. For instance, a study from Mexico found prevalence of narcolepsy among adults aged 18-64 in Mexico City, Mexico to be 0.9% (Jimenez-Genchi and Caraveo-Anduaga, 2017). Prevalence estimates of narcolepsy range from 25 to 50 per 100,000 people worldwide (Longstreth et al, 2007). The variation of prevalence may be explained by different study populations (ie, age, gender, race, geographic regions etc.), different measurements of narcolepsy, and different study designs. In the EU, the prevalence of narcolepsy ranges between 21 and 660 per 100,000 people. A 1994 Finland study reported prevalence estimates of 26 per 100,000 people using more intensive screening approaches. Likewise, a 1998 study conducted in France showed the prevalence estimate of 21 per 100,000 people using more intensive screening. The prevalence of narcolepsy in Italy and the UK is the same with the estimate of 40 per 100,000, which is similar to an estimate of 47 per 100,000 people in the European population from the 5 countries of UK, Germany, Italy, Portugal and Spain in a 2002 study (Ohayon et al, 2002). In another study of the population in Catalonia, Spain the overall prevalence for narcolepsy was 4.4 per 100,000 inhabitants (3.7 for narcolepsy Type I and 0.7 for narcolepsy Type II) (Tio et al, 2017). In the 2002 study conducted in Minnesota using medical records, the prevalence of narcolepsy was estimated 56 per 100,000 people. In the same 2002 US study mentioned above, the prevalence of narcolepsy with cataplexy ranges from 25 to 50 per100,000 people with the point prevalence estimate of 36 per 100,000 people (Silber et al, 2002).

1.2 Demographics of the target population in the authorized and proposed indication

Narcolepsy is not age related (Ohayon et al, 2002). It may occur at any age but has 2 typical peaks. Most cases of narcolepsy occur between 10 and 25 years of age, and the other cases usually occur between 35 and 45 years of age (Han, 2012; Peacock and Benca, 2010). The reports concerning gender disparity in narcolepsy vary. One study involving the general population of 5 European countries of UK, Germany, Italy, Portugal and Spain showed that narcolepsy occurred as frequently in men as in women (Ohayon et al, 2002). However, some recent studies reported that narcolepsy seemed to occur more in men than in women. The frequency of narcolepsy in men was 1.6 times higher than that in women (Han, 2012; Longstreth et al, 2007).

1.3 Risk factors for the disease

Studies suggest various risk factors for narcolepsy, including environmental, genetic, and biological factors, diseases and lifestyles (Peacock and Benca, 2010; Picchioni et al, 2007). Although the specific causes remain unknown, several facts support the genetic and environmental influence (Peacock and Benca, 2010). The disease does not occur at birth, but the disease commonly appears during the second decade of life. The disease onset occurs more often in Mar and less frequently in Sep. Studies revealed that first-degree relatives had an estimated 1% to 2% chance of developing narcolepsy, which was dramatically higher than the prevalence of narcolepsy in the general population. A study showed that narcolepsy was related to human leukocyte antigen (HLA) DR2 haplotype. Additionally, a strong association with HLA DQB1 0602/DRB1 1501 was observed, which is more prevalent in patients with narcolepsy and cataplexy. Hypocretin, a peptide derived from the dorsolateral hypothalamus which is often linked to sleep/wake cycles, is often absent in the cerebrospinal fluid of people with narcolepsy, especially in patients with cataplexy and HLA positivity (Peacock and Benca, 2010). Narcolepsy may be associated with multiple sclerosis, tumors, stroke, traumatic brain injury, encephalomyelitis, and congenital disorders such as Neimann-Pick type C disease, myotonic dystrophy, and Prader-Willi syndrome (Longstreth et al, 2007). Narcolepsy-like symptoms may result from the lesions of hypothalamus and nearby structures (Peacock and Benca, 2010). In addition, some unexplained fevers and influenza infections (influenza A [H1N1] and/or streptococcus pyogenes infections occurring in upper respiratory airway) have been associated with an increased risk of narcolepsy-cataplexy at 3.9-fold and 1.8-fold respectively (Han, 2012; Partinen et al, 2012). A review on the epidemiology of childhood narcolepsy suggests that a recent increase in the; number of childhood and adolescent cases of narcolepsy may be attributed to the H1N1 influenza virus (Dye et al, 2018). Lifestyles may have an impact on narcolepsy. A study showed that passive smoking (not active smoking) may be a risk factor for narcolepsy in subjects with HLA DQB1*0602 (odds ratio [OR]=5.1; 95% confidence interval [CI]=1.6 to 12.1) (Ton et al, 2009). Excessive alcohol consumption was also observed as a risk factor for narcolepsy (Longstreth, et al, 2007).

1.4 The main existing treatment options

Narcolepsy is a lifelong disease which is mainly managed using pharmaceutical treatment in addition to behavioral modification and education (Peacock and Benca, 2010; Khan et al, 2009; Nishino, 2007). There are no approved treatments for narcolepsy type 1 in children although

sodium oxybate has been used successfully off-label in the pediatric population (Moresco et al, 2018). There are several treatment options of amphetamine-like central nervous system stimulants, modafinil, sodium oxybate, tricyclic antidepressants and selegiline. Amphetamine-like central nervous system stimulants, such as amphetamines and methylphenidate in various formulations, have been most effective in the reduction of EDS but have little effect on catalepsy (Peacock, 2010; Billiard et al, 2006). Likewise, modafinil can be used as a wakefulness-promoting agent rather than a stimulant, which seems effective for the treatment of EDS but is not often effective for cataplexy. Sodium oxybate, a gamma-hydroxybutyric acid, has been approved for narcolepsy with cataplexy. It does not only effectively relieve daytime sleepiness but also controls cataplexy (Peacock and Benca, 2010; Nishino, 2007). In addition, tricyclic antidepressants are used for the suppression of rapid eye movement (REM), including protriptyline, desipramine, and imipramine, clomipramine (Peacock and Benca, 2010; Khan et al, 2009). Selective serotonin reuptake inhibitors antidepressants are prescribed to treat cataplexy, hypnagogic hallucinations, and sleep paralysis (Khan et al, 2009). Selegiline, a monoamine oxidase B inhibitor, is used for the reduction of EDS and is also effective to reduce cataplexy (Peacock and Benca, 2010). Most recently, a review of 4 clinical trials examining the use of the small molecule drug pitolisant, which acts as an inverse agonist/antagonist of the H3 receptor, has shown the drug to be effective in treating EDS and cataplexy in narcolepsy (Calik, 2017). Currently it is approved in the EU for treating Type 1 and Type 2 narcolepsy in adults.

1.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

Main symptoms of narcolepsy are 'sleep attacks', hypnogogic hallucinations, sleep paralysis, and cataplexy (Han, 2012; Wolkove et al, 2007). Not all symptoms occur in all patients. Cataplexy may last up to half an hour and it can occur when narcolepsy is absent. Patients with narcolepsy-cataplexy may have hallucinations, sleep paralysis and fatigue. More than 50% of these patients report disturbed nocturnal sleep and poor sleep quality (Han, 2012). Obstructive sleep apnoea-hypopnoea syndrome was reported in 26% of patients with narcolepsy and cataplexy at a mean age of 45 (Han, 2012). In a study of 80 patients with narcolepsy and cataplexy, severe fatigue was reported in 50 patients (62.5%) (Droogleever Fortuyn et al, 2012). Mortality evidence in patients with narcolepsy is less reported and not consistent. In a longitudinal Danish study of over 12 years, the mortality in patients with narcolepsy was not significantly higher than the control group without narcolepsy (hazard ratio=0.80, p=0.07) (Jennum et al, 2013). However, a report based upon a large US claims database over 3 years suggests that patients with narcolepsy have about 1.5 times increased risk for mortality than those who have no narcolepsy (Ohayon, 2014).

1.6 Important co-morbidities

The most common comorbidities that are linked to narcolepsy are diabetes, obesity, sleep disorders, cardiovascular diseases, mental conditions, and immunopathological diseases (Martínez-Orozco, 2014; Jennum et al, 2013; Ohayon, 2013; Pataka et al, 2012; Peacock and Benca, 2010; Sansa et al, 2010; Sonka et al, 2010). A Danish study showed that the following comorbidities were more prevalent after the diagnosis of narcolepsy compared to the population without narcolepsy: diabetes (OR=2.4, 95% CI: 1.2 to 4.7); obesity (OR=13.4, 95% CI: 3.1 to 57.6); and sleep apnea (OR=19.2, 95% CI: 7.7 to 48.3) (Jennum et al, 2013). A US study

showed that heart diseases (adjusted odd ratio [AOR]=2.07, 95% CI: 1.22 to 3.51) and specifically hypertension (AOR=1.32, 95% CI: 1.02 to 1.70) are more common in patients with narcolepsy compared to the general population (Ohayon, 2013). With regard to mental disorders, in the same US study, 10 frequently observed conditions were listed in descending order, major depressive disorder (17.1%), bipolar disorders (8.5%), posttraumatic stress disorder (11.3%), agoraphobia (8.5%), panic disorder (12.5%), social anxiety disorder (21.1%), obsessive compulsive disorder (3.7%), generalized anxiety disorder (5.5%), simple phobia (5.2%), and Attention deficit hyperactivity disorder in childhood (5.4%). A study abstract suggested that the immunopathological diseases including autoimmune diseases are highly prevalent in patients with narcolepsy, and cataplexy is much severe in patients with narcolepsy and immunopathological diseases (Martínez-Orozco, 2016).

A recent claims database study of adults 18 years or older found in that in the US the greatest excess prevalence in the narcolepsy cohort was for mental illness (31.1% excess prevalence; OR=3.8, 95% CI [3.6-4.0]) (Black et al, 2017). This was followed by digestive system diseases (21.4% excess prevalence, and nervous system/sense organs [excluding narcolepsy] disorders 20.7% excess prevalence). A study focused on childhood narcolepsy in the Danish National Patient Registry found that children with narcolepsy had elevated odds for morbidity for a number of other health conditions including endocrine and metabolic conditions (4.4 [95% CI, 1.9-10.4]; 3.8 [1.7-8.4]), nervous disorders (16.6 [8.0-34.4]; 198 [49.0-804]), psychiatric illnesses (4.5 [2.3-9.1]/5.8 [2.8-12.1]), pulmonary diseases, and other diseases (3.1 [2.0-4.9]; 3.1 [2.0-4.9]) (Jennum et al, 2017).

1.7 Concomitant medication(s)

Concomitant medications are used for the treatment of comorbidities in patients with narcolepsy. A US study showed that all types of antidepressants, except tetracyclic antidepressants, were significantly more frequently used in patients with narcolepsy compared to the general population (Ohayon, 2013). Among those patients who took antidepressants, 36% of patients with narcolepsy took antidepressants for the treatment of depression or anxiety disorder (OR=2.35, 95% CI: 2.57 to 4.38). In addition, hypnotics, antipsychotics, and 3 types of antihypertensive drugs (ie, angiotensin-converting genzyme inhibitors, β-blockers, and diuretics) were taken more frequently in narcoleptic population compared to the general population.

PART II: MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

1 SAFETY FINDINGS FROM NONCLINICAL STUDIES

Important safety findings from nonclinical studies and their relevance to human usage are summarized in Table 1–1.

Table 1–1: Summary of important nonclinical findings

Key safety findings (from nonclinical studies)	Relevance to human usage
Cardiovascular findings (including potential for QT interval prolongation) Electrocardiogram measurements taken during 3- and 12-month toxicology studies in dogs remained within normal limits. Published studies indicate consistent increase in blood pressure in rats and dogs. Other effects on cardiac output, heart rate, and blood pH tended to be dose and species dependent (Boyd et al, 1992; Baumann et al, 1982; Johansson et al, 1982; Artru et al, 1980; Persson et al, 1980a; Persson et al, 1980b).	Based on nonclinical data, there is no particular proarrhythmia risk associated with sodium oxybate. Since increased blood pressure was reported both in rats and dogs, a potential hypertensive effect in humans could be anticipated. Patients with pre-existing heart failure, hypertension, or compromised renal function should reduce their salt intake, as sodium oxybate represents an additional sodium intake of 0.18g for 1g of sodium oxybate dose.
Respiratory depression GHB consistently decreases respiratory function in rats by effects on minute volume and respiratory rate with neonate animals (4 days old) being more susceptible to these effects than older juvenile or adult rats (Morse et al, 2017; Hedner et al, 1985). Most studies show that GHB lacks significant effects on blood gases and acid/base balance. In rats, a small increase in pCO_2 and a small decrease in blood flow have been observed (Hedner et al, 1980). Other studies have generally showed no significant alterations in arterial p_aO_2, p_aCO_2, HCO_3, or mean arterial blood pressure (Baumann et al, 1982; Artru et al, 1980; MacMillan et al, 1978).	Evidence of respiratory depression has been consistently seen in rats and was confirmed by clinical data. Respiratory depression is included as an important identified risk in the Part II Module SVII of the current Risk Management Plan.

Table 1–1: Summary of important nonclinical findings

Key safety findings (from nonclinical studies)	Relevance to human usage
Growth hormone (GH) elevation In anesthetized rats, GHB (125mg/kg intraperitoneally [ip]) increased serum GH (Takahara et al, 1980) and a dose of 1000mg/kg ip has been reported to stimulate release of GH in conscious rats (Bluet-Pajot et al, 1980a; 1978). Lower doses of GHB (25 to 300mg/kg subcutaneously) failed to modify GH release in neonatal rats and higher doses (100 to 1500mg/kg ip) did not affect release in adult rats. A similar lack of effect of GHB (20 to 50mg/kg intravenous) on GH has been reported in dogs (Rigamonti, 2000).	In animals, the effect of GHB on GH is both species- and dose-dependent, so that its relevance for humans appeared unclear. A UCB-sponsored clinical study (C00301) with adult narcolepsy patients completed in 2008 showed the fluctuations of blood GH within normal range. In addition, review of adverse events collected in this study did not indicate any clinical manifestation of abnormal GH. The review of the publication by Donjacour et al (Effect of sodium oxybate on growth hormone secretion in narcolepsy patients and healthy controls. Am J Physiol Endocrinol Metab 300:E1069-E1075, 2011) did not identify any new safety signal. The increase in nocturnal GH secretion reported in this publication was consistent with previously described effects of sodium oxybate in rodents with regard to GH. Literature search performed to identify any new publication showed no new articles for sodium oxybate (broad terms) coupled with GH. The cumulative review of the cases related to GH secretion did not reveal any consistent pattern in reporting of GH abnormal levels. No cases have been reported where the abnormal secretion of GH was confirmed by the valid values for GH. Therefore, the safety signal of GH abnormal was refuted.

Table 1–1: Summary of important nonclinical findings

Key safety findings (from nonclinical studies)	Relevance to human usage
Nervous system findings In the rat, transient hypoactivity and prostration were seen at high doses (1000 and 1500mg/kg/day). In dog ataxia, hypoactivity and prostration were noted at a dose of 600mg/kg but subsided after the first weeks of treatment.	In dogs, there were no treatment-related behavioral adverse effects at 450mg/kg/day given for 52 weeks, corresponding to plasma concentrations in the dog (417µg/mL) approximately 3-fold higher than therapeutic concentrations in humans. Nevertheless, the neurobehavioral signs observed at high doses in animals are consistent with the central nervous system depressant properties of sodium oxybate and the related AEs reported in humans (somnolence, sedation). Central nervous system depression is an important identified risk described in the Part II Module SVII.
Abuse potential and dependence Studies were conducted to assess tolerance and the dependence/addiction potential of GHB in mice, rats, and nonhuman primates. GHB has minimal dependence liability in animals, as determined from its lack of ability to substitute for agents including phencyclidine and methylhexital. Development of tolerance has been demonstrated in mice after dosing at 300mg/kg for 14 days, and there may be a degree of tolerance between GHB and alcohol in rats.	Dependence, abuse, and withdrawal syndromes have been reported in association with illicit GHB and so are potentially risks for patients with narcolepsy with cataplexy receiving sodium oxybate. The available evidence indicates that when used as recommended for the treatment of narcolepsy with cataplexy, the risk is low. The literature indicates that problems arise when GHB is used for "social" reasons and is taken frequently and at high dose. Abuse/misuse and dependence/withdrawal risks are described in Part II Module SVII.
Single-dose and repeat-dose toxicity There were no significant findings in clinical chemistry, histology, and pathology in any repeat-dose toxicology study in either the rat or dog. From these studies, the no observed adverse effect level (NOAEL) in rats was determined as 350mg/kg/day and the no observed effect level (NOEL) in dogs determined as 150mg/kg/day. The key findings determining the NO(A)EL values were clinical observations (transient hypoactivity and prostration) and blood chemistry measurements (lower total protein and albumin mean values) in the rat at 1000mg/kg and microscopic findings in the salivary and mucosal glands in the dog at 450mg/kg.	Despite the apparent lack of conventional safety margin (measured by C_{max} and AUC_{24h} values), the toxicological observations of emesis, reduced weight gain and food consumption, and changes in blood chemistry parameters are of no obvious pathological significance. The glandular atrophy in the salivary and the esophageal glands in dogs were observed at plasma exposures twice that expected from the therapeutic dose in humans (2×4.5g).

Table 1–1: Summary of important nonclinical findings

Key safety findings (from nonclinical studies)	Relevance to human usage
Reproductive toxicity There were no significant treatment related findings for adult toxicity, reproductive toxicity, embryo-fetal toxicity, or pre- and postnatal developmental toxicity in studies in rats and rabbits. In a fertility and early embryonic development study in rats, the NOEL for adult toxicity was determined as 350mg/kg/day and the NOEL for reproductive effects was 1000mg/kg/day. The NOAEL for both maternal and developmental toxicity in an embryo-fetal development study in rats was 1000mg/kg/day. In the corresponding study in rabbits, the maternal NOAEL was determined as 600mg/kg/day and the embryo-fetal NOAEL as 1200mg/kg/day. The NOEL in the prenatal and postnatal development study in rats was considered to be 350mg/kg/day. Formal toxicokinetic parameters were not calculated in the reproductive toxicity studies.	In animal studies, no adverse effects on reproductive function or teratogenic effects were observed at doses equivalent to the maximum recommended dose in humans. However, as sodium oxybate was not studied in pregnant women, it is not recommended during pregnancy.

Table 1–1: Summary of important nonclinical findings

Key safety findings (from nonclinical studies)	Relevance to human usage
Juvenile toxicity In a pharmacokinetic/tolerability study (Study 1301-016), juvenile rats aged of 4, 5, 21, 28 or 49 days were treated with a single oral (200, 1000 or 2000mg/kg) or intravenous (120mg/kg) dose of sodium oxybate. Mortalities occurred at 2000mg/kg at postnatal day (PND) 4 and 21, but not in older pups or at lower doses. Exposure decreased with the increasing age of the pups, in particular at 2000mg/kg. In a 10-week repeat dose toxicity study (Study 20078509) with an 8-week recovery period conducted in juvenile rats from PND 21 to PND 90 (equivalent to 2 to 16 years of age in humans), mortalities preceded by sodium oxybate-related clinical signs (bradypnea, deep breathing, decreased activity, uncoordinated gait, impaired righting reflex) were observed at 300 and 900mg/kg/day orally during the first week of treatment, when animals were 21 to 27 days old. Slight reductions in body weight and body weight gain and/or in food consumption were observed from 300mg/kg/day. Therefore, the NOAEL for acute toxicity was considered to be the low dose of 100mg/kg/day. No adverse effects were noted on male and female sexual maturity and reproductive parameters, on behavioral assessments, or on bone growth parameters. Therefore, the NOAEL for growth and development was considered to be ≥900mg/kg/day.	The acute toxicity observed in young pups below the age of 28 days appeared at exposure below those expected in pediatric patients. The reason for this relatively stronger toxicity during the first week of treatment is not fully clear. It could be related to higher exposure in young animals than in older juvenile rats, or to higher sensitivity of pups to sodium oxybate compared to older juvenile and adult rats, and/or to a tolerance development phenomenon. It has to be noted that this age of 21 to 27 days in young rats is equivalent to children aged of 3-4 years, which is below the minimal recommended age in pediatric patients (7 years). The clinical signs and body weight/food consumption effects observed in juvenile animals are in line with the expected pharmacology of sodium oxybate and were already reported in adult animals. Additional respiratory signs (slow and deep breathing) were present in juvenile animals during the first 2 weeks of treatment. The NOAEL for growth and development provides a safety margin between 2-to 4-fold the exposure at the maximum recommended dose in pediatric patients (200mg/kg/day in pediatric patients with body weight less than 45kg or 9g/day in pediatric patients with body weight ≥45kg). Chronic studies conducted formerly with sodium oxybate in adult rats and dogs also showed a lack of safety margin with regard to general toxicity.

Table 1–1: Summary of important nonclinical findings

Key safety findings (from nonclinical studies)	Relevance to human usage
Excretion into breast milk The concentration of sodium oxybate in milk was not measured in animal repeat dose general or reproductive toxicity studies. However, in a pilot pharmacokinetics/tolerability study conducted in juvenile rats (Study 1301-016), lactational exposure in lactating F0 dams was evaluated after a single oral administration of sodium oxybate at 2000mg/kg, on Lactation Day 12. The sodium oxybate concentrations observed in milk were less than those measured in plasma, with a milk plasma concentration ratio of 0.323 at 1h postdose (T_{max}).	Nonclinical data in rats show that milk excretion occurs after single oral administration of sodium oxybate. There is also evidence that sodium oxybate and its metabolites are excreted into human breast milk (Busardo et al, 2016). Therefore, sodium oxybate should not be used during breastfeeding.
Genotoxicity There was no evidence of mutagenic potential in the bacterial reverse mutation assays, a chromosome aberration test in Chinese hamster ovary or in an in vivo rat bone marrow micronucleus study.	There was no evidence of genotoxic potential for sodium oxybate when assessed in the standard battery of in vitro and in vivo assays.
Carcinogenicity In a program of carcinogenicity studies in rats, using GHB and gamma-butyrolactone (GLB) (the 5-member lactone ring form of GHB which is rapidly and extensively converted to GHB) and mice (using GLB), there was no evidence of a carcinogenic effect at doses up to 1000mg/kg/day.	In animal studies, there was no evidence of a carcinogenic effect at doses up to 1000mg/kg.
Mechanisms for drug interactions There is no obvious liability for cytochrome P450 (CYP450) mediated interactions either on commonly used drugs, or by commonly used drugs. Non-P450-mediated effects on GHB metabolism are unclear.	The nonclinical data do not suggest a risk for humans for what regards CYP450 isoenzymes role. In addition, some in vitro studies with pooled human liver microsomes indicated that sodium oxybate does not significantly inhibit the activities of the human isoenzymes.

CYP450=cytochrome P450; ECG=electrocardiogram; F0=parental generation; GH=growth hormone; GHB=gamma-hydroxybutyrate; GLB=gamma-butyrolactone; HCO_3=bicarbonate; ip=intraperitoneally; iv=intravenously; NOAEL=no observed adverse effect level; NOEL=no observed effect level; paO_2=partial pressure of oxygen in arterial blood; $paCO_2$=partial pressure of carbon dioxide in arterial blood; pCO_2=partial pressure of carbon dioxide; PND=postnatal day; RMP=Risk Management Plan; sc=subcutaneously

PART II: MODULE SIII: CLINICAL TRIAL EXPOSURE

1 UCB EXPOSURE

The cumulative number of study participants from completed UCB-sponsored clinical trials exposed to the investigational medicinal product since the Development International Birth date was 25 study participants included in the Phase 4 clinical trial C00301. In study C00301, 25 Caucasian study participants (13 males and 12 females), aged between 17.6 and 69.0 years (mean±standard deviation: 38.99±13.94 years) and diagnosed with narcolepsy with cataplexy, were included and received sodium oxybate.

Table 1–1: Duration of exposure

Cumulative for all indications (person time)	
Duration of exposure	**Patients**
<1 month	0
1 to <3 months	25
3 to <6 months	0
>6 month	0

Data source(s): clinical database

Table 1–2: Age group and gender

Cumulative for all indications		
Age group	**Patients**	
	Male	**Female**
<18 years	1	0
18 to 65 years	11	12
>65 years	1	0
Total	**13**	**12**

Data source(s): clinical database

Table 1–3: Exposure by dose

Cumulative for all indications	
Dose of exposure	**Patients**
0g	3
3g	1
3.5g	1

Table 1–3: Exposure by dose

Cumulative for all indications	
Dose of exposure	**Patients**
4g	1
4.5g	25
5g	1
6g	22
7g	1
7.5g	14
10g	1
Total	**70**

Data source(s): clinical database

Table 1–4: Exposure by ethnic origin

Cumulative for all indications	
Ethnic origin	**Patients**
Asian	0
Black	0
Caucasian	25
Other	0
Unknown	0
Total	**25**

Data source(s): Clinical Database

2 JAZZ EXPOSURE

Cumulatively until 12 Oct 2020, 2076 study participants and more than 511 health volunteers have been exposed to Xyrem in the Jazz clinical development programs (as noted in Table 2–1). It also included sodium oxybate exposure from investigator-sponsored studies and the fibromyalgia program. A total of 104 pediatric study participants were exposed to sodium oxybate in the Trial 13-005.

A detailed description of cumulative exposure for completed studies (healthy volunteers are not included in these data) in the clinical development program by age, gender, and race is provided in Table 2–2 and Table 2–3.

Table 2–1: Estimated cumulative study participant exposure in ongoing and completed trials through 12 Oct 2020

Treatment	Total[a]
Sodium oxybate	2076[b]
Placebo	568

[a] Excludes healthy volunteers
[b] Includes Xyrem exposure from the narcolepsy and fibromyalgia programs, 1 legacy investigator-sponsored study, and 104 pediatric study participants in completed Study 13-005

Table 2–2: Estimated cumulative study participant exposure to Xyrem from completed clinical trials by age and sex through 12 Oct 2020

Age range	Male	Female	Total
<18 years	68	47	115
18 to 65 years	386	1473	1859
>65 years	35	67	102
Total	**489**	**1587**	**2076**

Table 2–3: Estimated cumulative study participant exposure to Xyrem from completed clinical trials by race group through 12 Oct 2020

Racial group	Total
Asian	21
Black	140
Caucasian	1650
Other	24
Unknown	241
Total	**2076**

PART II: MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMS

Table 1–1 below provides an overview of the key exclusion criteria in adults development programs and pediatric study conducted for sodium oxybate, the reason for exclusion and rationale if not included as missing information.

Table 1–1: Exclusion criteria in pivotal clinical studies within the development programs

Key exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
For adults			
Major depression	Depression may occur in patients treated with sodium oxybate.	No	Depression/Suicidality is an important identified risk for sodium oxybate (refer to EU-RMP Part II Module SVII). In addition, major depression is a contraindication for sodium oxybate use.
Concomitant use of opioids or barbiturates	Sodium oxybate has the potential to induce respiratory depression, so the concomitant use of opioids or barbiturates should be avoided.	No	Respiratory depression is an important identified risk for sodium oxybate (refer to EU-RMP Part II Module SVII). In addition, being treated with opioids or barbiturates is a contraindication for sodium oxybate use.
• Sleep apnea • Sleep apnea syndrome, defined as an apnea index of >10 per hour • Apnea-hypopnea index >15 per hour	To exclude the additional risk of respiratory depression.	No	Sodium oxybate has the potential to induce respiratory depression. Respiratory depression is an important identified risk (refer to EU RMP Part II Module SVII).

Table 1–1: Exclusion criteria in pivotal clinical studies within the development programs

Key exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
• Current or recent history of a substance use disorder	To exclude an abuse predisposition.	No	The active substance of sodium oxybate, which is the sodium salt of gamma-hydroxybutyrate, is a central nervous system (CNS)-depressant with well-known abuse potential. Abuse/misuse is an important identified risk (refer to EU-RMP Part II Module SVII).
• Any other cause of daytime sleepiness • Presence of any unstable disease that placed the patient at risk during the trial • Serum creatinine >2.0mg/dL • Liver function tests >2x upper limit of normal (ULN) • Serum bilirubin >1.5xULN • Abnormal electrocardiogram demonstrating clinically significant dysrhythmias • History of myocardial infarction • Occupation that requires variable shift work or routine night shifts • History of seizure disorder, head trauma,	To provide a homogeneous study population with participants in good general health other than the disease being studied.	No	These are general serious conditions which are not missing information but could have a significant impact on patient health. These conditions are not related to narcolepsy but have an impact on the study population other than the specific pathology and act as confusing variables.

Table 1–1: Exclusion criteria in pivotal clinical studies within the development programs

Key exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
or past invasive intracranial surgery			
From pediatric Jazz study 13-005 protocol synopsis			
Evidence of sleep-disordered breathing including: – Presence of clinically significant obstructive or central sleep apnea as determined by the Investigator or documented previously; or – Obstructive apnea hypopnea index (AHI) >5 for participants 7 to 11 years of age or obstructive AHI >10 for participants 12 to 17 years of age; or – Oxygen saturation nadir ≤85% at night; or – Clinically significant hypoventilation	Sodium oxybate has the potential to induce respiratory depression.	No	Respiratory depression is a known (documented) warning for adults and is an Important identified risk. In addition, data from postmarketing supports the same important identified risk for the pediatric population (refer to EU-RMP Part II Module SVII).
Oxygen saturation level <95% for at least 5 minutes on room air as measured by pulse oximetry while fully awake during daytime monitoring, or participants with known or suspected respiratory difficulty, or any condition that could have compromised a participant's breathing.	Sodium oxybate has the potential to induce respiratory depression.	No	Respiratory depression is a known (documented) warning for adults and is an Important identified risk. In addition, data from postmarketing supports the same important identified risk for the pediatric population (refer to EU-RMP Part II Module SVII).
Current suicidal risk as determined from history or Columbia Suicide Severity Rating Scale (C-SSRS) or history of suicide attempt.	Sodium oxybate has the potential to induce suicidal events	No	Depression/Suicidality is an important identified risk for sodium oxybate (refer to EU RMP Part II Module SVII). In addition, major depression is a

Table 1–1: Exclusion criteria in pivotal clinical studies within the development programs

Key exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			contraindication for sodium oxybate use and additional warning will be proposed to the summary of product characteristics (SmPC) specific to the pediatric population.
Clinically significant depression independent of narcolepsy symptoms. (If the T-score was at or above 65 on the Children's Depression Inventory 2nd Edition Self-Report Short Version (CDI 2:SR[S]), an evaluation of depression by the Investigator (if qualified as a mental health professional) or by the Investigator in consultation with a mental health professional had to be performed to exclude clinically significant depression.	Depression may occur in patients treated with sodium oxybate.	No	Depression/Suicidality is an important identified risk for sodium oxybate (refer to EU-RMP Part II Module SVII).In addition, major depression is a contraindication for sodium oxybate use and additional warning will be proposed to the SmPC specific to the pediatric population.

AHI= apnea hypopnea index; CDI=Children's Depression Inventory; CNS=central nervous system; C-SSRS=Columbia Suicide Severity Rating Scale; RMP=Risk Management Plan; SmPC=summary of product characteristics; SSADH= Succinic semi-aldehyde dehydrogenase deficiency; ULN=upper limit of normal

2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

General limitations to detect adverse reactions in clinical trials are the restrictions to certain study populations due to narrow inclusion and exclusion criteria and due to the time limit of clinical trials.

3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Table 3–1 provides an example of overview of exposure in special population typically under-represented in clinical trial development programs.

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Elderly patients	Only few elderly patients included in the clinical development program.
Pregnant women	Not included in the clinical development program.
Breastfeeding woman	
Patients with relevant comorbidities:	
Patients with hepatic impairment	Not included in the clinical development program.
Patients with renal impairment	Not included in the clinical development program.
Patients with other relevant comorbidity: Cardiac dysfunction and Psychiatric disorders	Participants with clinically relevant cardiac dysfunction were excluded from the clinical development program. Participants with major depression were excluded from adult clinical studies.
Patients with a disease severity different from inclusion criteria in clinical trials	In general, these patients were excluded from the clinical studies.
Subpopulations carrying relevant genetic polymorphisms	There were no inclusion or exclusion criteria based on genetic polymorphisms in the narcolepsy with cataplexy clinical development program.
Patients of different racial and/or ethnic origin	No restrictions with regards to ethnic origin were specified in the narcolepsy with cataplexy clinical development program. However, in the Phase 2/3 studies, nearly all participants exposed to sodium oxybate were white, constituting an under-representation of the other ethnic groups.

3.1 Elderly patients

The age range in the narcolepsy with cataplexy clinical development program was 18 years and older. Only few elderly patients were included in the clinical development program.

A warning has been included in the Summary of Product Characteristics (SmPC), Section 4.4:

"*Elderly*

There is very limited experience with sodium oxybate clinical trials in the elderly. Therefore, elderly patients should be monitored for impaired motor and/or cognitive function when taking sodium oxybate."

3.2 Pregnant or breastfeeding women

Pregnant or nursing women were excluded from the narcolepsy with cataplexy clinical development program. Sodium oxybate is not recommended for use in this population.

A warning has been included in the SmPC, Section 4.6:

"*Pregnancy*

Animal studies have shown no evidence of teratogenicity but embryolethality was seen in both rat and rabbit studies (see Section 5.3).

Data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of spontaneous abortions. To date no other relevant epidemiological data are available. Limited data from pregnant patients during second and third trimester indicate no malformative or foeto/neonatal toxicity of sodium oxybate.

Sodium oxybate is not recommended during pregnancy."

Lactation

Regarding lactation, safety postmarketing data have provided evidence that sodium oxybate is excreted in breastmilk.

The SmPC wording in 4.6 displays as follows:

"*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.*"

3.3 Patients with hepatic impairment

Patients with hepatic impairment were not included in the clinical development program.

Sodium oxybate undergoes significant presystemic (hepatic first-pass) metabolism. After a single oral dose of 25mg/kg, area under curve values were double in cirrhotic patients, with apparent oral clearance reduced from 9.1 in healthy adults to 4.5 and 4.1mL/min/kg in Class A (without ascites) and Class C (with ascites) patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control study participants (mean t½ of 59 and 32 versus 22 minutes). Since patients with compromised liver function will have an increased elimination half-life and systemic exposure to sodium oxybate, the starting dose should therefore be halved in such patients, and response to dose increments monitored closely.

A recommendation is included in the SmPC, Section 4.2:

"*Hepatic impairment-The starting dose should therefore be halved in such patients and response to dose increments monitored closely.*"

3.4 Patients with renal impairment

Patients with renal impairment were not included in the clinical development program.

Patients taking sodium oxybate will have an additional daily intake of sodium that ranges from 0.82g (for a 4.5g/day sodium oxybate dose) to 1.6g (for a 9g/day sodium oxybate dose). No studies have been conducted in participants with renal failure. Study participants with unstable cardiovascular or renal disease and those who had Baseline serum creatinine ≥2.0mg/dL or who were on a sodium-restricted diet were excluded from the Phase 2 and 3 studies. Impaired kidney function and renal failure were not reported in these studies. In the studied population, there were no notable mean changes or shifts from Baseline values in serum creatinine, sodium, or urea nitrogen.

A warning is included in the SmPC, Section 4.2:

"*Patients with renal impairment*

Patients with impaired renal function should consider a dietary recommendation to reduce sodium intake (see Section 4.4)."

3.5 Patients with other relevant comorbidities

Cardiac dysfunction

Participants with clinically relevant cardiac dysfunction were excluded from the clinical development program. Although sodium oxybate when used as directed has not been shown to have a negative impact on cardiac function and electrocardiogram, there is the potential for cardiac complications due to sodium overload.

Psychiatric disorders

Participants with major depression were excluded from adult clinical studies. Participants with suicidal risk or significant depression independent of narcolepsy symptoms or any other documented psychiatric conditions that might affect their safety and/or interfere with the conduct of the study in the opinion of the Investigator were excluded from the Jazz pediatric study 13-005.

3.6 Patients with a disease severity different from the inclusion criteria in the clinical study population

In general, patients were excluded from the clinical studies if they had mild or very severe cataplexy.

3.7 Subpopulations carrying known and relevant polymorphisms

Genetic polymorphisms were not expected to influence the pharmacokinetics of sodium oxybate. Consequently, there were no inclusion or exclusion criteria based on genetic polymorphisms in the cataplexy clinical development program.

3.8 Patients of different racial and/or ethnic origin

No restrictions with regards to ethnic origin were specified in the cataplexy clinical development program. However, in the Phase 2/3 studies, nearly all study participants exposed to sodium oxybate were white, constituting an under-representation of the other ethnic groups. No dose adjustment is needed based on ethnicity.

PART II: MODULE SV: POSTAUTHORIZATION EXPERIENCE

1 POST-AUTHORIZATION EXPOSURE

1.1 Method used to calculate exposure

A conservative view was adopted by assuming that all patients receive complete dosage regimens at the time of treatment. Patient exposure is estimated using the available UCB sales data from 01 Jan 2007 to 31 Dec 2020 for the cumulative time interval. Note that sales data are only available to UCB on a month to month basis.

The total amount of product distributed during the cumulative time interval is derived from the UCB sales data reported, while the defined daily dose (DDD) is assumed to be 7500mg according to the World Health Organization (WHO).

The patient exposure to sodium oxybate for the cumulative time interval is estimated using the following formula:

$$\text{Patient-years} = \frac{\text{(total amount of product distributed)/DDD)}}{\text{365.25* days in year}}$$

*0.25 is added to account for leap years

1.2 Exposure

For the cumulative time interval from 01 Jan 2007 to 31 Dec 2020, 77,445,990,000mg of product was distributed contributing to approximately 28,271 patient-years.

Data on exposure by region are presented for the cumulative time interval in Table 1–1.

Table 1–1: Patient exposure by region for the cumulative time interval 01 Jan 2007 to 31 Dec 2020

Region	Country	Patient-years for the cumulative interval
European Economic Area (EEA)	Austria	
	Belgium	
	Cyprus	
	Czech Republic	
	Denmark	
	Finland	
	France departments	
	Germany	
	Iceland	
	Ireland	
	Italy	

Table 1–1: Patient exposure by region for the cumulative time interval 01 Jan 2007 to 31 Dec 2020

Region	Country	Patient-years for the cumulative interval
	Netherlands	[redacted]
	Norway	
	Portugal	
	Romania	
	Slovakia	
	Slovenia	
	Spain	
	Sweden	
	United Kingdom	
Asia Pacific	Australia	
Europe (non EEA)	San Marino	
	Switzerland	
	Turkey	
Middle East and Africa		2
Total		**28271**

EEA=European Economic Area

PART II: MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Available data are mainly obtained from the illicit use of gamma-hydroxybutyric acid (GHB).

Gamma-hydroxybutyric acid causes anterograde amnesia, especially when combined with ethanol, often leaving the person unable to recall any details of the event (Ferraro et al, 2001). In addition some effects attributed to illicit GHB, such as a rapid onset of sedation, increased libido and suggestibility, might specifically lend illicit GHB for use in drug-facilitated sexual assault, particularly when combined with alcohol (Varela et al, 2004).

However, when considering sodium oxybate's clinical studies, it has been shown that the administration of sodium oxybate did not produce the same degree of anterograde amnestic effects that were observed after comparable doses of other central nervous system (CNS) depressant drug such as benzodiazepine triazolam (Carter et al, 2009).

Events of diversion of sodium oxybate were assessed by Wang et al (2009). Of the approximately 26,000 patients who have received the commercial drug worldwide and the approximately 600,000 bottles of sodium oxybate distributed during the same time period, there were 5 confirmed incidents (0.0009%) of drug diversion, where the drug was taken from patients and was used or was intended to be used by others. This is confirmed by postmarketing data, which show that the incidence of misuse and the risk of abuse, dependence, diversion, and drug-facilitated sexual assault with sodium oxybate are very low.

These results together with postmarketing data suggest that the concern that sodium oxybate present a comparable risk profile as illicit GHB are not supported by the available data.

Controls against diversion, abuse, and misuse of sodium oxybate are provided by the well-controlled distribution program, restrictions deriving from the status of sodium oxybate as a controlled substance; initiation of sodium oxybate by and remain under the guidance of specialist physicians experienced in the diagnosis and treatment of sleep disorders; a detailed educational program for patients and health care professionals (HCPs) (including abuse-specific information); and directions to discontinue the use of the drug in case of suspected abuse of sodium oxybate.

Abuse/misuse and Diversion/criminal use are important identified risks for sodium oxybate. For further information regarding this risk please refer to Part II Module SVII of this Risk Management Plan (RMP).

PART II: MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Not applicable.

2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable

3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

3.1 Presentation of important identified risks and important potential risks

3.1.1 Important identified risk: Alcohol interaction

Potential mechanisms: A toxicokinetics/toxicodynamics study conducted by Morse and colleagues found that gamma-aminobutyric acid ($GABA_B$) receptors appear to be involved in both sedation and respiratory depression in Gamma Hydroxybutyrate (GHB)-ethanol intoxication, whereas current data support little involvement of $GABA_A$ receptors in GHB-ethanol toxicodynamics (Morse et al, 2013).

Evidence source(s) and strength of evidence: The combined use of alcohol, or any CNS depressant medicinal product, with sodium oxybate may result in potentiation of the CNS depressant effects of sodium oxybate as well as increased risk of respiratory depression (UCB SmPC, 2018).

There are few surveillance studies of alcohol use and alcohol-related problems among children and pre-adolescents, a situation that makes estimation of alcohol burden in this population problematic. The available data indicate that whereas the rates of alcohol use are relatively low in this population, substantial numbers of children do in fact have experience with alcohol. With respect to wholly alcohol-attributable health conditions, the available data suggest very low levels of alcohol abuse and acute intoxication among children (NIH/NIAAA, 2018).

Characterization of the risk: No cases related to alcohol interaction were observed in clinical trials in adults and pediatric patients with sodium oxybate.

In the postauthorization safety study (PASS) C00302, the final analysis (23 Feb 2017) showed that although interactions are known between sodium oxybate use and alcohol intake, the occurrence of concomitant intake of sodium oxybate and alcohol was high in the study. However, the number of adverse events (AEs) reported in the study due to alcohol use during sodium oxybate treatment was low (36.0% patients with concomitant intake of sodium oxybate and alcohol, and 0.4% patients with AEs related to alcohol consumption). The treatment-emergent adverse events (TEAEs) due to alcohol consumption were alcohol poisoning, insomnia, cough, suffocation feeling, and alcohol use.

As of the data-lock point (DLP) of the RMP, a cumulative total of 2015 patients were included in the French monitoring program (FMP). A review of the cases entered into the UCB Global

Safety database as of the DLP identified 2 cases of alcohol interaction from the FMP involving an adult and an elderly patient. The AEs observed included temporary loss of consciousness, confusion, and amnesia.

Concomitant use of alcohol and medications may lead to potentially serious medical conditions, eg causing loss of consciousness, falls, overdoses, impaired breathing and sometimes even death (Johnson and Seneviratne, 2014).

When ethanol is consumed by a patient taking GHB, the threshold for inducing coma can be severely lowered. Ethanol is a positive allosteric modulator of (gamma-aminobutyric acid) $GABA_A$ receptors, and when consumed with GHB the combination produces synergistically greater levels of central nervous system depression. Alone, GHB produces only mild respiratory depression as it affords for a compensatory increase in tidal volume; however, this normally observed compensatory mechanism is lost on ingestion of ethanol (VanWert et al, 2014).

There is no specific data retrieved regarding the epidemiology of alcohol interaction in the specific population of narcoleptic patients.

Risk factors and risk groups: Patients at risk are those who are more prone to CNS and respiratory depression, including those who use other CNS depressant drugs or those suffering from concurrent illnesses predisposing them to CNS and respiratory depressant effects of sodium oxybate.

Preventability: Patients should be warned against the use of alcohol in conjunction with sodium oxybate (UCB SmPC, 2018).

Reinforcement of the information to physicians and patients concerning concomitant administration of alcohol with sodium oxybate in educational materials.

In the PASS C00302 the Educational material regarding alcohol use was provided to the patients and prescribers in Jun 2014, while the study started in 2006 and stopped in 2016. The percentage of patients with alcohol intake was lower in the group who started the study after 30 Jun 2014 as compared to the group who terminated the study prior to 30 Jun 2014 (24.1% [20/83] vs 37.9% [207/546]).

Impact on the risk-benefit balance of the product: The risk of alcohol interaction that may be potentially associated with respiratory depression has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive.

Routine pharmacovigilance activities are in place to monitor this risk. Additionally, an educational guide for pediatric patients and their caregivers is also added to the existing educational materials.

Information relating to alcohol interaction is described in the Special warnings and precautions for use (Section 4.4).

Public health impact: As mentioned by Liechti and colleagues, several deaths following the use of GHB in combination with alcohol or other illicit drugs have been reported (Liechti et al, 2006). However, these data derive from an illicit use of GHB with doses often exceeding therapeutic ones.

The Food and Drug Administration (FDA) evaluated reports of patients who died while taking sodium oxybate, in order to determine whether the drug caused the deaths. The FDA informed in

a Drug Safety Communication that a number of deaths occurred in patients who were reported to be concomitantly taking one or more medications that could depress the CNS. Such drugs included neuroleptics benzodiazepines, opioids and others, in a few patients; many such medications were being used concurrently. Other patients were reported to have ingested alcohol while taking sodium oxybate.

Although the information contained in those reports are incomplete and did not adequately address confounding factors such as pre-existing sleep apnea and/or chronic obstructive pulmonary disease; the FDA recommended that the labeling should be strengthened to more strongly remind HCPs and patients of the risks when using sodium oxybate with CNS depressant drugs and alcohol. The use of sodium oxybate along with these products or other CNS depressants increases the risk of breathing problems that may lead to loss of consciousness, coma and death (FDA Drug Safety Communication, 17 Dec 2012).

3.1.2 Important identified risk: Respiratory depression

Potential mechanisms: Sodium oxybate has the potential to induce respiratory depression. Special caution should be observed in patients with an underlying respiratory disorder (UCB SmPC, 2018).

There are several proposed actions of GHB, including 1) direct action at $GABA_B$ receptors, 2) direct action at its own putative GHB receptor and 3) indirect action at GABA receptors via GABA production/release. The current data indicate that the primary effect of GHB on respiration is a decrease in respiratory rate, accompanied by a compensatory increase in tidal volume, allowing minute volume to remain constant until doses approach lethality (Morse et al, 2012).

Sodium oxybate has the potential to induce respiratory depression. Apnea and respiratory depression have been observed in a fasting healthy volunteer after a single intake of 4.5g (twice the recommended starting dose; UCB SmPC, 2018).

Evidence source(s) and strength of evidence: Sodium oxybate has the potential to induce respiratory depression. Apnea and respiratory depression have been observed in a fasting healthy volunteer after a single intake of 4.5g (twice the recommended starting dose). Special caution should be observed in patients with an underlying respiratory disorder.

Pediatric patients with an underlying respiratory disorder may be at more risk of presenting respiratory adverse effects with sodium oxybate. Therefore, this risk was added as an exclusion criteria in the pediatric Jazz Study 13-005. Still, 4 study participants experienced nonserious events of central sleep apnea (see Table 3–2). One event was noticed in the double-blind treatment period where the participant received sodium oxybate; the remaining 3 events were observed during the open-label safety period. Two of the 4 participants had a medical history of asthma.

Characterization of the risk: Table 3–1 presents the frequency of AEs potentially related to respiratory depression in clinical trials in adults.

Table 3–1: Frequency of adverse events potentially related to respiratory depression in clinical trials in adults

Number (%) of study participants with	Placebo (N=81)	All sodium oxybate (N=421)
Dyspnea	0	6 (1)
Nocturnal dyspnea	0	2 (0)
Respiratory disorder	0	1 (0)
Respiratory failure	0	1 (0)
Sleep apnea syndrome	0	3 (1)

N=number
* Clinical trials: Common Technical Document (CTD) Module 2.7.4 Summary of Clinical Safety of the application for the indication 'treatment of cataplexy in patients with narcolepsy'

Table 3–2 presents the frequency of AEs potential related to respiratory depression in the pediatric Jazz study 13-005.

Table 3–2: Treatment-emergent adverse events potentially related to respiratory depression in the pediatric Jazz study 13-005

Number (N; %) of study participants with condition	Age (years)[a]		Xyrem status at study entry		Total (N=104)
	7 to 11 (N=37)	12 to 17 (N=67)	Xyrem naïve (N=72)	On Xyrem (N=32)	
Sleep apnoea syndrome	1 (2.7)	2 (3.0)	2 (2.8)	1 (3.1)	3 (2.9)
Cheyne-Stokes respiration	0	1 (1.5)	0	1 (3.1)	1 (1.0)

N=number
[a] Age in years at the first dispensation of study drug in Part 1

Of note, in PASS C00302, there were no AEs of respiratory depression or hypoventilation reported in any patient.

As of the DLP of the RMP, a cumulative total of 2015 patients were included in the FMP. A review of the cases entered into the UCB Global Safety database as of the DLP identified 76 cases from the FMP reporting AEs of respiratory depression. Six of these 76 cases involved pediatric patients (age range 13 to 17 years). The most frequently reported AEs (n≥5) in these 76 cases included apnea, dyspnea, and sleep apnea syndrome.

Respiratory depression is a common physical side effect of many central nervous system depressants such as opioids, GHB, benzodiazepines and alcohol. Sedation increases along with drug-induced respiratory depression and decreases the ability to ventilate up to respiratory failure which can be fatal without immediate medical attention (National Institute of Health [NIH], 2011).

The risk of respiratory depression is severe by nature. There are reports of compromise in the rate and depth of respiration and of life-threatening respiratory depression, necessitating intubation and ventilation (UCB SmPC, 2018).

There is no specific data retrieved regarding the epidemiology of respiratory depression in the specific population of narcoleptic patients.

Review of postmarketing data has identified that the use of sodium oxybate may predispose the patients to choking sensation during sleep. The SmPC Section 4.4 has been updated to add a warning related to choking sensation. Further, Section 4.8 of the SmPC has been updated to add choking sensation as an adverse drug reaction (ADR).

Risk factors and risk groups: Patients with an underlying respiratory disorder may be at more risk of presenting respiratory adverse effects with sodium oxybate.

Given the possibility of increasing the risk of respiratory depression, the concomitant use of benzodiazepines and sodium oxybate should be avoided.

The combined use of alcohol, or any CNS depressant medicinal product, with sodium oxybate may result in potentiation of the CNS-depressant effects of sodium oxybate as well as increased risk of respiratory depression.

It has been shown that the use of a GHB dehydrogenase inhibitor, valproate, may also be a risk factor for respiratory depression. This is mainly due to an increase of sodium oxybate plasma concentration.

There has been also a clinical observation of coma and increased plasma GHB concentration after co-administration of sodium oxybate with topiramate. Therefore, the co-administration of topiramate may also be a potential risk factor for respiratory depression (UCB SmPC, 2018).

In a 2012 safety communication, the FDA reminded HCPs and patients that the combined use of sodium oxybate with alcohol or CNS depressant drugs can markedly impair consciousness and may lead to severe breathing problems (respiratory depression) (FDA Drug Safety Communication, Dec 2012).

Preventability: Patients should be questioned regarding signs of CNS or respiratory depression. Special caution should be observed in patients with an underlying respiratory disorder.

Reinforcement of the information to physicians and patients concerning the risk of respiratory depression with sodium oxybate in educational materials.

An adapted posology is suggested for pediatric population in the proposed SmPC based on patient body weight. The patients should have their body weight checked at regular intervals especially during titration to ensure that the appropriate dose of sodium oxybate is administered. The patient's tolerability, especially with regard to potential signs of CNS and respiratory depression, should be carefully monitored with each dose increase during titration. Careful monitoring should include that the parent/caregivers observe the child's breath after sodium oxybate intake to assess if there is any abnormality in breathing during the first 2 hours, for example sleep apnea, rude breathing and cyanosis of lip/face. If abnormality in breathing is observed medical support should be sought. If any abnormality is noted after the first dose, the second dose should not be administered. If no abnormality is noted the second dose can be administered. The second dose should not be given earlier than 2.5 hours or later than 4 hours

after the first dose. In individual cases, eg if it is uncertain that the parent/caregivers can manage careful monitoring as described, sodium oxybate is not recommended unless medical supervision of treatment can be organized.

If in doubt about administration of a dose, do not re-administer the dose to reduce the risk of overdose.

The dose should be gradually titrated to effect based on efficacy and tolerability. A minimum of 1 to 2 weeks is recommended between dosage increments. In adults, the dose should be titrated up to a maximum of 9g/day divided into 2 equal doses of 4.5g/dose by adjusting up or down in dose increments of 1.5g/day (ie, 0.75g/dose). The recommended maximum total daily dose is 0.2g/kg/day in pediatric patients weighing less than 45kg. For pediatric patients weighing 45kg or more, the maximum total daily dose is 9g/day.

To ensure correct dose titration in pediatric population, the Xyrem syringe will be updated to add new markings for 0.5g and 1.0g below the current markings.

Caution is required in patients who are treated concomitantly with valproate or other GHB dehydrogenase inhibitors as pharmacokinetic and pharmacodynamic interactions have been observed when sodium oxybate is co-administered with valproate. If concomitant use is warranted, dose adjustment is to be considered; a decrease in sodium oxybate dose by 20% is recommended. If concomitant use is warranted, patient response and tolerability should be monitored and dose should be adapted accordingly. To ensure correct dosing when combined with valproate, it is proposed that a second scale be added along one side of the Xyrem syringe with graduations of 0.2g, indicating doses which correspond to 80% of the current dosing scale.

There have been clinical observation(s) of coma and increased plasma GHB concentration after co-administration of sodium oxybate with topiramate. Therefore, patients should be warned against the use of topiramate in conjunction with sodium oxybate.

Given the possibility of increasing the risk of respiratory depression, the concomitant use of benzodiazepines and sodium oxybate should be avoided.

Patients should be warned against the use of alcohol in conjunction with sodium oxybate. Given the risk of alcohol intake among adolescents, it is noted that alcohol may further increase the CNS and respiratory depressant effects of sodium oxybate in children – adolescents taking sodium oxybate.

Because of the higher risk of sleep apnea, patients with a body mass index (BMI) >40kg/m^2 should be monitored closely when taking sodium oxybate (UCB SmPC, 2018).

Impact on the risk-benefit balance of the product: The risk of respiratory depression has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive.

Information relating to respiratory depression is described in the Special warnings and precautions for use (Section 4.4). Respiratory depression, dyspnea, sleep apnea, and choking sensation are listed as ADRs in the SmPC (Section 4.8).

To increase the prescriber's awareness and enhance safety of sodium oxybate use in pediatric population, in line with the added exclusion criteria of the pediatric study, a warning is suggested to be added to the product label in Section 4.4:

Sodium oxybate has the potential to induce respiratory depression. *Patients should be assessed before treatment for sleep apnea and caution should be exercised when considering treatment.* Apnea and respiratory depression have been observed in a fasting healthy volunteer after a single intake of 4.5g (twice the recommended starting dose). Patients should be questioned regarding signs of CNS or respiratory depression. Special caution should be observed in patients with an underlying respiratory disorder. *Patients should be monitored during treatment if signs of respiratory depression are evident.*

Routine pharmacovigilance activities are in place to monitor this risk. Additionally, an educational guide for pediatric patients and their caregivers will be added to the existing education materials.

Public health impact: The potential public health impact of this safety concern is expected to be significant for the concerned population of narcoleptic patients. Respiratory depression is not a rare event and may potentially induce life threatening adverse effects. It is worth mentioning that the SmPC provides a number of recommendations that should significantly contain this risk. In addition, due to the already implemented risk minimization measures, patients will have access to adequate educational advices that will contribute to prevent drug induced respiratory depression.

3.1.3 Important identified risk: CNS depression

Potential mechanisms: Sodium oxybate is the sodium salt of GHB which is an endogenous neurotransmitter synthesized from glutamate. Gamma-hydroxybutyric acid acts principally upon G-protein coupled GHB receptors, possibly leading to the inhibition of GABA release. GHB also acts to prevent dopamine neurotransmission within the substantia nigra and mesolimbic regions (Schep et al, 2012) and it modulates the serotonin and opioid systems. In contrast to endogenous concentrations, exogenous sources of GHB, are typically elevated to an excess of 1000nmol/g tissue and can act directly as partial $GABA_B$-receptor agonist and indirectly through its metabolism to form GABA (Snead, 1991) both resulting in membrane hyperpolarization and subsequent CNS depression.

In clinical environment, polysomnography studies have demonstrated that the nocturnal administration of sodium oxybate increases slow-wave sleep, producing a dose-related increase in Stage 3 and 4 sleep compared with baseline. The combined use of alcohol or any CNS depressant medicinal product with sodium oxybate may result in potentiating of the CNS-depressant effects of sodium oxybate (UCB SmPC, 2018).

Evidence source(s) and strength of evidence: Sodium oxybate is the sodium salt of GHB. It has CNS depressant properties, but the exact physiological function and mode of action are not yet fully elucidated.

No data retrieved regarding the epidemiology of CNS depression in a specific population.

Two study participants experienced events of somnolence during the dose titration period and 1 participant experienced more pronounced levels of depressed consciousness (syncope) during the open-label safety period in the pediatric Jazz study 13-005. The events were mild or moderate in severity. The outcome of the events was reported as resolved. None led to discontinuation from the study.

Characterization of the risk: Table 3–3 presents the frequency of AEs potentially related to CNS depression in clinical trials in adults.

Table 3–3: Frequency of adverse events potentially related to CNS depression in clinical trials in adults

Number (%) of study participants with	Placebo (N=81)	All Sodium oxybate (N=421)
Somnolence	5 (6)	31 (7)
Sedation	0 (0)	5 (1)
Depressed level of consciousness	0 (0)	1 (0)

CNS=central nervous system; N=number
*Clinical trials: Common Technical Document (CTD) Module 2.7.4 Summary of Clinical Safety of the application for the indication "treatment of cataplexy in patients with narcolepsy"

Table 3–4 presents the frequency of AEs potential related to CNS depression in the pediatric Jazz study 13-005.

Table 3–4: Treatment emergent adverse events potentially related to CNS depression in the pediatric Jazz study 13-005

Number (N; %) of study participants with condition	Age (years)[a]		Xyrem status at study entry		Total (N=104)
	7 to 11 (N=37)	12 to 17 (N=67)	Xyrem naïve (N=72)	On Xyrem (N=32)	
Somnolence	1 (2.7)	1 (1.5)	2 (2.8)	0	2 (1.9)
Syncope	0	1 (1.5)	0	1 (3.1)	1 (1.0)

CNS=central nervous system; N=number
[a] Age in years at the first dispensation of study drug in Part 1

In PASS C00302, 10 patients (1.4%) presented with somnolence and 11 patients (1.5%) presented with confusional state.

As of the DLP of the RMP, a cumulative total of 2015 patients were included in the FMP. A review of the cases entered into the UCB Global Safety database as of the DLP identified 175 cases from the FMP reporting AEs of CNS depression. Sixteen of these 175 cases involved pediatric patients (age range 10 to 17 years). The most frequently reported AEs (n≥5) in these 175 cases included somnolence, confusional state, loss of consciousness, sedation, and coma.

Central nervous system depression refers to physiological depression of the CNS that can result in decreased rate of breathing, decreased heart rate, and loss of consciousness possibly leading to coma or death (NIH, 2011).

CNS depression is considered to be a severe risk with symptoms ranging from sudden drowsiness through to unresponsive and profound coma.

There is no specific data retrieved regarding the epidemiology of CNS depression in the specific population of narcoleptic patient unexposed to a specific medication.

As a reference, incidence and severity of CNS depression has been evaluated for other drugs such as opioids drugs and was found to be influenced by many factors, including whether the patient is opioid tolerant or opioid naive (Pasero and McCaffery, 2002), concurrent administration of other sedating medications (such as benzodiazepines) (Szalados and Boysen, 1998), and the patient's general health and clinical condition (Smith, 2007).

Risk factors and risk groups: Patient at risk of overdose (refer to the identified risk of overdose).

Patient concomitantly treated with CNS depressant drugs.

The combined use of alcohol, or any CNS depressant medicinal product, with sodium oxybate may result in potentiation of the CNS-depressant effects of sodium oxybate as well as increased risk of respiratory depression.

It has been shown that the use of a GHB dehydrogenase inhibitor, valproate, may also be a risk factor for CNS depression. This is mainly due to an increase of sodium oxybate plasma concentration.

There have been also a clinical observation(s) of coma and increased plasma GHB concentration after co-administration of sodium oxybate with topiramate. Therefore, the co-administration of topiramate may also be a potential risk factor for CNS depression (UCB SmPC, 2018).

In a 2012 safety communication, the FDA reminded HCPs and patients that the combined use of sodium oxybate with alcohol or CNS depressant drugs can markedly impair consciousness and may lead to severe breathing problems (respiratory depression) (FDA Drug Safety Communication, Dec 2012).

These statements are also considered applicable for children and adolescents.

Preventability: Reinforcement of the information to physicians and patients concerning the risk of CNS depression with sodium oxybate in educational materials.

Patients should be questioned regarding signs of CNS or respiratory depression.

Health care professionals and patients education to avoid combined use of alcohol or any CNS depressant medicinal product with sodium oxybate and the risk of overdose may contribute to CNS somnolence prevention.

When patients first start taking sodium oxybate, until they know whether this medicinal product will still have some carryover effect on them the next day, they should use extreme care while driving a car, operating heavy machines, or performing any other task that could be dangerous or require full mental alertness.

An adapted posology is suggested in the proposed SmPC for pediatric population based on patient body weight. The patients should have their body weight checked at regular intervals especially during titration to ensure that the appropriate dose of sodium oxybate is administered. The patient's tolerability, especially with regard to potential signs of CNS and respiratory depression, should be carefully monitored with each dose increase during titration. Careful monitoring should include that the parent/caregivers observe the child's breath after sodium oxybate intake to assess if there is any abnormality in breathing during the first 2 hours, for example sleep apnea, rude breathing and cyanosis of lip/face. If abnormality in breathing is observed medical support should be sought. If any abnormality is noted after the first dose, the

second dose should not be administered. If no abnormality is noted the second dose can be administered. The second dose should not be given earlier than 2.5 hours or later than 4 hours after the first dose. In individual cases, eg if it is uncertain that the parent/caregivers can manage careful monitoring as described, sodium oxybate is not recommended unless medical supervision of treatment can be organized. If in doubt about administration of a dose, do not re-administer the dose to reduce the risk of overdose.

The dose should be gradually titrated to effect based on efficacy and tolerability. A minimum of 1 to 2 weeks is recommended between dosage increments. In adults, the dose should be titrated up to a maximum of 9g/day divided into 2 equal doses of 4.5g/dose by adjusting up or down in dose increments of 1.5g/day (ie, 0.75g/dose). The recommended maximum total daily dose is 0.2g/kg/day in pediatric patients weighing less than 45kg. For pediatric patients weighing 45kg or more, the maximum total daily dose is 9g/day.

To ensure correct dose titration in pediatric population, the Xyrem syringe will be updated to add new markings for 0.5g and 1.0g below the current markings.

Caution is required in patients who are treated concomitantly with valproate or other GHB dehydrogenase inhibitors as pharmacokinetic and pharmacodynamic interactions have been observed when sodium oxybate is co-administered with valproate. If concomitant use is warranted, dose adjustment is to be considered; a decrease in sodium oxybate dose by 20% is recommended. If concomitant use is warranted, patient response and tolerability should be monitored and dose should be adapted accordingly. To ensure correct dosing when combined with valproate, it is proposed that a second scale be added along one side of the Xyrem syringe with graduations of 0.2g, indicating doses which correspond to 80% of the current dosing scale.

There have been clinical observation(s) of coma and increased plasma GHB concentration after co-administration of sodium oxybate with topiramate. Therefore, patients should be warned against the use of topiramate in conjunction with sodium oxybate.

Patients should be warned against the use of alcohol in conjunction with sodium oxybate (UCB SmPC, 2018).

Impact on the risk-benefit balance of the product: The risk of CNS depression has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive.

Information relating to CNS depression is described in the Special warnings and precautions for use (Section 4.4) and Overdose (Section 4.9) sections. Somnolence, sedation and loss of consciousness are listed as ADRs in the SmPC (Section 4.8).

Routine pharmacovigilance activities are in place to monitor this risk. Additionally, an educational guide for pediatric patients and their caregivers will be added to the existing education materials.

Public health impact: The potential public health impact of this safety concern is expected to be significant. Central nervous system depression is not a rare event and may potentially induce life threatening adverse effects. However, the SmPC provides a number of recommendations that should significantly contain this risk. In addition, due to the already implemented risk minimization measures, patients have access to adequate educational advices that contribute to prevent drug induced CNS depression.

3.1.4 Important identified risk: Dependence/withdrawal

Potential mechanisms: Clinical observations suggest that GHB abuse leads to tolerance and increased frequency of dosing; it is postulated that GHB tolerance is associated with dysregulation of inhibitory neurotransmitter systems including GABA and GHB. Decreased GHB consumption and the withdrawal state may be associated with excitotoxicity involving neurotransmitter systems such as glutamate, norepinephrine, and dopamine (Miotto et al, 2001).

Due to the drug's short duration of action and rapid elimination, the signs and symptoms of GHB withdrawal syndrome appear rapidly, generally within 1-6 hours after the last dose (Miotto et al, 2001).

Evidence source(s) and strength of evidence: There have been case reports of dependence after illicit use of GHB at frequent repeated doses (18 to 250g/day) in excess of the therapeutic dose range. Whilst there is no clear evidence of emergence of dependence in patients taking sodium oxybate at therapeutic doses, this possibility cannot be excluded.

The discontinuation effects of sodium oxybate have not been systematically evaluated in controlled clinical trials in patients with narcolepsy. In some patients, cataplexy may return at a higher frequency on cessation of sodium oxybate therapy, however, this may be due to the normal variability of the disease. Although the clinical trial experience with sodium oxybate in narcolepsy/cataplexy patients at therapeutic doses does not show clear evidence of a withdrawal syndrome, in rare cases, events such as insomnia, headache, anxiety, dizziness, sleep disorder, somnolence, hallucination, and psychotic disorders were observed after GHB discontinuation (UCB SmPC, 2018).

Illicit use of GHB is often seen in teenagers and young adults (Oyemade, 2012). Acute withdrawal of GHB with its cardiovascular and delirant symptoms is of particular importance for child and adolescent psychiatrists. Acute GHB-withdrawal syndrome can present with symptoms close to psychotic episodes or acute alcohol withdrawal (Zepf et al, 2009).

In the pediatric Jazz study 13-005, AEs that could possibly represent symptoms of sodium oxybate withdrawal were reported in patients who were withdrawn from sodium oxybate treatment and randomized to placebo during the double-blind treatment period. The AEs included irritability (n=1, 3.1%), abnormal dreams (n=1, 3.1%), and sleep talking (n=1, 3.1%). While these events may represent possible symptoms of mild GHB withdrawal, they are also consistent with returning symptoms of narcolepsy. Further, the patients who were withdrawn from sodium oxybate treatment and randomized to placebo during the double-blind treatment period, experienced a gradual partial return in weekly cataplexy attacks over the 2-week placebo treatment period.

Characterization of the risk: In clinical trials in adults, no AEs were directly reported regarding dependence and withdrawal. No evidence of dependence in pediatric study participants taking sodium oxybate at therapeutic doses was found.

The placebo arm of Study OMC-SXB-21, in which patients who had been treated with chronic sodium oxybate were randomized to double-blind treatment with continued sodium oxybate or placebo, was used to assess sodium oxybate withdrawal symptoms.

The number of patients is small, but the data indicate that patients abruptly withdrawn from chronic therapeutic doses of sodium oxybate are more likely to experience headache (7%) or

anxiety (7%) than those patients continuing on sodium oxybate therapy. When taking into account the investigators' opinions of causality, anxiety was the most commonly seen side effect of sodium oxybate withdrawal.

In PASS C00302, the profile and incidence of AEs observed after sodium oxybate discontinuation (including potential withdrawal symptoms) was low (2.4%) and mostly related to the System Organ Class (SOC) Nervous system disorders and Psychiatric disorders. The ADRs reported in the study were consistent with the ADRs reported in SmPC.

As of the DLP of the RMP, a cumulative total of 2015 patients were included in the FMP. A review of the cases entered into the UCB Global Safety database as of the DLP identified no cases from the FMP that were suggestive of physical dependence on sodium oxybate.

Drug dependence is an adaptive state that develops from repeated drug administration, and which results in withdrawal upon cessation of the drug.

The withdrawal state may include physical-somatic symptoms (physical dependence), emotional-motivational symptoms (psychological dependence), or both. Addiction is a complex but treatable condition. For some people, addiction becomes chronic, with periodic relapses even after long periods of abstinence. If left untreated, dependence on drugs can be dangerous. An increase in drug use as the body adapts to the drugs is common. This can result in overdose or death (NIH, 2014).

This risk is more associated with the use of sodium oxybate outside of therapeutic range (see above). A review of the postmarketing data on rebound effect/withdrawal identified that the symptoms of dependence and withdrawal were reported often with the use of sodium oxybate at higher than recommended doses, though some case descriptions suggested possibility of dependence to sodium oxybate when used at recommended doses. Much of this evidence was drawn from case reports involving adult patients and minimal evidence was identified from the cases involving pediatric patients.

Withdrawal can occur rapidly following the last dose taken by the user; in one case series, it developed within 1 to 12 hours. The duration of these clinical effects may continue for 3 to 21 days. In severe cases, delirium, psychosis, rhabdomyolysis, and seizures, are observed which may become life-threatening (Schep et al, 2012).

The rate of persons aged 12 or older who had substance dependence or abuse in 2012 (8.5%) was lower than the rate in each year from 2002 through 2006 (9.4% in 2002, 9.1% in 2003, 9.4% in 2004, 9.1% in 2005, and 9.2% in 2006), was similar to the rate in each year from 2007 through 2010 (9.0% in 2007, 2008, and 2009 and 8.8% in 2010), and was higher than the rate in 2011 (8.0%) (Substance Abuse and Mental Health Services Administration, 2013).

Risk factors and risk groups: McDonough and his colleagues found that frequent dosing was a key feature of dependent use. An 8-hourly dosing was found to be the minimum frequency associated with withdrawal delirium. The minimum daily GHB dose associated with withdrawal was 18g (about 9 teaspoons-full; McDonough et al, 2004). This is in accordance with the SmPC (UCB SmPC, 2018).

Preventability: Identification of patients at risk of addiction such as patients with psychological problems. Physicians should evaluate patients for a history of drug abuse and follow such patients closely and in case of suspected abuse discontinue treatment with sodium oxybate.

Correct dose titration: The dose should be gradually titrated to effect based on efficacy and tolerability. A minimum of 1 to 2 weeks is recommended between dosage increments. In adults, the dose should be titrated up to a maximum of 9g/day divided into 2 equal doses of 4.5g/dose by adjusting up or down in dose increments of 1.5g/day (ie, 0.75g/dose). The recommended maximum total daily dose is 0.2g/kg/day in pediatric patients weighing less than 45kg. For pediatric patients weighing 45kg or more, the maximum total daily dose is 9g/day.

Avoiding abrupt discontinuation of treatment.

Patients and physicians education (educational materials).

Controlled distribution.

Impact on the risk-benefit balance of the product: The risk of dependence/withdrawal has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive.

Information relating to Dependence/withdrawal is described in the Special warnings and precautions for use (Section 4.4) and Overdose (Section 4.9) sections. Insomnia, headache, anxiety, dizziness, sleep disorder, somnolence, hallucination, and psychotic disorders are listed as observed ADRs after GHB discontinuation, in the SmPC (Section 4.8).

Routine pharmacovigilance activities are in place to monitor this risk. Additionally, an educational guide for pediatric patients and their caregivers will be added to the existing education materials.

Public health impact: Considering the low incidence of dependence and withdrawal with sodium oxybate at therapeutic doses, the potential public health impact is not considered to be high.

3.1.5 Important identified risk: Overdose

Potential mechanisms: An overdose is defined as being a dose superior to the maximum dose of 9g/day. Gamma- hydroxybutyrate is an endogenous neurotransmitter that is predominantly distributed within discrete regions of the mammalian brain, though it is also present in the blood, urine, and other peripheral tissues. Gamma-hydroxybutyrate is both a metabolite and a precursor of the inhibitory neurotransmitter GABA, and acts as a neuromodulator in the GABA system. While endogenous concentrations of GHB function as a neuromodulator in various neurobiochemical pathways, supratherapeutic doses of GHB can readily cross the blood – brain barrier leading to profound CNS and respiratory depression (Schep et al, 2012).

Evidence source(s) and strength of evidence: Information about signs and symptoms associated with sodium oxybate overdose is limited. Most data derives from the illicit use of GHB. Sodium oxybate is the sodium salt of GHB. Events associated with withdrawal syndrome have been observed outside the therapeutic range.

Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even with impaired consciousness), diaphoresis, headache, and impaired psychomotor skills may be observed. Blurred vision has been reported. An increasing depth of coma has been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported. There are reports of compromise in the rate and depth of respiration and of life-threatening respiratory depression,

necessitating intubation and ventilation. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact. Bradycardia has been responsive to atropine intravenous administration.

Characterization of the risk: One case with intentional overdose and apnea was reported in clinical trials in adults. No cases of overdose were described in the pediatric Jazz study 13-005.

In the PASS C00302, 4 cases of overdose (up to 12g) were reported (3 [0.4%] in the intention-to-treat population). The patients experienced psychosis, hallucinations, attempted suicide, central sleep apnea, dizziness and confusion. The total number of patients in this study was 730.

As of the DLP of the RMP, a cumulative total of 2015 patients were included in the FMP. A review of the cases entered into the UCB Global Safety database as of the DLP identified 38 cases of overdose from the FMP. Five of these 38 cases involved pediatric patients (age range 10 to 17 years). The most frequently reported AEs ($n \geq 5$) along with overdose in these 38 cases included amnesia, confusional state, diarrhea, dizziness, fatigue, hallucinations, headache, insomnia, nausea, nightmares, and somnolence.

The term drug overdose describes the ingestion or application of a drug or other substance in quantities greater than recommended or generally practiced. An overdose may result in a toxic state or death. Information about signs and symptoms associated with overdosage with sodium oxybate is limited. Most data derives from the illicit use of GHB. Events which might occur are described below.

The severity of overdose of sodium oxybate is related mainly to its CNS and respiratory depression. Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even with impaired consciousness), diaphoresis, headache, and impaired psychomotor skills may be observed. Blurred vision has been reported. An increasing depth of coma has been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported. There are reports of compromise in the rate and depth of respiration and of life-threatening respiratory depression, necessitating intubation and ventilation. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact. Bradycardia has been responsive to atropine intravenous administration (UCB SmPC, 2018).

It is difficult to identify the prevalence of overdose in the disease population or the general population. Instead death rate from overdose was reported. The actual overdose rate could be higher.

Deaths from drug overdose have been rising steadily over the past 2 decades and have become the leading cause of injury death in the US. In 2010, 30,006 (78%) of the 38,329 drug overdose deaths in the US were unintentional, 5298 (14%) of suicidal intent, and 2963 (8%) were of undetermined intent (Centers of Disease Control and Prevention, 2013).

Risk factors and risk groups: Dependence to sodium oxybate may be risk factors for the administration of an overdose of the product.

Depressed patients with tendency for suicidal may be at more risk for administering an intentional overdose.

Preventability: Patients and physicians education (educational materials).

Controlled distribution.

The dose of 9g/day should not be exceeded due to the possible occurrence of severe symptoms at doses of 18g/day or above (UCB SmPC, 2018).

An adapted posology is suggested for pediatric population in the proposed SmPC based on patient body weight. The patients should have their body weight checked at regular intervals especially during titration to ensure that the appropriate dose of sodium oxybate is administered. The patient's tolerability, especially with regard to potential signs of CNS and respiratory depression, should be carefully monitored with each dose increase during titration. Careful monitoring should include that the parent/caregivers observe the child's breath after sodium oxybate intake to assess if there is any abnormality in breathing during the first 2 hours, for example sleep apnea, rude breathing and cyanosis of lip/face. If abnormality in breathing is observed medical support should be sought. If any abnormality is noted after the first dose, the second dose should not be administered. If no abnormality is noted the second dose can be administered. The second dose should not be given earlier than 2.5 hours or later than 4 hours after the first dose. In individual cases, eg if it is uncertain that the parent/caregivers can manage careful monitoring as described, sodium oxybate is not recommended unless medical supervision of treatment can be organized.

If in doubt about administration of a dose, do not re-administer the dose to reduce the risk of overdose.

Correct dose titration: The dose should be gradually titrated to effect based on efficacy and tolerability. A minimum of 1 to 2 weeks is recommended between dosage increments. In adults, the dose should be titrated up to a maximum of 9g/day divided into 2 equal doses of 4.5g/dose by adjusting up or down in dose increments of 1.5g/day (ie, 0.75g/dose). The recommended maximum total daily dose is 0.2g/kg/day in pediatric patients weighing less than 45kg. For pediatric patients weighing 45kg or more, the maximum total daily dose is 9g/day.

To ensure correct dose titration in pediatric population, the Xyrem syringe will be updated to add new markings for 0.5g and 1.0g below the current markings.

Impact on the risk-benefit balance of the product: The risk of overdose has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive.

Information relating to overdose is described in Overdose (Section 4.9).

Routine pharmacovigilance activities are in place to monitor this risk. Additionally, an educational guide for pediatric patients and their caregivers will be added to the existing education materials.

Public health impact: The actual prevalence of death from illicit GHB overdose is difficult to determine because of the lack of objective assessments, such as sensitive, specific assays for measuring GHB in biological matrices; the high prevalence of concomitant drug use; and differences in reporting practices within the medical community. Moreover, the risk profile of sodium oxybate is different from that of GHB provided the different settings of use and the controlled distribution of sodium oxybate.

Therefore, considering the above, the potential public health impact of this safety concern is not expected to be significant.

3.1.6 Important identified risk: Misuse/abuse

Potential mechanisms: Sodium oxybate is the sodium salt of GHB which is an endogenous neurotransmitter synthesized from glutamate. GHB is considered to be a recreational drug. The recreational dose of GHB is believed to be approximately 20 to 30mg/Kg. However, the concentration that users take is quite difficult to determine because there is no means of control over the purity of the products that they use (Gonzalez et al, 2005).

When the concentration of GHB exceeds the physiological micro molar levels in the brain, there is general agreement that GHB activates $GABA_B$-receptors on neurons. As $GABA_B$-receptors are found throughout the cerebral cortex, cerebellum, and thalamus, activation of this system has widespread effects on the CNS. Therefore, given its various effects on neurons and neuro-modulator systems in the CNS, it is not surprising that GHB is linked to a range of clinical scenarios (Drasbek et al, 2006).

Evidence source(s) and strength of evidence: The active substance is sodium oxybate, which is the sodium salt of GHB, a CNS depressant active substance with well-known abuse potential.

A number of studies have looked at different associations between symptoms of narcolepsy and impulsiveness, which suggest an increased probability to engage in risk-taking behavior, such as substance abuse (AAC, 2018).

According to the Substance Abuse and Mental Health Services Administration, the rate of persons aged 12 or older who had substance dependence or abuse in 2012 was 8.5% which was similar to the rate in each year from 2007 through 2010 (between 8.8 to 9.0%), but higher than 8.0% in 2011 (Substance Abuse and Mental Health Services Administration, 2013).

Characterization of the risk: No AEs were reported regarding misuse/abuse in clinical trials in adults. No cases of abuse/misuse were described in the pediatric Jazz study 13-005.

As of the DLP of the RMP, a cumulative total of 2015 patients were included in the FMP. A review of the cases entered into the UCB Global Safety database as of the DLP identified 5 cases from the FMP that were suggestive of drug abuse with sodium oxybate; no evidence of physical dependence on sodium oxybate was identified from these 5 cases. None of these 5 cases involved pediatric patients. A total of 46 cases reported events suggestive of product misuse, of which 5 involved pediatric patients (age range 12 to 17 years). The majority of these 46 cases reported misuse in the context of wrong dose, incorrect dosing schedule, and/or missing the dose of sodium oxybate.

In PASS C00302, all protocol deviations were reviewed and no safety concerns were noted. The most frequent protocol deviation was potential abuse or misuse of sodium oxybate (41.9%). The most common reasons were "Xyrem taken less than 2 hours after eating" seen in 20.0% patients and "Xyrem taken not according to recommended time schedule" seen in (28.1%). It should be noted that the frequency of TEAEs associated with these checklist items was ≤1.0%. There was 1 case of sodium oxybate abuse in the study (accidental or deliberate use of sodium oxybate by others in the patient's household). The total number of patients included in this study was 730.

All drugs have the potential to be misused, whether legally prescribed by a doctor, purchased over-the-counter at the local drug store, or bought illegally on the street. Taken in combination

with other drugs or with alcohol, even drugs normally considered safe can cause death or serious long-term consequences.

The risk associated with sodium oxybate abuse is related to the use of supratherapeutic doses, which have shown that although patients report positive subjective effects comparable to those of alcohol or a benzodiazepine, they also report greater negative subjective effects such as nausea and gastrointestinal distress (Carter et al, 2009).

The risks associated with product misuse depend on the nature and extent of misuse (inappropriate or incorrect dose or frequency, incorrect duration, unapproved indication, etc.).

Risk factors and risk groups: There are certain individuals who are believed to be at increased risk of abusing GHB. Athletes, body builders, gymnasium members, models, disk jockeys, ravers, frequent travelers across different time zones, and employees who are subject to regular drug testing, among others (Gonzalez et al, 2005).

Other risk factors include those associated with drug abuse in general, eg, previous history of drug abuse, family history of drug addiction, male gender, psychiatric problems and socio-economic conditions.

Preventability: Physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (eg, increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy).

Educational program to improve patient and physician knowledge.

Controlled distribution to adults and adult caregivers only is recommended. Pediatric patients will not receive the medication directly.

Impact on the risk-benefit balance of the product: The risk of misuse/abuse has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive.

Information relating to misuse/abuse is described the Special warnings and precautions for use (Section 4.4).

Routine pharmacovigilance activities are in place to monitor this risk. Additionally, an educational guide for pediatric patients and their caregivers will be added to the existing education materials.

Public health impact: It is difficult to distinguish between illicit GHB and licit GHB or sodium oxybate from clinical case reports of abuse and dependence. Many of the epidemiological studies or case reports that describe the effects of illicit GHB refer to the molecule simply as GHB. Pharmaceutical sodium oxybate can differ from illicit GHB in accessibility, purity, and dosing. However, studies examining the effects of GHB are applicable to sodium oxybate. The European Monitoring Centre for Drugs and Drug Addiction 2007 and 2008 Annual Reports and thematic paper on GHB and gamma-butyrolactone showed that the prevalence of illicit GHB use in Europe is low, with levels of use limited to specific subpopulations of drug users (EMCDDA, 2007; 2008). This is also applicable for the US where the reported rates of non-medical use of GHB were lower than those of other sedatives, tranquilizers and over-the-counter cough medicines (Carter et al, 2009).

According to Wang and colleagues, human abuse liability studies have shown that the abuse liability of sodium oxybate is comparable to that of other scheduled and unscheduled depressant

drugs such as triazolam and alcohol. However, national surveys of drug use, illicit drug confiscation, and emergency room and poison control center calls in the US indicate that the prevalence of illicit use of GHB is very low, has declined since 2000, and is much lower than that of the major drugs of abuse and club drugs including 3,4,-methylenedioxymethamphetamine (street name: ecstasy; Wang et al, 2009).

Moreover, it is worth mentioning that sodium oxybate distribution is restricted which minimizes the impact of misuse and abuse of licit sodium oxybate on public health.

3.1.7 Important identified risk: Diversion/criminal use

Potential mechanisms: Sodium oxybate is the sodium salt of GHB which is an endogenous neurotransmitter synthesized from glutamate. Gamma-hydroxybutyrate acts principally upon G-protein coupled GHB receptors, possibly leading to the inhibition of GABA release. GHB also acts to prevent dopamine neurotransmission within the substantia nigra and mesolimbic regions (Schep et al, 2012) and it modulates the serotonin and opioid systems. In contrast to endogenous concentrations, exogenous sources of GHB, typically elevated to an excess of 1000nmol/g tissue and can act directly as partial $GABA_B$-receptor agonist and indirectly through its metabolism to form GABA (Snead, 1991) both resulting in membrane hyperpolarization and subsequent CNS depression.

Like many CNS depressants, GHB causes anterograde amnesia, especially when combined with ethanol, often leaving the victim unable to recall any details of the event (Ferraro et al, 2001). In addition some effects attributed to illicit GHB, such as a rapid onset of sedation, increased libido and suggestibility, might specifically lend illicit GHB for use in drug-facilitating sexual assault, particularly when combined with alcohol (Varela et al, 2004).

Ease of accessibility, its undetectable properties, and potent amnesiac effect on the victim facilitate its use in sexual assault. GHB's rapid metabolism facilitates non-detection of the drug as unconscious patients recover within 4-6 hours. Difficulties lie in documenting exact numbers of GHB-assisted sexual assault due to the narrow detection window of 12 hours in the victims' bloodstream (Brennan and Van Hout, 2014).

Evidence source(s) and strength of evidence: The potential for diversion and criminal use of sodium oxybate may have legal and social implications. Psychological traumatism and impact on body integrity for victims in case of sexual abuse.

No cases of diversion/criminal use were described in the pediatric Jazz study 13-005.

Characterization of the risk: No AEs were reported regarding diversion or criminal use neither in clinical trials in adults and pediatric participants nor in the postmarketing programs (PASS C00302 and FMP).

Four cases of drug diversion were reported cumulatively in UCB territories up to 17 Dec 2020.

A population-based study on toxicological findings in Swedish homicide victims and offenders from 2007 to 2009 found that GHB was used by 0.8% of offenders (1 case out of 120 total) and by none of the victims (265 in total) (Hedlund et al, 2014).

Drug diversion (and criminal use) is a medical and legal concept involving the transfer of any legally prescribed controlled substance from the individual for whom it was prescribed to another person for any illicit use (Berge et al, 2012).

Controlled prescription drug classes which are commonly diverted include benzodiazepines, opioids, stimulants and sleep medications (McCabe et al, 2006). Prescription drug diversion has significant health, legal and social implications. Deaths from misuse of prescription drugs account for a significant proportion of overdose deaths (Wood, 2015).

The potential for diversion and criminal use of sodium oxybate may have legal and social implications. Psychological traumatism and impact on body integrity for victims in case of sexual abuse.

Forensic analyses of cases of suspected drug-facilitated sexual assault have typically reported a lower prevalence of illicit GHB use compared to other drugs. In 2 studies conducted in the US, forensic analysis showed that among the samples in which only 1 drug was detected; GHB was found in 0 to 3%. Of the samples in which 1 or more drugs were detected, GHB was found in 3 to 4%, whereas alcohol, tetrahydrocannabinol, or a benzodiazepine was found in 19 to 56% of samples (ElSohly and Salamone, 1999).

In the EU, the prevalence estimates for 6 partially overlapping types of drug use could be identified: "problem opiate use," "problem opiate or cocaine use." "Problem amphetamine or opiate use," "problem drug use," "(current) injecting," and "life-time injecting" ranged from 2.6 in Germany to 4.8 in Luxembourg per 1000 population aged 15–64 years (Kraus et al, 2003).

Risk factors and risk groups: Personal and familial history of drug abuse and a history of criminal behavior are known risk factors of drug diversion (Walker and Webster, 2012).

Preventability: Patient close monitoring for the risk of diversion, misuse, and abuse of sodium oxybate (UCB SmPC, 2018).

Secured distribution system to minimize the risk for potential product diversion of sodium oxybate.

Educational program to improve patient and physician knowledge regarding the risk of diversion or criminal use related to sodium oxybate.

Impact on the risk-benefit balance of the product: The risk of diversion/criminal use has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive.

Routine pharmacovigilance activities are in place to monitor this risk. Additionally, an educational guide for pediatric patients and their caregivers will be added to the existing education materials.

Public health impact: In the US, data from national surveys of drug use and abuse, law enforcement activity, emergency department visits, and poison control center suggest that the rate of GHB abuse has remained low over the past several years, even as sodium oxybate was introduced to the market (Carter et al, 2009). These data, and the very low rates of diversion of Xyrem, support the conclusion that this remains exceptional events. This is reinforced by the fact that Xyrem follows a restrictive distribution which prevents the risk of its diversion. Hence, the potential public health impact of this safety concern is not expected to be high given its low frequency.

3.1.8 Important identified risk: Depression/suicidality

Potential mechanisms: Sodium oxybate is the sodium salt of GHB which is an endogenous neurotransmitter synthesized from glutamate. Gamma-hydroxybutyrate acts principally upon

G-protein coupled GHB receptors, possibly leading to the inhibition of GABA release. Gamma-hydroxybutyrate also acts to prevent dopamine neurotransmission within the substantia nigra and mesolimbic regions (Schep et al, 2012) and it modulates the serotonin and opioid systems. In contrast to endogenous concentrations, exogenous sources of GHB, typically elevated to an excess of 1000nmol/g tissue and can act directly as partial $GABA_B$-receptor agonist and indirectly through its metabolism to form GABA (Snead, 1991) both resulting in membrane hyperpolarization and subsequent CNS depression.

Pathogenic mechanism of sodium oxybate on depressive disorders is still unclear but might be related to its action on the GABA receptor.

Evidence source(s) and strength of evidence: The emergence of depression when patients are treated with sodium oxybate requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored especially carefully for the emergence of depressive symptoms while taking sodium oxybate.

In the general population, the pediatric population is not more at risk than other subpopulations (WHO, 2018). However, in narcolepsy population, the risk could be higher (Drapeau 2017, Ruoff 2017).

The review of suicidal AEs from clinical data revealed that 1 suicidal ideation and 2 depression events occurred in a pediatric patient in 13-005 study, whereas 2 completed suicides, 1 suicide attempt, and 1 intentional overdose were noted in the clinical summary of safety (Scharf study excluded).

The postmarketing data analysis for PASS C00302 also shows overlapping 95% confidence intervals for Suicide attempt, which was the only PT reported for pediatric population.

The review of UCB Global Safety database reports at the DLP of 30 Jun 2017, highlighted an increased reporting of suicide attempt events in pediatric population (22 occurrences) compared to adults (195), with non-overlapping 95% confidence intervals. Among the cases reported in pediatric population, 21 of the 22 concerned adolescents. It is worthwhile to mention that no completed suicides were reported for pediatric population.

Therefore, "for adolescents extra care should be taken to assess any potential suicidal condition before starting treatment with sodium oxybate."

Characterization of the risk: Table 3–5 presents the frequency of AEs potentially related to depression/suicidality in clinical trials in adults.

Table 3–5: Frequency of adverse events potentially related to depression/suicidality in clinical trials in adults

Number (%) of study participants with	Placebo (N=81)	All Sodium oxybate (N=421)
Depressed mood	0 (0)	4 (1)
Depression	1 (1)	6 (1)

N=number
* Clinical trials: Common Technical Document (CTD) Module 2.7.4 Summary of Clinical Safety of the application for the indication 'treatment of cataplexy in patients with narcolepsy'

Table 3–6 presents the frequency of AEs potential related to depression/suicidality in the pediatric Jazz study 13-005.

Table 3–6: Treatment emergent adverse events potentially related to depression/suicidality in the pediatric Jazz study 13-005

Number (N; %) of study participants with condition	Age (years)[a]		Xyrem status at study entry		Total (N=104)
	7 to 11 (N=37)	12 to 17 (N=67)	Xyrem naïve (N=72)	On Xyrem (N=32)	
Depression	1 (2.7)	1 (1.5)	2 (2.8)	0	2 (1.9)
Suicidal ideation	0	1 (1.5)	1 (1.4)	0	1 (1.0)

N=number
[a] Age in years at the first dispensation of study drug in Part 1

In a case/non case study in the French Pharmacovigilance Database looking at the events of depression received between Jan 2007 and Dec 2011, the reporting odds ratio with 95% CI for sodium oxybate was 13.5 (5.5, 33.4; p<0.001). The comparators were antiepileptics (topiramate, levetiracetam), anti-infective and especially anti-retroviral drugs (efavirenz, emtricitabine, tenofovir, etravirine, raltegravir), interferons and other agents including isotretinoin, methylphenidate, varenicline, montelukast, flunarizine, adalimumab, anastrozole (Lafay-Chebassier et al, 2015).

In PASS C00302, the most frequent serious TEAEs were reported in SOC Psychiatric disorders 16 patients (2.2%) and the most frequent TEAE was depression reported in 3 patients (0.4%). Among all TEAEs in the intention-to-treat population, depression was reported in 60 (8.2%) study participants, depressed mood in 9 (1.2%) study participants, suicide attempt in 2 (0.3%) study participants and depression suicidal in 1 (0.1%) study participant.

As of the DLP of the RMP, a cumulative total of 2015 patients were included in the FMP. A review of the cases entered into the UCB Global Safety database as of the DLP identified 81 cases from the FMP reporting AEs suggestive of depression/suicidality. Five of these 81 cases involved pediatric patients (age range 10 to 17 years). The most frequently reported AEs (n≥5) in these 81 cases included depression, depressed mood, suicidal ideation, and suicide attempt; none of these cases reported completed suicide.

Several drugs can cause or exacerbate depression, whether in abuse, intoxication, withdrawal, and from chronic use. These include alcohol, sedatives, opioids, stimulants, hallucinogens, and inhalants (American Psychiatric Association, 2013). Morbidity associated with depression is difficult to quantify, but the lethality of depression takes the measurable form of completed suicide (Andrew, 2014).

Depression is a potentially life-threatening mood disorder that affects 1 in 6 persons in the United States, or approximately 17.6 million Americans each year. Depressed patients are more likely to develop type 2 diabetes and cardiovascular disease. Not counting the effect of secondary disease states, over the next 20 years, unipolar depression is projected to be the second

leading cause of disability worldwide and the leading cause of disability in high-income nations, including the United States (Andrew, 2014).

In 2010, the Centers for Disease Control and Prevention (CDC) released a report estimating the prevalence of current depression in adults from 2006-2008. Of 235,067 adults, 9% met the criteria for current depression, including 3.4% who met the criteria for major depression (CDC, 2010). Internationally reported adult prevalence rates of depression generally mirror those of the US, and estimates of 1-month prevalence of depression in community-dwelling elderly are relatively consistent (eg, England, 2.9%; The Netherlands, 2.0%; Sweden, 5.6%; Nigeria, 1.6%).

However, sparse data are available on the international incidence of major depression in children and adolescents.

Risk factors and risk groups: Risk factors for depression and suicidality include mental disorders substance abuse and life circumstances (WHO, 2016).

Educational achievement was inversely associated with risk of suicide attempt (Petronis et al, 1990).

Preventability: Contraindicated in case of major depression.

Careful monitoring of patients with history of a depressive illness or suicide attempt for emergence of depression while receiving sodium oxybate may prevent from suicidality (UCB SmPC, 2018).

Immediate evaluation of patients experiencing depression while receiving sodium oxybate is recommended to assess the need of treatment discontinuation.

Reinforcement of the information to physicians and patients concerning the risk of suicidality in children and adolescents in SmPC and educational materials.

An enhancement of the risk minimization via the product label is suggested with the inclusion of a warning in Section 4.4 (changes are shown in *Italics*):

Neuropsychiatric events

Patients may become confused while being treated with sodium oxybate. If this occurs, they should be evaluated fully, and appropriate intervention considered on an individual basis. Other neuropsychiatric events include psychosis, paranoia, hallucinations, and agitation. The emergence of thought disorders including thoughts of committing violent acts (including harming others) and/or behavioural abnormalities when patients are treated with sodium oxybate requires careful and immediate evaluation.

For children and adolescents extra care should be taken to assess any potential suicidal or depressive condition before starting treatment with sodium oxybate and to monitor any treatment-emergent events. The emergence of depression when patients are treated with sodium oxybate requires careful and immediate evaluation. Patients with a previous history of *affective disorders (including* depressive illness, *bipolar disorder and anxiety*), suicide attempt *and psychosis* should be monitored especially carefully for the emergence of depressive symptoms *and/or suicidal ideation* while taking sodium oxybate.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

The educational material has been updated to reflect this new information.

Impact on the risk-benefit balance of the product: The risk of depression/suicidality has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive.

Information relating to depression/suicidality is described in the Special warnings and precautions for use (Section 4.4). Depression, suicidal ideation and suicidal attempt are listed as ADRs in the SmPC (Section 4.8).

Public health impact: The potential public health impact of this safety concern is expected to be significant. Depressive disorders and their psychosocial consequences are frequently observed in narcoleptic patient treated with sodium oxybate. In addition the risk of suicidal attempt is substantial. However, the causal role of sodium oxybate is difficult to assess since narcolepsy by itself is associated with important depressive disorders (Douglas, 1998). As mentioned in the SmPC, careful monitoring of patient at risk may contribute to minimize the risk of suicide.

3.1.9 Important identified risk: Convulsion

Potential mechanisms: GHB is an endogenous neurotransmitter synthesized from glutamate. GHB acts principally upon G-protein coupled GHB receptors, possibly leading to the inhibition of GABA release. GHB also acts to prevent dopamine neurotransmission within the substantia nigra and mesolimbic regions, (Schep et al, 2012) and it modulates the serotonin and opioid systems. In contrast to endogenous concentrations, exogenous sources of GHB, typically elevated to an excess of 1000nmol/g tissue and can act directly as partial $GABA_B$-receptor agonist and indirectly through its metabolism to form GABA (Snead, 1991).

Evidence source(s) and strength of evidence: Seizures have been observed in patients treated with sodium oxybate. In patients with epilepsy, the safety and efficacy of sodium oxybate has not been established, therefore use is not recommended (UCB SmPC, 2018).

No seizures have been reported in the pediatric Jazz study 13-005.

Characterization of the risk: No AEs were reported regarding convulsion in clinical trials in adults.

As of the DLP of the RMP, a cumulative total of 2015 patients were included in the FMP. A review of the cases entered into the UCB Global Safety database as of the DLP identified 10 cases from the FMP reporting AEs suggestive of convulsions. One of these 10 cases involved a pediatric patient aged 17 years.

PASS C00302: For the AE of special interest "convulsions," events of epilepsy and myoclonus were reported in 0.3% patients each and generalized tonic-clonic seizures and seizures were reported in 0.1% patients each. The total number of patients in this study was of 730.

There is evidence that seizures cause brain injury, including neuronal death and physiological dysfunction. Mortality rates are 4-7 times higher in people with medically refractory seizures, and injury rates are substantial, ranging from 1 per 20 person-years to as much as 1 per 3 person-years (Sperling, 2004).

The consequences of epilepsy can be severe and include shortened lifespan, excessive bodily injury, neuropsychological and psychiatric impairment, and social disability (Sperling, 2004).

From postmarketing cases of sodium oxybate, it appears that the most reported Preferred Terms (PTs) are Seizure, Seizure like phenomena and Generalized tonic-clonic seizure. The most reported associated events include fall, anxiety, insomnia, somnambulism, fatigue, nausea, and dizziness.

The incidence of single unprovoked seizures is 23-61 cases per 100,000 persons-years, while the incidence of acute symptomatic seizures is 29-39 cases per 100,000 population per year (Hauser and Beghi, 2008).

Risk factors and risk groups: Acute symptomatic seizures predominate in men, in the youngest age class and in the elderly (Hauser and Beghi, 2008).

In patients with epilepsy, the safety and efficacy of sodium oxybate has not been established, therefore use is not recommended (UCB SmPC, 2018).

Pediatric population may be at risk due to brain immaturity (Nardou et al, 2013).

Preventability: Individualized dosing, titration to give the minimal clinically efficient dose.

An adapted posology is suggested in the proposed SmPC for pediatric population based on patient body weight. The patients should have their body weight checked at regular intervals especially during titration to ensure that the appropriate dose of sodium oxybate is administered.

If in doubt about administration of a dose, do not re-administer the dose to reduce the risk of overdose.

The dose should be gradually titrated to effect based on efficacy and tolerability. A minimum of 1 to 2 weeks is recommended between dosage increments. In adults, the dose should be titrated up to a maximum of 9g/day divided into 2 equal doses of 4.5g/dose by adjusting up or down in dose increments of 1.5g/day (ie, 0.75g/dose). The recommended maximum total daily dose is 0.2g/kg/day in pediatric patients weighing less than 45kg. For pediatric patients weighing 45kg or more, the maximum total daily dose is 9g/day.

To ensure correct dose titration in pediatric population, the Xyrem syringe will be updated to add new markings for 0.5g and 1.0g below the current markings.

Myoclonus and tonic-clonic seizures have been reported, in relation with overdose (UCB SmPC, 2018).

Patients and physicians education (educational materials).

Impact on the risk-benefit balance of the product: The risk of convulsion has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive.

Information relating to convulsion is described in the Special warnings and precautions for use (Section 4.4) and Overdose (Section 4.9) sections. Convulsion is listed as ADRs in the SmPC (Section 4.8).

Routine pharmacovigilance activities are in place to monitor this risk. Additionally, an educational guide for pediatric patients and their caregivers will be added to the existing education materials.

Public health impact: Due to its low frequency and the fact that treatment discontinuation in most of the cases is sufficient to avoid the risk of recurrence, potential public health impact of this safety concern is not expected to be high.

3.1.10 Important identified risk: Psychosis

Potential mechanisms: Sodium oxybate is the sodium salt of GHB which is an endogenous neurotransmitter synthesized from glutamate. Gamma-hydroxybutyrate acts principally upon G-protein coupled GHB receptors, possibly leading to the inhibition of GABA release. Gamma-hydroxybutyrate also acts to prevent dopamine neurotransmission within the substantia nigra and mesolimbic regions (Schep et al, 2012) and it modulates the serotonin and opioid systems.

The pathogenic mechanism of sodium oxybate on psychosis during sodium oxybate treatment is unknown but may be related to its action on the GABA receptor as post-mortem studies of schizophrenia have yielded definitive evidence of GABAergic abnormalities (Taylor and Tso, 2015).

Cessation of GHB use results in a sudden and rapid increase of dopamine levels which may persist and are thought to explain symptoms such as hypertension, insomnia, agitation, paranoia, disorientation, confusion, aggression and auditory and visual hallucinations in severe cases of withdrawal/abstinence (Kamal et al, 2016).

Evidence source(s) and strength of evidence: Neuropsychiatric events include psychosis, paranoia, hallucinations, and agitation. The emergence of thought disorders including thoughts of committing violent acts (including harming others) and/or behavioral abnormalities when patients are treated with sodium oxybate requires careful and immediate evaluation.

In the pediatric Jazz study 13-005, 1 patient reported acute psychosis as psychiatric serious AE. Vivid dreams were described in medical history for this patient.

Characterization of the risk: Psychosis is an uncommon (≥1/1,000 to <1/100) undesirable effect (UCB SmPC, 2018).

One case of acute psychosis was reported in clinical trials in adults. It was assessed as not related.

PASS C00302: One case of acute psychosis (PT) was suspected, but not confirmed. The total number of patients in the study was 730.

As of the DLP of the RMP, a cumulative total of 2015 patients were included in the FMP. A review of the cases entered into the UCB Global Safety database as of the DLP identified 46 cases from the FMP reporting AEs suggestive of psychosis. Three cases reported the AE of psychotic disorder. Among the remaining 43 cases, the most frequently reported AEs (n≥5) were aggression and irritability. Six of these 46 cases involved pediatric patients (age range 11 to 16 years).

Psychosis is an abnormal condition of the mind that involves a loss of contact with reality. This may be accompanied by unusual or bizarre behavior, as well as difficulty with social interaction and impairment in carrying out daily life activities.

People with an anti-social personality can sometimes pose a threat to others because they can be violent. Most people with psychosis are more likely to harm themselves than others.

Psychosis is a complex symptom that may include hallucinations, delusions, disorders of thought, and disorganized speech or behavior. Acute psychosis may be symptomatic of a psychiatric disorder (primary), or caused by a specific medical condition (secondary) including pharmacologic causes (Griswold et al, 2015). For patients with narcolepsy, acute secondary psychosis may be symptomatic of the psychotic form of narcolepsy.

In the general population, there is an approximate 3% lifetime prevalence of psychotic disorders, with 0.21% accounting for psychosis caused by a specific medical condition (Perälä et al, 2007). Illicit drug use (substance abuse and/or withdrawal) is the most common medical cause of acute psychosis (Griswold et al, 2015).

The incidence of violent behavior and/or homicidal ideation associated with psychosis is difficult to quantify. Douglas et al (2009) found that psychosis was the most important predictor of violent behavior in a meta-analysis of 204 studies examining the relationship between psychopathology and aggression. In one US study, 89% of patients who were involuntarily committed from the emergency room for homicidal ideation were psychotic (Stern et al, 1991).

Many people who experience homicidal ideation do not commit homicide and homicidal ideation is not restricted to patients with psychosis and/or delirium. In a survey which was conducted with men and women from the Austin community in Texas, 76% of women and 91% of men reported having at least one homicidal thought in their lifetime (Duntley, 2005). In another study (Kenrick and Sheets, 1993) with 760 undergraduate students, the figures were 55% and 76% for women and men, respectively.

However, women were more likely than men to report having a thought of murdering a family member (Duntley, 2005) and other findings suggest that injuries to staff members on a unit treating both men and women are as likely to be caused by violence by female patients as by male patients (Lam et al, 2000).

Risk factors and risk groups: Risk factors for psychosis include concomitant psychiatric disorder(s), recreational drug use, and pregnancy.

In one primary care population study, psychotic symptoms were most commonly associated with depressive, anxiety, and panic disorders (42.4%, 38.6%, and 24.8%, respectively), followed by substance abuse (13.8%) (Olfson et al, 2002).

Preventability: Other neuropsychiatric events include psychosis, paranoia, hallucinations, and agitation. The emergence of thought disorders including thoughts of committing violent acts (including harming others) and/or behavioral abnormalities when patients are treated with sodium oxybate requires careful and immediate evaluation.

Psychosis is a listed uncommon event. Homicidal ideation is listed with a frequency unknown as well as irritability and aggression (UCB SmPC, 2018). In children aged 7 to <18 years, postmarketing surveillance has shown that sodium oxybate was discontinued in children due to abnormal behavior, aggression, and mood alteration.

Patients and physicians education (educational materials).

Impact on the risk-benefit balance of the product: The risk of psychosis has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive.

Information relating to psychosis is described in Special warnings and precautions for use (Section 4.4). Psychosis, homicidal ideation, irritability and aggression are listed as ADRs in the SmPC (Section 4.8).

Routine pharmacovigilance activities are in place to monitor this risk. Additionally, an educational guide for pediatric patients and their caregivers will be added to the existing education materials.

Public health impact: Due to its low frequency and the fact treatment discontinuation is in most of the cases sufficient to avoid the risk of recurrence, potential public health impact of this safety concern is not expected to be high.

3.1.11 Important Potential Risk: Aggravation of cardiac failure due to additional sodium load

Potential mechanisms: In heart failure (HF), there is a compensatory increase in blood volume, which serves to increase ventricular preload, thereby enhancing stroke volume by the Frank-Starling mechanism. Blood volume is augmented by several factors; reduced renal perfusion results in decreased urine output and retention of fluid. Moreover, a combination of reduced renal perfusion and sympathetic activation of the kidneys stimulates the release of renin, thereby activating the renin-angiotensin system. This enhances aldosterone secretion. There is also an increase in circulating arginine vasopressin (antidiuretic hormone) that contributes to renal retention of water. The final outcome of humoral activation is an increase in renal reabsorption of sodium and water.

Due to its high salt content, sodium oxybate induce sodium loading. This results in an additional increase in the intravascular volume leading to increased venous return, which raises venous pressures. This will worsen a cardiac failure potentially leading to pulmonary and systemic edema.

Evidence source(s) and strength of evidence: Patients taking sodium oxybate will have an additional intake of 0.18g of sodium per 1g of sodium oxybate dose. A recommendation to reduce sodium intake should be carefully considered in the management of patients with HF, hypertension, or compromised renal function.

These are also applicable for children and adolescents, even if the probability of HF, hypertension, or compromised renal function is considered lower in this age group.

Characterization of the risk: No cases of aggravation of cardiac failure due to additional sodium load were observed in clinical trials in adults and pediatric study participants.

As of the DLP of the RMP, a cumulative total of 2015 patients were included in the FMP. A review of the cases entered into the UCB Global Safety database as of the DLP identified 2 cases of cardiac failure in the context of the FMP.

In the PASS C00302, 1 fatal case of cardiac failure was received, which was assessed as not related to sodium oxybate use by the investigator. The total number of patients included in this study was of 730.

Heart failure develops when the heart, via an abnormality of cardiac function (detectable or not), fails to pump blood at a rate commensurate with the requirements of the metabolizing tissues.

Heart failure is a common, disabling, and potentially fatal condition (McMurray and Pfeffer, 2005).

Acute HF decompensation may lead to a cardiogenic pulmonary edema and ultimately cardiogenic shock and death.

Heart failure is a major public health issue with a current prevalence of over 5.8 million in the US and over 23 million worldwide. Every year in the US, more than 550,000 individuals are diagnosed with HF for the first time, and there is a lifetime risk of 1 in 5 individuals developing this syndrome. A diagnosis of HF carries substantial risk of morbidity and mortality, despite advances in management. Over 2.4 million hospitalized patients have HF as a primary or secondary diagnosis, and nearly 300,000 deaths annually are directly attributable to HF (Bui et al, 2011). A study showed that the incidence rates for HF were higher in men than in women, while they were varied with race. A report from the National Heart, Lung, and Blood Institute revealed that among white men, the annual rates for new HF cases per 1000 population for the 3 age groups of 65 to 74 years, 75 to 84 years, and ≥85 years were 15.2, 31.7, and 65.2, respectively, whereas among white women, the estimated rates for the same age groups were 8.2, 19.8, and 45.6, respectively. For black men, the estimated rates were 16.9, 25.5, and 50.6, respectively, for the same age groups, while those rates were 14.2, 25.5, and 44.0, respectively, for black women. Similar results in terms of gender were reported in the Atherosclerosis Risk in Communities (ARIC) study (Go et al, 2013).

However, HF incidences in blacks were greater than those in whites. The ARIC study found that the age-adjusted incidence rate per 1000 person-years was 9.1 for black men versus 6.0 for white men and 8.1 for black women versus 3.4 in white women.

Risk factors and risk groups: Patient with severe HF as classified in the different scoring of the disease (Goldraich et al, 2009) and the association with other comorbidities are risk factors for severe cardiac decompensation (Chinali et al, 2010).

Preventability: A dietary recommendation to reduce sodium intake should be carefully considered in the management of patients with HF, hypertension, or compromised renal function (UCB SmPC, 2018).

Impact on the benefit-risk balance of the product: The potential risk of aggravation of cardiac failure due to additional sodium load has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive.

Information related to sodium intake is described in the Special Warnings and Precautions for Use (Section 4.4). More information regarding HF, hypertension, or compromised renal function can be found in Sections 4.2 and 4.9. Hypertension is a listed ADR in the SmPC (Section 4.8).

Routine pharmacovigilance activities are in place to monitor this risk.

Public health impact: Risk of aggravation of cardiac failure due to additional sodium load appears to be particularly significant due to its severity and the risk of life-threatening complications and potentially fatal outcome. However, considering the frequency of HF and number of concerned patient treated with sodium oxybate, the overall public health impact of the risk appears to be moderate. Moreover, adequate risk minimization measures are already implemented in the SmPC.

3.1.12 Important potential risk: Fluid retention in patients with compromised renal function due to additional sodium load

Potential mechanisms: Sodium oxybate is the sodium salt of GHB. Due to its high salt content, sodium oxybate may induce significant sodium loading. As hypernatremia develops, extracellular sodium does not diffuse into the cell, but remains an obligatory extracellular ion. Water then leaves the cell and enters the extracellular space because of the high osmolarity of the extracellular fluid. This movement of water bolsters the intravascular volume, but at the expense of cellular size and function. In a healthy individual, water intake and loss are matched. To maintain sodium and extracellular fluid volume homeostasis, the kidneys similarly adjust renal sodium excretion to match sodium intake and any extra renal losses.

However, when compensative mechanism are exceeded, as could be the case when the renal function is impaired, fluid retention will result from increased movement of fluid from the interstitial space to the intravascular space or decreased movement of water from the capillaries or lymphatic vessels into the interstitium (Palmer, 2008).

Evidence source(s) and strength of evidence: Patients taking sodium oxybate will have an additional intake of 0.18g of sodium per 1g of sodium oxybate dose. A recommendation to reduce sodium intake should be carefully considered in the management of patients with HF, hypertension, or compromised renal function.

These are also considered applicable for children and adolescents, even if their probability is considered lower in this age group.

Characterization of the risk: No studies have been conducted in participants with renal failure. Participants with unstable cardiovascular or renal disease and those who had baseline serum creatinine level ≥2.0mg/dL or were on a sodium-restricted diet were excluded from Phase 2 and 3 studies.

In most cases, fluid retention does not cause serious problems. However, sometimes, fluid retention can cause dangerous effects such as prolonged pulmonary edema, which increases the risk of HF.

The excess fluid builds up in various locations in the body and leads to an increase in weight, swelling in the legs and arms (peripheral edema), and/or fluid in the abdomen (ascites). Eventually, this could induce a pleural effusion, causing hypoxemia and dyspnea.

Of note, hypertension, which could be a consequence of fluid retention, is also known to occur with sodium oxybate. As of the DLP of the RMP, a cumulative total of 2015 patients were included in the FMP. A review of the cases entered into the UCB Global Safety database as of the DLP identified no cases suggestive of fluid retention due to compromised renal function due to additional sodium load.

Epidemiological data regarding fluid retention in patient with altered renal function are not available in the general population. Prevalence retention not specific to an etiology has been found to be between 0.5% and 2.0% in a population of hospitalized patients (Palmer, 2008).

According to a systematic review, the median prevalence of chronic kidney disease (CKD) was 7.2% in people aged 30 years or older. In persons aged 64 years or older, the prevalence of CKD varied from 23.4% to 35.8% (Zhang and Rothenbacher, 2008).

Number of patients with chronic kidney disease worldwide is rising markedly (Lysaght, 2002). In European countries, the average annual incidence of end-stage renal disease is around 135 per million population (336 per million in the US; USRDS, 2004 annual report).

In patients with CKD, dietary sodium recommendation for the general population in public health guidelines is less than 5 to 6g daily.

Risk factors and risk groups: Patients with impaired renal function and congestive HF (Clark et al, 2013).

Preventability: Dietary recommendation to reduce sodium intake should be carefully considered to prevent fluid retention in patients with HF, hypertension, or compromised renal function (UCB SmPC, 2018).

Impact on the benefit-risk balance of the product: The potential risk of fluid retention in patients with compromised renal function due to additional sodium load has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive.

Information related to sodium intake is described in the Special Warnings and Precautions for Use (Section 4.4). More information regarding HF, hypertension, or compromised renal function can be found in Sections 4.2 and 4.9. Hypertension is a listed ADR in the SmPC (Section 4.8).

Routine pharmacovigilance activities are in place to monitor this risk.

Public health impact: Ascite, pleural effusion, and pulmonary edema are severe medical conditions that may jeopardize the patient's safety. However, based on the very low exposure to sodium oxybate for the specific population of patients with renal insufficiency and the fact that the SmPC already provides appropriate risk minimization measures, the public health impact is not expected to be major.

3.2 Presentation of the missing information

3.2.1 Missing information: Long-term impact on children and adolescents, including growth and neurocognitive development

Evidence source: Jazz pediatric study 13-005: Overall, a total of 104 study participants took the study drug for a median duration of 370.5 days. There is still no controlled information regarding long-term growth and neurocognitive development. Therefore, the long-term impact of sodium oxybate on children remains to be evaluated.

Population in need of further characterization: There is not enough information on the effect of using sodium oxybate for long periods of time in children aged 7 to younger than 17 years. The SmPC and educational materials have been updated to remind the prescribers to perform an initial assessment of growth and learning performance of children and report any event suggestive of behavioral changes (including social behavior and learning ability) during treatment with Xyrem. The educational materials remind the patients and their caregivers to report all AEs, including behavioral changes, especially in school, to the healthcare professionals. Additionally, 2 separate standard medical follow-up questionnaires (SMFQs) for neurocognitive and growth disorders have been formulated. The intent of each SMFQ is to gather information regarding the diagnosis of the respective disorder, the diagnostic procedures, the signs and symptoms of the disorder, information regarding developmental milestones (if

available), evolution of the disorder before and during treatment with Xyrem, risk factors (if any), and treatment and the outcome of the disorder.

3.2.2 Missing information: Use in pregnancy

Evidence source: Animal studies have shown no evidence of teratogenicity but embryolethality was seen in both rat and rabbit studies.

Data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of spontaneous abortions. To date no other relevant epidemiological data are available. Limited data from pregnant patients during second and third trimester indicate no malformative or feto/neonatal toxicity of sodium oxybate.

Sodium oxybate is not recommended during pregnancy.

Population in need of further characterization: There is not enough information on the safety of sodium oxybate in women who are pregnant. Sodium oxybate should not be taken during pregnancy unless clearly necessary.

3.2.3 Missing information: Use in elderly patients

Evidence source: There is limited experience with sodium oxybate in the elderly. Adverse events in integrated clinical studies for narcolepsy were summarized by age group. There was little difference between the 2 age groups (<65 years and ≥65 years) with respect to the incidence of adverse events; all events combined and treatment-related events. However, there were relatively few patients aged 65 years and older (n=44 compared with 377 aged <65 years) and it is difficult to draw any firm conclusions about the tolerability of sodium oxybate in the elderly, but confusional state and sleepwalking appeared both to be more common in the elderly than in the younger patients receiving sodium oxybate therapy.

Population in need of further characterization: Therefore, elderly patients should be monitored for impaired motor and/or cognitive function when taking sodium oxybate.

3.2.4 Missing information: Use in patients with BMI ≥40kg/m^2

Evidence source: There is limited experience with sodium oxybate in this subpopulation. Narcolepsy is associated with increased body weight. Several age-matched controlled studies have noted a higher BMI in patients with narcolepsy that with control study participants. Several other studies have shown that obesity (BMI >30kg/m^2) is a risk factor for all-cause mortality.

Population in need of further characterization: Because of the higher risk of sleep apnea, patients with a BMI >40kg/m^2 should be monitored when taking sodium oxybate.

PART II: MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Table 1: Summary of safety concerns

Important identified risks	Alcohol interaction Respiratory depression Central nervous system depression Dependence/withdrawal Overdose Misuse/abuse Diversion/criminal use Depression/suicidality Convulsion Psychosis
Important potential risks	Aggravation of cardiac failure due to additional sodium load Fluid retention in patients with compromised renal function due to additional sodium load
Missing information	Long-term impact on children and adolescents, including growth and neurocognitive development Use in Pregnancy Use in Elderly patients Use in patients with Body Mass Index>40kg/m^2

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION STUDIES)

1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

- Specific adverse reaction follow-up questionnaires for safety concerns:

  Two SMFQs have been formulated to address the missing information of long-term impact on children and adolescents, including growth and neurocognitive development.

  The intent of each SMFQ is to gather information regarding diagnosis of the respective disorder, the diagnostic procedures, the signs and symptoms of the disorder, information regarding developmental milestones (if available), evolution of the disorder before and during treatment with Xyrem, risk factors (if any), and treatment and outcome of the disorder.

  The finalized SMFQs for both disorders are appended in Annex 4 of this RMP.

- Other forms of routine pharmacovigilance activities for safety concerns:

  In order to address the safety concern of long-term impact in children and adolescents, including growth and neurocognitive development, the healthcare provider checklist also includes a checklist for pediatric patients. This checklist serves to remind the prescriber to assess the patient's height, weight, social and psychiatric behavior, and learning performance and report any event that is suggestive of a negative impact on growth and neurocognitive development.

  The guide for pediatric patients and their caregivers reminds them to report all behavior changes, especially in school, and side effects to healthcare professionals.

2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

2.1 Active surveillance through French monitoring program (postauthorization safety study C00304):

Study short name and title: French monitoring program (FMP)

Rationale and study objectives: The French health authority requested a number of additional measures to be put in place in France in addition to the European RMP:

- A unique telephone number which can be contacted 24h/24, 7d/7 for any question, documentation requests and/or notification of adverse events or misuse regarding sodium oxybate.
- A sodium oxybate coordinating center staffed 24h/24, 7d/7 by physicians and pharmacists to oversee all steps involved in the use of sodium oxybate, from specialized consultation to initial dispensation and prescription renewals.
- A secured database maintained by the sodium oxybate coordinating center with a register of patients, physicians, and pharmacists in order to permit a real-time follow-up of sodium oxybate prescription and dispensation. This database includes also data from a patient follow-up booklet that is to be handled to the patient by the initial prescriber together with

information guide on sodium oxybate and narcolepsy. The booklet should be kept by the patient and brought to all consultations and pharmacy visits pertaining to sodium oxybate. This booklet contains several forms to be completed by the patient, physician(s), and pharmacist(s). This permits to establish a detailed overview of the use of sodium oxybate for each individual patient. Any suspicion of an adverse event or misuse should be notified to the appropriate regional center of pharmacovigilance or French authorities and can be notified to the coordinating center using specific forms that are also included in the booklet.

- The prescribing physician should complete the annual initial and the first monthly renewal sodium oxybate forms of the patient follow-up booklet and the dispensing pharmacist should subsequently complete and send the applicable completed forms to this center. Pharmacists will also be able to receive such overviews on request.
- Initially, monthly reports were sent to the French health authority including an overview of all French reports on adverse events, dependence, and abuse as well as information on the amount and conditions of sodium oxybate use. Since Jul 2008, the French health authority agreed to receive quarterly reports. Since Oct 2010, the French health authority agreed to receive annual reports.
- Since Jul 2013, the French health authority decided that local reports (same periodicity as Periodic Benefit-Risk Evaluation Report) are still required, but they will only include: Council for International Organizations of Medical Sciences form of French suspected cases of drug dependence, abuse, or diversion and data on sodium oxybate use. Nevertheless, the Marketing Authorization Holder committed to keep performing an analysis of all French reports on adverse events regarding all important risks, as stated in the Pharmacovigilance plan of the EU-RMP via EU Periodic Safety Update Report.
- On 28 Jun 2016, the technical committee of evaluation and information centers on pharmacodependence (CEIP), has agreed on the rapporteur's (CEIP of Bordeaux) proposal regarding the discontinuation of the national addictovigilance monitoring considering the absence of signal related to diversion or abuse for 10 years. However, an assessment will be made in the context of an official evaluation in 2 years. The current conditions of prescription and dispensation have limited drug abuse and diversion of sodium oxybate, the technical committee considers that a reduction of risk minimization measures must be progressive. Therefore, a positive opinion was provided by the technical committee to the maintenance of the registry with an annual report to be provided by the Marketing Authorization Holder to the French health authority and CEIP of Bordeaux and a negative opinion regarding the modifications of current condition of prescription and dispensation.

This FMP covers important identified risks as well as potential risks and missing information with a focus on abuse, misuse, dependence, and diversion of sodium oxybate.

Milestones: Study initiation in the second quarter of 2006. Last annual report covering the period from 13 Oct 2019 to 12 Oct 2020 was submitted to Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) in Dec 2020. Following the termination of the FMP on 26 Jan 2021, the new educational material was distributed in France.

3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The summary of ongoing and planned additional pharmacovigilance activities is provided in Table 3–1.

Table 3–1: Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None.				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities by French Authority and European Medicines Agency				

French monitoring program (postauthorization safety study C00304)	To assure a safe prescription and distribution of sodium oxybate; ensure traceability of sodium oxybate and patients; and encourage the spontaneous notification of supposed adverse effects and cases of abuse or misuse, dependence, and diversion of sodium oxybate. The EU-Risk Management Plan has been supplemented by a procedure of national pharmacovigilance monitoring (stopped in 2012) and a procedure for addictovigilance monitoring (ongoing). Several risk minimization measures have also been put in place at the national level with the implementation of a secure distribution, prescribing and dispensing program supervised by a coordinating center, feeding a database of patients, prescribers and hospital pharmacies (also called registry), a patient booklet and information materials for patients, physicians and pharmacists. The secure database, also called Xyrem French registry, allowed a real-time monitoring of consumption and use of Xyrem in France, including an overview of off-label use for population, for indication, and for dose. Each patient was identified by a unique Patient ID. Potential cases of misuse, pharmacodependance and	This French monitoring program covers important identified risks as well as potential risks and missing information with a focus on abuse, misuse, dependence, and diversion of sodium oxybate.	Last annual report covering the period from 13 Oct 2019 to 12 Oct 2020 was submitted to Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) in Dec 2020. French monitoring program was terminated on 26 Jan 2021. A final report presenting cumulative and up-to-date data on the consumption and use of Xyrem in France will be submitted with the next Periodic Safety Update Report (PSUR; Data Lock Point of 12 Oct 2021).	The adverse events collected from this French monitoring program appear in the PSUR line listings.

Table 3–1: Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	diversion identified/reported in the frame of the secure distribution program were registered in the UCB global database and discussed in EU Periodic Safety Update Reports (PSURs).			

PSUR=Periodic safety update report

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing imposed postauthorization efficacy studies that are conditions of the marketing authorization or that are specific obligations for sodium oxybate.

RMP PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

1 ROUTINE RISK MINIMIZATION MEASURES

Description of routine risk minimization measures by safety concern is presented in Table 1–1.

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Alcohol interaction	Routine risk communication In the Summary of Product Characteristics (SmPC), statements and recommendations are provided in the following sections: 4.4: Special Warnings and Precautions for Use under CNS depression 4.5: Interaction With Other Medicinal Products and Other Forms of Interaction The Patient Information Leaflet (PIL) provides advice in Section 2, What You Need to Know Before You Take Xyrem, under Xyrem with food, drink, and alcohol. Other routine risk minimization measures beyond the Product Information: Prescription-only medicine
Respiratory depression	Routine risk communication In the SmPC, statements and recommendations are provided in the following sections: 4.2: Posology and Method of Administration 4.3: Contraindications 4.4: Special Warnings and Precautions for Use under Respiratory depression, Respiratory events, and Weight loss 4.5: Interaction With Other Medicinal Products and Other Forms of Interaction, specifically Sedative hypnotics and Tramadol 4.8: Undesirable Effects, under Respiratory, thoracic and mediastinal disorders 4.9: Overdose The PIL provides advice in: Section 2, What You Need to Know Before You Take Xyrem, under Do not take Xyrem if and Warnings and Precautions Section 4, Possible Side Effects Other routine risk minimization measures beyond the Product Information: • Prescription-only medicine • Update to Xyrem syringe to add new graduations of 0.5g and 1.0g below the current markings • Update to Xyrem syringe to add a second scale along one side of Xyrem syringe with graduations of 0.2g to ensure correct dosing when combined with valproate

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
CNS depression	Routine risk communication In the SmPC statements and recommendations are provided in the following sections: 4.2: Posology and Method of Administration 4.3: Contraindications 4.4: Special Warnings and Precautions for Use, under CNS depression, Alcohol and CNS depressants, GHB dehydrogenase inhibitors, Topiramate, and Weight loss 4.5: Interaction With Other Medicinal Products and Other Forms of Interaction, specifically Alcohol, Sedative hypnotics, Tramadol, Antidepressants, Modafinil, Omeprazole, Ibuprofen, Diclofenac, GHB dehydrogenase inhibitors and Topiramate 4.7: Effects on Ability to Drive and Use Machines 4.8: Undesirable Effects 4.9: Overdose The PIL provides advice in: Section 2, What You Need to Know Before You Take Xyrem under Other medicines and Xyrem, Driving and using machines Section 4, Possible Side Effects Other routine risk minimization measures beyond the Product Information: • Prescription-only medicine • Update to Xyrem syringe to add new graduations of 0.5g and 1.0g below the current markings • Update to Xyrem syringe to add a second scale along one side of Xyrem syringe with graduations of 0.2g to ensure correct dosing when combined with valproate
Dependence/ withdrawal	Routine risk communication In the SmPC, statements and recommendations are provided in the following sections: 4.4: Special Warnings and Precautions for Use, under Abuse potential and dependence and Rebound effects and withdrawal syndrome 4.8: Undesirable Effects The PIL provides advice in: Section 2, What You Need to Know Before You Take Xyrem under Warnings and precautions Section 3, How to Take Xyrem under If you stop taking Xyrem Section 4, Possible Side Effects Other routine risk minimization measures beyond the Product Information: Prescription-only medicine
Overdose	Routine risk communication

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
	In the SmPC, statements and recommendations are provided in the following sections: 4.2: Posology and Method of Administration 4.4: Special Warning and Precautions for Use under Weight loss 4.9 Overdose including Symptoms and Management The PIL provides advice in: Section 3, How to Take Xyrem under If you take more Xyrem than you should. Other routine risk minimization measures beyond the Product Information: • Prescription-only medicine • Update to Xyrem syringe to add new graduations of 0.5g and 1.0g below the current markings • Update to Xyrem syringe to add a second scale along one side of Xyrem syringe with graduations of 0.2g to ensure correct dosing when combined with valproate
Misuse/abuse	Routine risk communication In the SmPC, statements and recommendations are provided in the following sections: 4.2: Posology and Method of Administration 4.3: Contraindications 4.4: Special Warnings and Precautions for Use under Abuse potential and dependence 4.8: Undesirable Effects under Psychiatric disorders The PIL provides advice in: Section 2, What You Need to Know Before You Take Xyrem under Warnings and precautions Section 3, How to Take Xyrem Section 4, Possible Side Effects Other routine risk minimization measures beyond the Product Information: Prescription-only medicine
Diversion/ criminal use	Routine risk communication In the SmPC, statements and recommendations are provided in the following sections: 4.2: Posology and Method of Administration 4.4: Special Warnings and Precautions for Use under Abuse potential and dependence The PIL provides advice in: Section 2, What You Need to Know Before You Take Xyrem under Warnings and precautions. Other routine risk minimization measures beyond the Product Information: Prescription-only medicine

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Depression/ suicidality	Routine risk communication In the SmPC, statements and recommendations are provided in the following sections: 4.3: Contraindications 4.4: Special Warnings and Precautions for Use under Neuropsychiatric events Additional wording for children and adolescents that extra care should be taken to assess any potential suicidal or depressive condition before starting treatment with sodium oxybate. 4.8: Undesirable Effects under Psychiatric disorders Additional wording specific to pediatric population stating adverse drug reaction of suicidal ideation (1%) and of acute psychosis (1%) were reported in a clinical study in children/adolescents. Several terms listed under Psychiatric disorders. The PIL provides advice in: Section 2, What You Need to Know Before You Take Xyrem under Do not take Xyrem if, Take special care with Xyrem, Warnings and precautions, Other medicines and Xyrem Section 4, Possible Side Effects Other routine risk minimization measures beyond the Product Information: Prescription-only medicine
Convulsion	Routine risk communication In the SmPC statements and recommendations are provided in the following sections: 4.2: Posology and Method of Administration 4.4: Special Warnings and Precautions for Use under Epileptic patients and Weight loss 4.8: Undesirable Effects under Nervous system disorders 4.9: Overdose The PIL provides advice in: Section 2, What You Need to Know Before You Take Xyrem under Warnings and precautions Other routine risk minimization measures beyond the Product Information: • Prescription-only medicine • Update to Xyrem syringe to add new graduations of 0.5g and 1.0g below the current markings • Update to Xyrem syringe to add a second scale along one side of Xyrem syringe with graduations of 0.2g to ensure correct dosing when combined with valproate
Psychosis	Routine risk communication In the SmPC, statements and recommendations are provided in the following sections:

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
	4.4: Special Warnings and Precautions for Use under Neuropsychiatric events 4.8: Undesirable Effects under Psychiatric disorders The PIL provides advice in: Section 2, What You Need to Know Before You Take Xyrem under Warnings and precautions Other routine risk minimization measures beyond the Product Information: Prescription-only medicine
Important potential risks	
Aggravation of cardiac failure due to additional sodium load	Routine risk communication In the SmPC, statements and recommendations are provided in the following Sections: 4.2 Posology and method of administration under renal impairment 4.4 Special warnings and precautions for use under sodium intake 4.8 Undesirable effects under general disorders and administration site conditions The PIL provides advice in: Section 2 What you need to know before you take Xyrem under Xyrem with food, drink and alcohol Other routine risk minimization measures beyond the Product Information: Prescription-only medicine
Fluid retention in patients with compromised renal function due to additional sodium load	Routine risk communication In the SmPC, statements and recommendations are provided in the following Sections: 4.2 Posology and method of administration under renal impairment 4.4 Special warnings and precautions for use under sodium intake 4.8 Undesirable effects under general disorders and administration site conditions The PIL provides advice in: Section 2 What you need to know before you take Xyrem under Xyrem with food, drink and alcohol Other routine risk minimization measures beyond the Product Information: Prescription-only medicine
Missing information	
Long-term impact on children and adolescents, including growth and	Routine risk communication In the SmPC, statements and recommendations regarding children and adolescents are provided in the following sections: 4.2: Posology and Method of Administration under Pediatric population 4.4: Special Warnings and Precautions for Use under Pediatric population

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
neurocognitive development	4.8: Undesirable Effects The PIL provides advice in: Section 2, What You Need to Know Before You Take Xyrem under Children and adolescents
Use in Pregnancy	Routine risk communication In the SmPC, statements and recommendations are provided in the following Sections: 4.6 Fertility, pregnancy and lactation under pregnancy The PIL provides advice in: Section 2 What you need to know before you take Xyrem under Pregnancy and breastfeeding
Use in Elderly patients	Routine risk communication In the SmPC, statements and recommendations are provided in the following Sections: 4.2 Posology and method of administration under elderly population 4.4 Special warnings and precautions for use under elderly The PIL provides advice in: Section 2 What you need to know before you take Xyrem under Warnings and precautions
Use in patients with body mass index ≥40kg/m^2	Routine risk communication In the SmPC, statements and recommendations are provided in the following Sections: 4.4 Special warnings and precautions for use under respiratory depression The PIL provides advice in: Section 2 What you need to know before you take Xyrem under Warnings and precautions

CNS=central nervous system; GHB=gamma-hydroxybutyrate; PIL=patient information leaflet; SmPC=summary of product characteristics

2 ADDITIONAL RISK MINIMIZATION MEASURES

Additional risk minimization measures include educational materials for prescribers, caregivers, and patients to reinforce information in the SmPC and PIL and controlled distribution.

2.1 Additional risk minimization

2.1.1 Educational materials

Objectives/Rationale for the additional risk minimization activity:

- **Healthcare provider checklist**

Healthcare professionals should use the checklist when first prescribing sodium oxybate and at subsequent visits. The checklist serves to remind the prescriber to check the patient's medical history and to counsel the patient on proper dosing and on side effects.

All important identified risks are addressed.

In order to address the safety concern of long-term impact in children and adolescents, including growth and neurocognitive development, the healthcare provider checklist also includes a checklist for pediatric patients. This checklist serves to remind the prescriber to assess the patient's height, weight, social and psychiatric behavior, and learning performance, and report any event that is suggestive of a negative impact on growth and neurocognitive development.

- **Frequently asked questions for patients**

Frequently asked questions provide information on the disease (eg, symptoms, prevalence) and treatment (eg, administration, important side effects) of sodium oxybate and the importance of getting medical help immediately when needed.

All important identified risks are addressed.

- **Patient alert card**

It is a wallet-sized card that patients should keep with them at all times. The card warns of risks and explains when to seek emergency help straight away (eg, overdose) and provides important safety information for treating physicians.

- **Patient instructions for administration of sodium oxybate**

This will be provided by the prescriber and provides instructions on how to administer the right dose of sodium oxybate.

- **Guide for pediatric patients and their caregivers**

Provides important information about the safe use and handling of sodium oxybate by caregivers.

This guide answers important questions about how to use Xyrem properly, how to store it safely, and how to get the child's Xyrem. It also gives important information about Xyrem and reminds the patients and their caregivers to report all side effects to the healthcare professionals, including behavior changes, especially in school.

All important identified risks are addressed.

Target audience and planned distribution path:

The target audience consists of prescribers, caregivers and patients. Distribution occurs via healthcare professionals to caregivers and patients.

More details of educational materials are provided in EU-RMP Annex 6.

Plans to evaluate the effectiveness of the interventions and criteria for success:

According to the European legislation of Good Vigilance Practice, the MAH has proposed to assess the effectiveness of the Xyrem RMP educational materials. In order to assess the effectiveness of risk minimization measures, the proposed activities are outlined below in the form of outcome indicators.

Outcome indicators:

The outcome indicators will be followed via routine pharmacovigilance, which includes evaluation of spontaneous reports and reports from registries, signal management, and aggregate reporting. The effectiveness of additional risk minimization measures (aRMMs) will be evaluated by assessing the frequency and/or severity of adverse reactions reported from UCB territories in relation to pediatric patients' exposure to sodium oxybate before and after implementing the aRMM.

2.1.2 Controlled distribution system

Sodium oxybate is a controlled substance delivered upon prescription.

Objectives/Rationale for the additional risk minimization activity:

The steps described in this section are intended to allow sodium oxybate to reach the intended population of narcolepsy patients while minimizing the risk of sodium oxybate being diverted by those seeking to misuse it (see Important Identified Risks of Dependence/Withdrawal, Misuse/Abuse and Diversion/Criminal use): In the frame of the European pharmaceutical distribution system for a controlled substance, a distribution model has been established by the MAH that enhances the existing controls for sodium oxybate.

Target audience and planned distribution path:

1. Whole distribution chain of sodium oxybate:
   - Shipments of sodium oxybate unlabeled bottles between US-based contract manufacturing organization (CMO) and UCB Pharma Ltd.'s UK storage facility
   - From the UCB Pharma Ltd.'s storage facility, the bottles are sent to a UK-based CMO, who performs the transformation of sodium oxybate bulk unlabeled product into sodium oxybate country-specific labeled and packed product. Post-transformation, the finished goods are shipped back to the UCB Pharma Ltd.'s storage facility.
   - Sodium oxybate is shipped from UCB Pharma Ltd.'s UK finished goods storage facility to UCB SA's Belgium finished goods storage facility, then to EU-based affiliate warehouses.
   - Shipments of sodium oxybate country-specific labeled and packed product from UCB's EU-based affiliate warehouses to third party logistics and affiliate.
   - Since sodium oxybate is a controlled drug, export licenses and import licenses are needed for all the shipments from the US to the UK, from the UK to the EU, within the EU, and to Switzerland, Turkey, the UK, and Australia.
2. Summary of the full end-to-end process review and mapping:
   - Standard operating procedures on global distribution processes govern the ocean shipments of bulk unlabeled product between the US and the UK.
   - Internal corporate audit is performed by the Quality Assurance department on all activities handled by the MAH in the UK-based CMO with appropriate follow-up of corrective action preventive action.

– A track-and-trace report is maintained showing full data reconciliation for all batches originally shipped from the US and finally delivered to local markets in Europe. These sets of reports are maintained showing every movement (import/export) of Xyrem products at any stage of its distribution versus its import and/or export license, which have been granted by the Health Authorities of the country from which the movement is initiated. Additionally, the batch reconciliation is available in the UCB Enterprise Resource Planning (ERP) System.

2.2 Removal of additional risk minimization activities

Not applicable

3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 3–1 provides a summary table of pharmacovigilance activities and risk minimization activities by safety concern.

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Alcohol interaction	Routine risk minimization measures: Prescription-only medicine SmPC sections: 4.4 and 4.5 PIL section: 2 Additional risk minimization measures: Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: French monitoring program (FMP): postauthoriztion safety study (PASS) C00304

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Respiratory depression	Routine risk minimization measures: Prescription-only medicine SmPC sections: 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9 PIL sections: 2 and 4 Update to Xyrem syringe to add new graduations of 0.5g and 1.0g below the current markings Update to Xyrem syringe to add a second scale along one side of Xyrem syringe with graduations of 0.2g to ensure correct dosing when combined with valproate Additional risk minimization measures: Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304
CNS depression	Routine risk minimization measures: Prescription-only medicine SmPC sections: 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, and 4.9 PIL sections: 2 and 4 Update to Xyrem syringe to add new graduations of 0.5g and 1.0g below the current markings Update to Xyrem syringe to add a second scale along one side of Xyrem syringe with graduations of 0.2g to ensure correct dosing when combined with valproate Additional risk minimization measures: Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Dependence/ withdrawal	Routine risk minimization measures: Prescription-only medicine SmPC sections: 4.4 and 4.8 PIL sections: 2, 3, and 4 Additional risk minimization measures: Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card) Controlled distribution system	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304
Overdose	Routine risk minimization measures: Prescription-only medicine SmPC sections: 4.2 and 4.9 PIL section: 3 Update to Xyrem syringe to add new graduations of 0.5g and 1.0g below the current markings Update to Xyrem syringe to add a second scale along one side of Xyrem syringe with graduations of 0.2g to ensure correct dosing when combined with valproate Additional risk minimization measures: Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card) Controlled distribution system	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Misuse/abuse	Routine risk minimization measures: Prescription-only medicine SmPC sections: 4.2, 4.3, 4.4, and 4.8 PIL sections: 2, 3, and 4 Additional risk minimization measures: Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card) Controlled distribution system	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304
Diversion/ criminal use	Routine risk minimization measures: Prescription-only medicine SmPC sections: 4.2 and 4.4 PIL section: 2 Additional risk minimization measures: Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card) Controlled distribution system	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304
Depression/ suicidality	Routine risk minimization measures: Prescription-only medicine SmPC sections: 4.3, 4.4, and 4.8 PIL sections: 2, 3, and 4 Additional risk minimization measures: Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Convulsion	Routine risk minimization measures: Prescription-only medicine SmPC sections: 4.2, 4.4, 4.8, and 4.9 PIL section: 2 Update to Xyrem syringe to add new graduations of 0.5g and 1.0g below the current markings Update to Xyrem syringe to add a second scale along one side of Xyrem syringe with graduations of 0.2g to ensure correct dosing when combined with valproate Additional risk minimization measures: Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304
Psychosis	Routine risk minimization measures: Prescription-only medicine SmPC sections: 4.4 and 4.8 PIL section: 2 Additional risk minimization measures: Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304
Important potential risks		
Aggravation of cardiac failure due to additional sodium load	Routine risk minimization measures: Prescription-only medicine SmPC sections: 4.2, 4.4, and 4.8 PIL Section: 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Fluid retention in patients with compromised renal function due to additional sodium load	Routine risk minimization measures: Prescription-only medicine SmPC sections: 4.2, 4.4 and 4.8 PIL section: 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304
Missing information		
Long-term impact on children and adolescents, including growth and neurocognitive development	Routine risk minimization measures: SmPC sections: 4.2, 4.4, and 4.8 PIL section: 2 Additional risk minimization measures: Educational materials (HCP checklist)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: • Checklist for pediatric patients in HCP checklist and information in Guide for Pediatric Patients and Caregivers to prompt them to report adverse events related to patient's height, weight, social and psychiatric behavior, and learning performance • Standard medical follow-up questionnaire for "Neurocognitive disorder" and "Growth disorder" Additional pharmacovigilance activities: FMP: PASS C00304
Use in Pregnancy	Routine risk minimization measures: SmPC section: 4.6 PIL Section: 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304
Use in Elderly patients	Routine risk minimization measures: SmPC sections: 4.2 and 4.4 PIL Section: 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use in patients with body mass index ≥40kg/m^2	Routine risk minimization measures: SmPC section: 4.4 PIL section: 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections: None Additional pharmacovigilance activities: FMP: PASS C00304

CNS=central nervous system; FAQ=frequently asked question; FMP=French monitoring program; HCP=healthcare professional; PASS=postauthorization safety study; PIL=patient information leaflet; SmPC=summary of product characteristics

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Xyrem (sodium oxybate)

This is a summary of the Risk Management Plan (RMP) for Xyrem ® (sodium oxybate) The RMP details important risks of Xyrem, how these risks can be minimized, and how more information will be obtained about Xyrem's risks and uncertainties (missing information).

Xyrem's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Xyrem should be used. The educational material provides important information about the appropriate use and handling of Xyrem. The controlled distribution allows Xyrem to reach the intended population of narcolepsy patients while minimizing the risk of Xyrem being diverted by those seeking to misuse it.

Important new concerns or changes to the current ones will be included in updates of Xyrem's RMP.

1 THE MEDICINE AND WHAT IT IS USED FOR

Xyrem is authorized for treatment of narcolepsy with cataplexy in adult patients, adolescents and children from the age of 7 years. It contains sodium oxybate as the active substance and it is given by oral route of administration.

Further information about the evaluation of Xyrem's benefits can be found in Xyrem's European public assessment reports, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000593/human_med_001163.jsp&mid=WC0b01ac058001d124

2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Xyrem, together with measures to minimize such risks and the completed and ongoing studies for learning more about Xyrem's risks, are outlined below (Sections 2.1, 2.2 and 2.3).

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) - can help to minimize its risks.

Together, these measures constitute *routine risk minimization measures*.

In the case of Xyrem, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including aggregate reports - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the appropriate use of Xyrem is not yet available, it is listed under "missing information" below (see Section 2.2).

2.1 List of important risks and missing information

Important risks are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be appropriately administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of medicinal product. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently not available and still needs to be collected (eg, on the long-term use of the medicine).

Table 2–1: List of important risks and missing information

List of important risks and missing information	
Important identified risks	Alcohol interaction Respiratory depression Central nervous system depression Dependence/withdrawal Overdose Misuse/abuse Diversion/criminal use Depression/suicidality Convulsion Psychosis
Important potential risks	Aggravation of cardiac failure due to additional sodium load Fluid retention in patients with compromised renal function due to additional sodium load
Missing information	Long-term impact on children and adolescents, including growth and neurocognitive development Use in pregnancy Use in elderly patients Use in patients with body mass index of $\geq$40kg/m^2

2.2 Summary of important risks

Table 2–2: Summary of important identified risks - Alcohol interaction

Important identified risks - Alcohol interaction	
Evidence for linking the risk to the medicine	The combined use of alcohol, or any CNS depressant medicinal product, with Xyrem may result in potentiation of the CNS depressant effects of Xyrem as well as increased risk of respiratory depression (UCB SmPC, 2018). There are few surveillance studies of alcohol use and alcohol-related problems among children and pre-adolescents, a situation that makes estimation of alcohol burden in this population problematic. The available data indicate that whereas the rates of alcohol use are relatively low in this population, substantial numbers of children do in fact have experience with alcohol. With respect to wholly alcohol-attributable health conditions, the available data suggest very low levels of alcohol abuse and acute intoxication among children (NIH/NIAAA 2018).
Risk factors and risk groups	Patients at risk are those who are more prone to CNS and respiratory depression, including those who use other CNS depressant drugs or those suffering from concurrent illnesses predisposing them to CNS and respiratory depressant effects of Xyrem.
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine Additional risk minimization activities: • Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card)
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

CNS=central nervous system; FAQ=frequently asked question; HCP=healthcare professional; NIAAA=National Institute on Alcohol Abuse and Alcoholism; NIH=National Institute of Health; PIL= patient information leaflet; SmPC=summary of product characteristics

Table 2–3: Summary of important identified risks - Respiratory depression

Important identified risks - Respiratory depression	
Evidence for linking the risk to the medicine	Xyrem has the potential to induce respiratory depression. Apnea and respiratory depression have been observed in a fasting healthy subject after a single intake of 4.5g (twice the recommended starting dose). Special caution should be observed in patients with an underlying respiratory disorder (UCB SmPC, 2018). Pediatric patients with an underlying respiratory disorder may be at more risk of presenting respiratory adverse effects with Xyrem. No data was found

Table 2–3: Summary of important identified risks - Respiratory depression

Important identified risks - Respiratory depression	
	which indicated that adolescents and children are more prone to respiratory depression than adults.
Risk factors and risk groups	Patients with an underlying respiratory disorder may be at more risk of presenting respiratory adverse effects with Xyrem. Given the possibility of increasing the risk of respiratory depression, the concomitant use of benzodiazepines and Xyrem should be avoided. The combined use of alcohol, or any CNS depressant medicinal product, with Xyrem may result in potentiation of the CNS-depressant effects of Xyrem as well as increased risk of respiratory depression. It has been shown that the use of a GHB dehydrogenase inhibitor, valproate, may also be a risk factor for respiratory depression. This is mainly due to an increase of Xyrem plasma concentration. There has been also a clinical observation of coma and increased plasma GHB concentration after co-administration of Xyrem with topiramate. Therefore, the co-administration of topiramate may also be a potential risk factor for respiratory depression (UCB SmPC, 2018). In a 2012 safety communication, the FDA reminded HCPs and patients that the combined use of Xyrem with alcohol or CNS depressant drugs can markedly impair consciousness and may lead to severe breathing problems (respiratory depression) (FDA Drug Safety Communication, Dec 2012).
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine • Update to Xyrem syringe to add new graduations of 0.5g and 1.0g below the current markings • Update to Xyrem syringe to add a second scale along one side of Xyrem syringe with graduations of 0.2g to ensure correct dosing when combined with valproate Additional risk minimization activities: • Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card)
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

CNS=central nervous system; FAQ=frequently asked question; FDA=Food and Drug Administration (US); GHB=gamma-hydroxybutyrate; HCP=health care professional; PIL=patient information leaflet; SmPC=summary of product characteristics

Table 2–4: Summary of important identified risks - CNS depression

Important identified risks - CNS depression	
Evidence for linking the risk to the medicine	Xyrem is the sodium salt of GHB. It has CNS depressant properties, but the exact physiological function and mode of action are not yet fully elucidated. No data retrieved regarding the epidemiology of CNS depression in a specific population.
Risk factors and risk groups	Patient at risk of overdose (refer to the identified risk of overdose). Patient concomitantly treated with CNS depressant drugs. The combined use of alcohol, or any CNS depressant medicinal product, with Xyrem may result in potentiation of the CNS-depressant effects of Xyrem as well as increased risk of respiratory depression. It has been shown that the use of a GHB dehydrogenase inhibitor, valproate, may also be a risk factor for CNS depression. This is mainly due to an increase of Xyrem plasma concentration. There have been also a clinical observation(s) of coma and increased plasma GHB concentration after co-administration of Xyrem with topiramate. Therefore, the co-administration of topiramate may also be a potential risk factor for CNS depression (UCB SmPC, 2018). In a 2012 safety communication, the FDA reminded HCPs and patients that the combined use of Xyrem with alcohol or CNS depressant drugs can markedly impair consciousness and may lead to severe breathing problems (respiratory depression) (FDA Drug Safety Communication, Dec 2012).
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine • Update to Xyrem syringe to add new graduations of 0.5g and 1.0g below the current markings • Update to Xyrem syringe to add a second scale along one side of Xyrem syringe with graduations of 0.2g to ensure correct dosing when combined with valproate Additional risk minimization activities: • Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card)
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

CNS=central nervous system; FAQ=frequently asked question; FDA=Food and Drug Administration (US); GHB=gamma-hydroxybutyrate; HCP=health care professional; PIL=patient information leaflet; SmPC=summary of product characteristics

Table 2–5: Summary of important identified risks - Dependence/withdrawal

Important identified risks - Dependence/withdrawal	
Evidence for linking the risk to the medicine	There have been case reports of dependence after illicit use of GHB at frequent repeated doses (18 to 250g/day) in excess of the therapeutic dose range. Whilst there is no clear evidence of emergence of dependence in patients taking Xyrem at therapeutic doses, this possibility cannot be excluded. The discontinuation effects of Xyrem have not been systematically evaluated in controlled clinical trials in patients with narcolepsy. In some patients, cataplexy may return at a higher frequency on cessation of Xyrem therapy, however, this may be due to the normal variability of the disease. Although the clinical trial experience with Xyrem in narcolepsy/cataplexy patients at therapeutic doses does not show clear evidence of a withdrawal syndrome, in rare cases, events such as insomnia, headache, anxiety, dizziness, sleep disorder, somnolence, hallucination, and psychotic disorders were observed after GHB discontinuation (UCB SmPC, 2018). Illicit use of GHB is often seen in teenagers and young adults (Oyemade, 2012). Acute withdrawal of GHB with its cardiovascular and delirant symptoms is of particular importance for child and adolescent psychiatrists. Acute GHB-withdrawal syndrome can present with symptoms close to psychotic episodes or acute alcohol withdrawal (Zepf et al, 2009).
Risk factors and risk groups	McDonough and his colleagues found that frequent dosing was a key feature of dependent use. An 8-hourly dosing was found to be the minimum frequency associated with withdrawal delirium. The minimum daily GHB dose associated with withdrawal was 18g (about 9 teaspoons-full; McDonough et al, 2004). This is in accordance with the SmPC (UCB SmPC, 2018).
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine Additional risk minimization activities: • Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card) • Controlled distribution
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

FAQ=frequently asked question; GHB=gamma-hydroxybutyrate; HCP=healthcare professional; PIL=patient information leaflet; SmPC=summary of product characteristics

Table 2–6: Summary of important identified risks - Overdose

Important identified risks – Overdose	
Evidence for linking the risk to the medicine	Information about signs and symptoms associated with overdosage with Xyrem is limited. Most data derives from the illicit use of GHB. Xyrem is the sodium salt of GHB. Events associated with withdrawal syndrome have been observed outside the therapeutic range. Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even with impaired consciousness), diaphoresis, headache, and impaired psychomotor skills may be observed. Blurred vision has been reported. An increasing depth of coma has been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported. There are reports of compromise in the rate and depth of respiration and of life-threatening respiratory depression, necessitating intubation and ventilation. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact. Bradycardia has been responsive to atropine intravenous administration.
Risk factors and risk groups	Dependence to Xyrem may be risk factors for the administration of an overdose of the product. Depressed patients with tendency for suicidal may be at more risk for administering an intentional overdose.
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine • Update to Xyrem syringe to add new graduations of 0.5g and 1.0g below the current markings • Update to Xyrem syringe to add a second scale along one side of Xyrem syringe with graduations of 0.2g to ensure correct dosing when combined with valproate Additional risk minimization activities: • Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card) • Controlled distribution system
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

AE=adverse event; FAQ=frequently asked question; GHB=gamma-hydroxybutyrate; HCP=healthcare professional; PIL=patient information leaflet; SmPC=summary of product characteristics

Table 2–7: Summary of important identified risks - Misuse/abuse

Important identified risks - Misuse/abuse	
Evidence for linking the risk to the medicine	The active substance of Xyrem is sodium oxybate, which is as the sodium salt of GHB, a CNS depressant active substance with well-known abuse potential. A number of studies have looked at different associations between symptoms of narcolepsy and impulsiveness, which suggest an increased probability to engage in risk-taking behavior, such as substance abuse (AAC, 2018). According to the Substance Abuse and Mental Health Services Administration, the rate of persons aged 12 or older who had substance dependence or abuse in 2012 was 8.5% which was similar to the rate in each year from 2007 through 2010 (between 8.8 to 9.0%), but higher than 8.0% in 2011 (Substance Abuse and Mental Health Services Administration, 2013).
Risk factors and risk groups	There are certain individuals who are believed to be at increased risk of abusing GHB. Athletes, body builders, gymnasium members, models, disk jockeys, ravers, frequent travelers across different time zones, and employees who are subject to regular drug testing, among others (Gonzalez et al, 2005). Other risk factors include those associated with drug abuse in general, eg, previous history of drug abuse, family history of drug addiction, male gender, psychiatric problems and socio-economic conditions.
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine Additional risk minimization activities: • Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card) • Controlled distribution system
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

AAC=American Addiction Centers; CNS=central nervous system; FAQ=frequently asked question; GHB=gamma-hydroxybutyrate; HCP=healthcare professional; PIL=patient information leaflet; SmPC=summary of product characteristics

Table 2–8: Summary of important identified risks - Diversion/criminal use

Important identified risks - Diversion/criminal use	
Evidence for linking the risk to the medicine	The potential for diversion and criminal use of Xyrem may have legal and social implications. Psychological traumatism and impact on body integrity for victims in case of sexual abuse.

Table 2–8: Summary of important identified risks - Diversion/criminal use

Important identified risks - Diversion/criminal use	
Risk factors and risk groups	Personal and familial history of drug abuse and a history of criminal behavior are known risk factors of drug diversion (Walker and Webster, 2012).
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine Additional risk minimization activities: • Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card) • Controlled distribution system
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

FAQ=frequently asked question; HCP=healthcare professional; PIL=patient information leaflet; SmPC=summary of product characteristics

Table 2–9: Summary of important identified risks - Depression/suicidality

Important identified risks - Depression/suicidality	
Evidence for linking the risk to the medicine	The emergence of depression when patients are treated with Xyrem requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored especially carefully for the emergence of depressive symptoms while taking Xyrem. In the general population, the pediatric population is not more at risk than other subpopulations (WHO, 2018). However, in narcolepsy population, the risk could be higher (Drapeau, 2017; Ruoff, 2017).
Risk factors and risk groups	Risk factors for depression and suicidality include mental disorders substance abuse and life circumstances (WHO, 2016). Educational achievement was inversely associated with risk of suicide attempt (Petronis et al, 1990).
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine Additional risk minimization activities: • Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card)

Table 2–9: Summary of important identified risks - Depression/suicidality

Important identified risks - Depression/suicidality	
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

FAQ=frequently asked question; HCP=healthcare professional; PIL=patient information leaflet; SmPC=summary of product characteristics

Table 2–10: Summary of important identified risks – Convulsion

Important identified risks – Convulsion	
Evidence for linking the risk to the medicine	Seizures have been observed in patients treated with Xyrem. In patients with epilepsy, the safety and efficacy of Xyrem has not been established, therefore use is not recommended (UCB SmPC, 2018).
Risk factors and risk groups	Acute symptomatic seizures predominate in men, in the youngest age class and in the elderly (Hauser and Beghi, 2008). In patients with epilepsy, the safety and efficacy of Xyrem has not been established, therefore use is not recommended (UCB SmPC, 2018).
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine • Update to Xyrem syringe to add new graduations of 0.5g and 1.0g below the current markings • Update to Xyrem syringe to add a second scale along one side of Xyrem syringe with graduations of 0.2g to ensure correct dosing when combined with valproate Additional risk minimization activities: • Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card)
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

FAQ=frequently asked question; HCP=healthcare professional; PIL=patient information leaflet; SmPC=summary of product characteristics

Table 2–11: Summary of important identified risks – Psychosis

Important identified risks – Psychosis	
Evidence for linking the risk to the medicine	Neuropsychiatric events include psychosis, paranoia, hallucinations, and agitation. The emergence of thought disorders including thoughts of committing violent acts (including harming others) and/or behavioral abnormalities when patients are treated with Xyrem requires careful and immediate evaluation (UCB SmPC, 2018).
Risk factors and risk groups	Risk factors for psychosis include concomitant psychiatric disorder(s), recreational drug use, and pregnancy. In one primary care population study, psychotic symptoms were most commonly associated with depressive, anxiety, and panic disorders (42.4%, 38.6%, and 24.8%, respectively), followed by substance abuse (13.8%) (Olfson et al, 2002).
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine Additional risk minimization activities: • Educational materials (HCP Checklist, Frequently Asked Questions [FAQs] for patients, Patient instructions for Administration of sodium oxybate, Guide for Pediatric Patients and Caregivers, and Patient Alert Card)
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

FAQ=frequently asked question; HCP=healthcare professional; PIL=patient information leaflet; SAE=serious adverse event; SmPC=summary of product characteristics

Table 2–12: Summary of important potential risks - Aggravation of cardiac failure due to additional sodium load

Important potential risks - Aggravation of cardiac failure due to additional sodium load (due to component of the drug)	
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine Additional risk minimization activities: • None
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

Table 2–12: Summary of important potential risks - Aggravation of cardiac failure due to additional sodium load

Important potential risks - Aggravation of cardiac failure due to additional sodium load (due to component of the drug)

Table 2–13: Summary of important potential risks - Fluid retention in patients with compromised renal function due to additional sodium load

Important potential risks - Fluid retention in patients with compromised renal function due to additional sodium load (due to the component of the drug)	
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine Additional risk minimization activities:
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

Table 2–14: Summary of missing information - Long-term impact on children and adolescents, including growth and neurocognitive development

Missing information - Long-term impact on children and adolescents, including growth and neurocognitive development	
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine Additional risk minimization measures: • Educational materials (healthcare provider checklist)
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.
PIL=patient information leaflet; SmPC=summary of product characteristics	

Table 2–15: Summary of missing information - Use in pregnancy

Missing information - Use in pregnancy	
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine Additional risk minimization measures: • None
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

Table 2–16: Summary of missing information - Use in elderly patients

Missing information - Use in elderly patients	
Risk minimization measures	Routine risk minimization activities: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine Additional risk minimization measures: • None
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

Table 2–17: Summary of missing information - Use in patients with BMI ≥40kg/m^2

Missing information - Use in patients with BMI ≥40kg/m^2	
Risk minimization measures	Routine risk minimization measures: • Summary of Product Characteristics and Patient Information Leaflet and prescription-only medicine Additional risk minimization measures: • None
Additional pharmacovigilance activities	French monitoring program (postauthorization safety study C00304) See Section 2.3 of this summary for an overview of the postauthorization development plan.

BMI=body mass index

2.3 Postauthorization development plan

2.3.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Xyrem.

2.3.2 Other studies in post-authorization development plan

2.3.2.1 French monitoring program (PASS C00304)

Purpose of the study: To assure safe prescription and distribution of Xyrem; traceability of Xyrem and patients; and encourage spontaneous notification of supposed adverse effects and cases of abuse or misuse, dependence, and diversion of Xyrem.

RMP PART VII: ANNEXES

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

UCB Global DS database #: **UCB LAM ID #:**

Growth disorder: DIAGNOSIS *(incl. presumptive and differential)*:

_____

Age at diagnosis of narcolepsy:_____

Age at Xyrem treatment onset: _____

Growth disorder: signs and symptoms:

- Please describe or append any patient growth curve and all developmental milestones datapoints available:

  _____

  _____

- If not available, please provide:

	At any developmental milestone data	At Xyrem treatment initiation	At the time of the event notification
Height	**Date: _____** **Value: _____cm** **Date: _____** **Value: _____cm** **Date: _____** **Value: _____cm**	**Date: _____** **Value: _____cm**	**Date: _____** **Value: _____cm**
Weight	**Date:_____** **Value: _____Kg** **Date:_____** **Value: _____Kg** **Date:_____** **Value: _____Kg**	**Date:_____** **Value: _____Kg**	**Date:_____** **Value: _____Kg**

Pubertal status (Tanner stage)	**Date:**_____ **Status:**_____ **Date:**_____ **Status:**_____	**Date:**_____ **Status:**_____ _____	**Date:**_____ **Status:**_____ _____

- Growth disorder outcome: (resolved, resolving, not resolved, resolved with sequelae (please specify), fatal or unknown): _____

Growth disorder: Diagnostic procedures:

Please specify performed tests/ procedures. Provide below or enclose a copy of diagnostic procedure findings and lab reports. ***If a specialist or generalist pediatrician report is available, please append to this form.***

- Height below 3rd percentile of the age and gender-matched population? □ yes/□ no/□ unk. If yes please provide: _____
- Midparental height performed?□ yes/□ no/□ unk. If yes please provide: _____
- Bone age test performed?□ yes/□ no/□ unk. If yes please provide: _____
- Hormonal testing performed? If yes which ones and what were the results:

  _____

  _____
- Genetic testing performed? □ yes/□ no/□ unk. If yes please specify and provide the results:

  _____
- Features suggesting underlying systemic condition?□ yes/□ no/□ unk. If yes please specify:

  _____
- Other (specify):_____

Growth disorder: risk factors

- Age of diagnosis of narcolepsy:_____
- Age of puberty (breast growth in girls; testis >4mm in boys): _____
- Age of menarche (girls only):_____
- Was there any developmental milestone not reached at any assessment timepoint? □ yes/□ no/□ unk. If yes please specify: _____

- Is there known familial short stature □ yes/□ no/□ unk.
- Is there known familial pubertal delay (mother) □ yes/□ no/□ unk. If yes please specify: _____
- Is there known familial pubertal delay (father) □ yes/□ no/□ unk. If yes please specify: _____
- Is there known familial pubertal delay (siblings) □ yes/□ no/□ unk. If yes please specify: _____
- Does the patient suffer from a systemic disease or malnutrition. □ yes/□ no/□ unk. If yes, please specify: _____
- Does the patient suffer from congenital problem affecting growth? □ yes/□ no/□ unk. If yes please specify: _____
- Does the patient suffer from an endocrine disease? □ yes/□ no/□ unk. If yes please specify: _____
- Has the patient been prescribed/taken methylphenidate/other CNS stimulant medication? □ yes/□ no/□ unk. If yes please specify: _____
- Other (specify): _____

Growth disorder: Event treatment:

Please specify the therapeutic measures taken to treat the event

- Medications, specify:_____
- Treatment procedures, specify: _____
- Other measures, specify:_____

	Standard Medical Follow up Query (SMFQ) – Neurocognitive disorder	**Sop-af- V** **Associated to sop-ai-014552** **Page 1 of 2**

UCB Global DS database #: **UCB LAM ID #:**

Neurocognitive Disorder DIAGNOSIS *(incl. presumptive and differential)***:**

_____

Age at diagnosis of narcolepsy: _____
Age at Xyrem treatment onset: _____

Neurocognitive disorder: succinct details, signs and symptoms:

- Provide patient's (neuro)developmental chronological milestones, including the disorder of interest:
  _____
  _____
- Describe evolution of the neurocognitive disorder before Xyrem treatment initiation (if applicable):
  _____
  _____
- Describe evolution of the neurocognitive disorder under Xyrem:
  _____
  _____
- Neurocognitive disorder outcome: (resolved, resolving, not resolved, resolved with sequelae (please specify), fatal or unknown):_____

Neurocognitive disorder: diagnostic procedures:

Please specify performed tests/ procedures based on which the diagnosis was made. Provide below or enclose a copy of diagnostic procedure findings and lab supportive of the diagnosis.
If a specialist or generalist pediatrician report is available, please append to this form

_____
_____
_____

Neurocognitive disorder : risk factors:

- Does the patient have any other history of neurocognition/neurobehavioral issue before starting Xyrem? □ yes/□ no/□ unk. If yes, provide the details:

  _____

  Is there an established diagnosis of any neurocognition/neurobehavioral disease before starting Xyrem?□ yes/□ no/□ unk. If yes, provide the details:_____
- Is there a relevant family history to the referenced disease?□ yes/□ no/□ unk. If yes please specify:

  _____
- Has the patient ever experienced a blunt trauma to the head? If yes, was it further investigated at the time of occurrence?□ yes/□ no/□ unk. If yes please specify circumstances and date as well as investigations results if any: _____
- Has the patient ever experienced a severe systemic illness? □ yes/□ no/□ unk. If yes please specify: _____
- Has the patient experienced any perinatal event (asphyxia, infection, other)?□ yes/□ no/□ unk. If yes please specify: _____
- Has the patient ever experienced a central nervous system infection? □ yes/□ no/□ unk. If yes please specify: _____

Neurocognitive disorder: Event treatment:

Please specify the therapeutic measures taken to treat the event

- Medications, specify:
- Treatment procedures, specify:
- Other measures, including specific medical follow-up, please specify:

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Approved key messages of the additional risk minimization measures

Educational material:

- **Healthcare provider checklist**

Healthcare professionals should use the checklist when first prescribing sodium oxybate and at subsequent visits. The checklist serves to remind the prescriber to check the patient's medical history and to counsel the patient/caregiver on proper dosing and on side effects. All important identified risks are addressed.

- Verification if patient meets criteria for appropriate use of Xyrem
- Assessment of medical history (eg, depression/suicidality)
- Review of patient's concomitant medications and adjustment as necessary
- Counseling patient on specific situations and the need to seek medical advice where appropriate (eg, depression/suicidality)
- Explain conditions of safe storage of Xyrem
- Instruct patients on proper dosing and use of the dosing syringe
- Instruct patients regarding the importance of reading the PIL, and in particular to the section on the dose adjustment period
- Provide the patient with the following educational materials

In order to address the safety concern of long-term impact in children and adolescents, including growth and neurocognitive development, the healthcare provider checklist also includes a checklist for pediatric patients. This checklist serves to remind the prescriber to assess the patient's height, weight, social and psychiatric behavior, and learning performance, and report any event that is suggestive of a negative impact on growth and neurocognitive development.

- **Frequently asked questions for patients**

Healthcare professionals will provide this to each patient/caregiver. Frequently asked questions (FAQ) provides information on the disease (eg, symptoms, prevalence) and the treatment (eg, administration, important side effects) of sodium oxybate and the importance of getting medical help immediately when needed. All important identified risks are addressed.

Examples:

- What are the primary/other symptoms of narcolepsy?
- How common is narcolepsy?
- At what age do people get narcolepsy?
- What is the cause of narcolepsy?
- What is Xyrem?

- May I drink alcohol while I am taking Xyrem?
- What are the serious side effects of Xyrem?
- Can Xyrem be abused? Is it addictive?
- Why do I have to be in bed, ready to sleep, before taking Xyrem?
- Can I use Xyrem if I am pregnant or breastfeeding?

Warnings:

- Do not share Xyrem with anyone.
- Use only the dose your doctor prescribed. If you believe the dose needs to be changed, contact your doctor.
- Do not take Xyrem if you are less than 7 years old.
- Always respect a 2-hour interval between the last meal and the intake of Xyrem.
- Always keep Xyrem, and its syringe, in its original package, in a safe location.
- Keep Xyrem out of the reach of children.
- If you experience any unusual symptoms, like strange thoughts, including thoughts of hurting others, whilst taking Xyrem, inform your doctor straight away.
- Return any unused product to your pharmacy.

- **Patient alert card**

This is a wallet-sized card that patients should keep with them at all times. The card warns of risks and explains when to seek emergency help straight away (eg, overdose) and provides important safety information for treating physicians.

- **Patient instructions for administration of sodium oxybate**

This will be provided by the prescriber and provides instructions on how to administer the right dose of sodium oxybate.

Step-by-step guide: Exact steps on how to handle the provided material and how to prepare doses are described.

- **Guide for pediatric patients and their caregivers**

Provides important information about the safe use and handling of sodium oxybate by caregivers. All important identified risks are addressed.

"WARNING: XYREM can cause serious side effects. Your child should not drink alcohol or take other medicines that cause sleepiness.

XYREM is a prescription medicine used to treat the following symptoms in people who fall asleep frequently during the day, often at unexpected times:

- Excessive daytime sleepiness (Narcolepsy)
- Suddenly weak or paralyzed muscles when they feel strong emotions (cataplexy)

WHAT ARE THE POSSIBLE SIDE EFFECTS OF XYREM?

XYREM can cause serious side effects, including breathing problems (slower breathing, trouble breathing, and short periods of no breathing while asleep), mental health problems (confusion, seeing or hearing things that are not real, unusual or disturbing thoughts, feeling anxious or upset, depression, thoughts of suicide), and sleepwalking. If your child has any of these side effects, call your child's healthcare provider right away.

The most common side effects with XYREM in pediatric patients are bedwetting, nausea, throwing up, and weight loss. Side effects may increase with higher doses.

These are not the only possible side effects with XYREM. If you or your child are worried about any possible side effects with XYREM, talk with your child's healthcare provider or the pharmacist.

IMPORTANT INFORMATION ABOUT XYREM INCLUDES THE FOLLOWING:

- When taking XYREM, your child should not drink alcohol or take other medicines that may slow his or her breathing or mental activity or make him or her sleepy. Your child could have serious side effects.
- XYREM can cause serious side effects, including slow breathing or changes in alertness. Call your child's doctor right away if your child has any of these serious side effects.
- XYREM has the potential for abuse and dependence. When XYREM is stopped, especially when it is stopped suddenly, withdrawal symptoms can develop, such as insomnia, headache, anxiety, dizziness, sleep disorder, sleepiness, somnolence, hallucination, and abnormal thinking.
- Whilst the doctor is adjusting the dose which may take a number of weeks, parent/caregivers should carefully monitor the child's breath during the first 2 hours after XYREM intake to assess if there is any abnormality in breathing, for example stoppage of breathing for short periods while sleeping, noisy breathing, and bluish color of the lips and face. If abnormality in breathing is observed, medical support should be sought and the doctor should be informed as soon as possible. If any abnormality is noted after the first dose, the second dose should not be administered. If no abnormality is noted the second dose can be administered. The second dose should not be given earlier than 2.5 hours or later than 4 hours after the first dose.
- Patients usually fall asleep in about 5 to 15 minutes, although some patients have reported falling asleep more quickly (without first feeling drowsy) and others take more time. The time that it takes to fall asleep might be different from night to night. You should give each dose of XYREM while your child is sitting up in bed and have your child lie down immediately after. The first dose should be given at bedtime and the second should be given at the time prescribed by your healthcare provider, 2½ to 4 hours after the first dose. You may need to set an alarm to awaken to give the second dose. For children who sleep longer than 8 hours but less than 12 hours, the first dose may be given after the child has been sleeping for 1 to 2 hours. If in doubt about administration of a dose, do not re-administer the dose to reduce the risk of overdose.

- Your child should not do anything that requires him or her to be fully alert for at least the first 6 hour s after taking XYREM. When your child first starts taking XYREM, or when the dose has been increased, you and your child will need to be careful until you know how XYREM affects him or her.
- Keep XYREM out of the reach of children and pets. Get emergency medical help right away if a child who has not been prescribed XYREM drinks XYREM.
- Report all side effects to your child's healthcare provider, including behavioral changes, especially in school.

WHAT WILL YOU FIND IN THIS GUIDE?

This guide answers important questions about how to use XYREM properly, how to store it safely, and how to get your child's XYREM. It also gives you important information about XYREM."

Controlled distribution system:

Sodium oxybate is a controlled substance delivered upon prescription.

Objectives/Rationale for the additional risk minimization activity:

The steps described in this section are intended to allow sodium oxybate to reach the intended population of narcolepsy patients while minimizing the risk of sodium oxybate being diverted by those seeking to misuse it (see Important Identified Risks of Dependence/Withdrawal, Misuse/Abuse and Diversion/Criminal use): In the frame of the European pharmaceutical distribution system for a controlled substance, a distribution model has been established by the MAH that enhances the existing controls for sodium oxybate.

Target audience and planned distribution path:

1. Whole distribution chain of sodium oxybate:
   - Shipments of sodium oxybate unlabeled bottles between US-based contract manufacturing organization (CMO) and UCB Pharma Ltd.'s UK storage facility
   - From the UCB Pharma Ltd.'s storage facility, the bottles are sent to a UK-based CMO, who performs the transformation of sodium oxybate bulk unlabeled product into sodium oxybate country-specific labeled and packed product. Post-transformation, the finished goods are shipped back to the UCB Pharma Ltd.'s storage facility.
   - Sodium oxybate is shipped from UCB Pharma Ltd.'s UK finished goods storage facility to UCB SA's Belgium finished goods storage facility, then to EU-based affiliate warehouses.
   - Shipments of sodium oxybate country-specific labeled and packed product from UCB's EU-based affiliate warehouses to third party logistics and affiliate.
   - Since sodium oxybate is a controlled drug, export licenses and import licenses are needed for all the shipments from the US to the UK, from the UK to the EU, within the EU, and to Switzerland, Turkey, the UK, and Australia.
2. Summary of the full end-to-end process review and mapping:

- Standard operating procedures on global distribution processes govern the ocean shipments of bulk unlabeled product between the US and the UK.
- Internal corporate audit is performed by the Quality Assurance department on all activities handled by the MAH in the UK-based CMO with appropriate follow-up of corrective action preventive action.
- A track-and-trace report is maintained showing full data reconciliation for all batches originally shipped from the US and finally delivered to local markets in Europe. These sets of reports are maintained showing every movement (import/export) of Xyrem products at any stage of its distribution versus its import and/or export license, which have been granted by the Health Authorities of the country from which the movement is initiated. Additionally, the batch reconciliation is available in the UCB Enterprise Resource Planning (ERP) System.