LEADING ARTICLE

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# The Xyrem® Risk Management Program

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## Abstract

Sodium oxybate, also known as gamma-hydroxybutyric acid (GHB), was discovered in 1960 and has been described both as a therapeutic agent with high medical value and, more recently, a substance of abuse. The naturally occurring form of this drug is found in various body tissues but has been studied most extensively in the CNS where its possible function as a neurotransmitter continues to be studied. Sodium oxybate has been approved in different countries for such varied uses as general anaesthesia, the treatment of alcohol withdrawal and addiction, and, most recently, cataplexy associated with narcolepsy.

During the 1980s, easy access to GHB-containing products led to various unapproved uses, including weight loss, bodybuilding and the treatment of sleeplessness, sometimes with serious long-term effects. The availability of these unapproved and unregulated forms of the drug led to GHB and its analogues[1] being popularised as substances of abuse and subsequent notoriety as agents used in drug-facilitated sexual assault, or 'date rape', eventually leading to the prohibition of GHB sales in the US.

Legal efforts to control the sale and distribution of GHB and its analogues nearly prevented the clinical development of sodium oxybate for narcolepsy in the US. However, following extensive discussions with a variety of interested parties, a satisfactory solution was devised, including legislative action and the development of the Xyrem® Risk Management Program.

Amendments to the US Controlled Substances Act made GHB a schedule I drug, but also contained provisions that allow US FDA-approved products to be placed under schedule III. This unique, bifurcated schedule for sodium oxybate/GHB allowed the clinical development of sodium oxybate to proceed and, in July 2002, it was approved by the FDA as an orphan drug for the treatment of cataplexy in patients with narcolepsy as Xyrem® (sodium oxybate) oral solution.

To promote the safe use of sodium oxybate, as well as alleviate concerns over possible diversion and abuse following product approval, a proprietary restricted drug distribution system was created, called the Xyrem® Success Program℠. Components of the programme include a centralised distribution and dispensing system, a physician and patient registry, compulsory educational materials for patients and physicians, a specially trained pharmacy staff, a method for tracking

1 In this article, the term analogue refers to substances that are either structurally related to, or have pharmacological activity similar to GHB.

prescription shipments, and an initial post-marketing surveillance programme. The system has created a unique opportunity to provide both physician and patient education and ongoing patient counselling, promoting greater drug safety and enhanced patient compliance.

## 1. Introduction

In 1994, the National Organization for Rare Disorders (NORD) and the US FDA Office of Orphan Products Development each approached the newly formed Orphan Medical, Inc., suggesting the development of a novel medication for the treatment of narcolepsy. This medication, identified chemically as the sodium salt of gamma-hydroxybutyrate (GHB) and generically as sodium oxybate, was a known CNS depressant shown to have therapeutic promise for the treatment of cataplexy, a symptom of narcolepsy. As the development of this drug was consistent with its corporate mission, the company agreed to take on this challenge.

The clinical development of sodium oxybate soon became highly controversial in the US due to growing concerns regarding the abuse of previously unregulated GHB and related analogue and precursor compounds. By this time, GHB had gained notoriety as a 'club drug', reportedly producing effects of alcohol-like euphoria, disinhibition and sexual arousal. It was also being used by body builders for alleged anabolic effects and by others as a 'natural' sleep aid. GHB abuse was becoming associated with serious adverse effects including dependence, overdose and death. In addition, GHB and its analogues were gaining notoriety as agents involved in some cases of drug-facilitated sexual assault. Because of these concerns, the FDA banned all GHB sales in 1990. In 1999, following a subsequent increase in the abuse of GHB analogues, dietary supplements containing the GHB analogues gamma-butyrolactone (GBL) and 1,4-butandiol (1,4-BD) were also banned.

Against this background of increasing abuse and misuse of GHB, various stakeholders (listed in table I) were understandably concerned about the potential for diversion of sodium oxybate following approval. Indeed, the level of GHB abuse had attracted national attention and eventually led to a Congressional Hearing in July 1998 and a proposal to classify GHB as schedule I substance, which would have greatly impeded further clinical development of sodium oxybate.

It quickly became clear that the continued development of sodium oxybate required a solution that would address the concerns of all stakeholders. To that end, input from interested parties was proactively sought for the purpose of developing a comprehensive framework of risk management that would address illicit GHB abuse yet permit the continued clinical development of sodium oxybate and subsequently encourage appropriate medical use. To be successful, this system would require specific legislative, operational and educational components.

This article describes the development of Xyrem® (sodium oxybate) oral solution, the Xyrem® Risk Management Program and also provides a history of the pharmacology and therapeutic use of sodium oxybate and the abuse and misuse of GHB and its related analogues.

**Table I.** Stakeholders who provided input on the development of the Xyrem® Risk Management Program

| |
|---|
| Drug abuse experts |
| Criminal prosecutors |
| Forensics experts |
| Rape crisis centres, victim advocates and sexual assault investigators |
| Experts in drug abuse trends |
| Legislative personnel |
| Field law enforcement including drug recognition experts |
| Emergency room physicians, toxicologists and poison control centres |
| The National Association of State Controlled Substances Authorities (NASCSA) |
| The National Association of Drug Diversion Investigators, Inc. (NADDI) |
| Narcolepsy patients and narcolepsy support groups |
| Physicians who are experts in treating narcolepsy |

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## 2. Gamma-Hydroxybutyrate (GHB)

### 2.1 Chemical and Physical Properties

Sodium oxybate is also known by the chemical synonyms GHB and sodium 4-hydroxybutyric acid. It has the molecular formula $C_4H_7NaO_3$ and a molecular weight of 126.09 g/mol. Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. It may be easily synthesised from the precursor compound GBL.

### 2.2 Neurotransmitter Properties

Sodium oxybate was discovered in 1960 by Henri Laborit[1] while searching for therapeutically useful analogues of gamma-aminobutyrate (GABA), an inhibitory neurotransmitter that would readily cross the blood-brain barrier. It was later discovered to be a naturally occurring substance in the mammalian brain[2] and since that time, researchers have endeavoured to determine its function in the physiology of the CNS. Mounting evidence suggests that it may be a neurotransmitter or neuromodulator acting at specific GHB binding sites.[3]

The *in vivo* synthesis occurs by the metabolism of GABA to succinic semialdehyde and reduction to GHB. Conversely, GHB metabolism involves oxidative conversion to succinic semialdehyde and then succinic acid, which enters the Krebs cycle. Thus, GHB is metabolised to carbon dioxide and water, leaving no active metabolites. Minor routes of GHB metabolism include either conversion to GABA or β-oxidation to carbon dioxide.[3]

Following neuronal synthesis, GHB is located within discrete storage vesicles where it is subsequently released in a calcium-dependent manner and reuptake occurs via a sodium-dependent, high-affinity membrane transport system. GHB binds to high- and low-affinity binding sites located in neural tissue that have high specificity for GHB and appear to be associated with G-protein-linked second messenger systems.[3]

Although the specific function of naturally-occurring GHB beyond possible neuromodulation is currently unknown, the administration of exogenous GHB results in several actions within the CNS, including a dose-dependent increase in dopamine concentration, increased serotonin turnover,[3] and the release of growth hormone.[4] Electrophysiology studies indicate that it has an inhibitory effect in the substantia nigra and neocortex areas of the brain.[3]

Sodium oxybate also produces significant effects on sleep. Polysomnography (PSG) studies in normal subjects,[5] in non-narcoleptic patients with depression[6] and in postsurgical patients[7] have demonstrated that the nocturnal administration of sodium oxybate increases slow-wave sleep, which occurs during sleep stages 3 and 4. In addition, PSG has been used in several studies to assess the effect of sodium oxybate in narcoleptic patients. These data also indicate that the administration of sodium oxybate produces dose-related increases in stage 3 and 4 sleep compared with baseline.[5,8-10] This is in contrast to commonly used hypnotics, which lack this beneficial effect.

## 3. Clinical Use of GHB

During the past 40 years, GHB has been investigated as a therapeutic agent for a variety of disorders, ranging from depression and anxiety to fibromyalgia.[11] However, it has only been approved for the following uses in the countries indicated.

Currently, GHB is approved for anaesthetic use in France and Italy, although the use of this agent for anaesthesia is declining as GHB-induced anaesthesia is associated with myoclonus and, compared with newer agents, has a relatively slow onset and offset of action.[11] GHB is also marketed in Italy as a treatment for alcohol withdrawal[12] and maintenance of alcohol abstinence[13] (Alcover®[2], CT Laboratorio Farmaceutico, Italy) as it appears to be an effective agent for both. Investigations into the use of GHB for the treatment of opiate withdrawal and long-term abstinence from opiates also show promising results.[13]

**2** The use of trade names is for product identification purposes only and does not imply endorsement.

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### 3.1 Narcolepsy

Narcolepsy is a rare sleep disorder (estimated prevalence of approximately 0.05%) characterised by the primary symptoms of excessive daytime sleepiness, fragmented night-time sleep and abnormal manifestations of rapid eye movement (REM) sleep such as cataplexy and other REM sleep-related phenomena including periods of paralysis and/or vivid hallucinations while falling asleep or upon awakening.[14] Cataplexy is defined as sudden episodes of bilateral skeletal muscle weakness stimulated by strong emotion and is the second most common and most specific symptom of narcolepsy, affecting up to 93% of patients with narcolepsy.[15] The most common emotional trigger is laughter or mirth, but it may also be caused by anger, embarrassment or even sexual arousal.[16] Most of these symptoms, including cataplexy, are believed by some to be the outward manifestations of normal REM sleep, inappropriately intruding into periods of wakefulness.[14]

The use of GHB for the treatment of narcolepsy was suggested by observations during GHB-induced anaesthesia where it was noted that GHB produced a state of sleep closely resembling natural sleep. Beginning in the 1970s, Broughton and Mamelak[17] began administering GHB to their narcoleptic patients at bedtime to alleviate their disrupted night-time sleep. Surprisingly, the nightly administration of GHB also brought about a significant improvement in their daytime symptoms, most notably cataplexy. This and other trials demonstrated that the nightly administration of GHB increased total nocturnal sleep time, decreased night-time awakenings and increased the total duration of stage 3 and 4 sleep. These improvements in nocturnal sleep were associated with improvements in daytime sleep attacks, cataplexy, sleep paralysis and hypnagogic hallucination.[8,17]

#### *3.1.1 Efficacy of Sodium Oxybate for the Treatment of Cataplexy*

Currently, sodium oxybate is approved in the US for the treatment of cataplexy associated with narcolepsy. The safety and efficacy of sodium oxybate for this indication was established with data obtained from two blinded randomised placebo-controlled studies: trial 1 and trial 2. Data from trial 1 indicated that the administration of sodium oxybate at doses of 3.0–9.0g per night for 4 weeks resulted in a significant, dose-related median reduction in cataplexy attacks of up to 69% ($p = 0.0016$).[18]

These changes were accompanied by meaningful clinical benefit. In blinded investigator ratings of their narcolepsy disease status, 80% of patients taking nightly sodium oxybate 9.0g were rated as 'very much improved' or 'much improved' compared with 32% of placebo patients ($p = 0.0014$).[18] Data from trial 2,[19] and other open-label studies,[9,17] indicates that anti-cataplectic activity was safely and effectively maintained long-term.

Sodium oxybate clinical trials also assessed several secondary efficacy measures including daytime sleepiness, the number of sleep attacks and nocturnal awakenings. These results suggest that, in general, reductions in cataplexy were associated with improvements in other narcolepsy symptoms.[18] Ongoing clinical trials seek to confirm the efficacy of sodium oxybate on these secondary conditions, especially the symptom of daytime sleepiness, using objective measures.

#### *3.1.2 Safety of Sodium Oxybate for the Treatment of Cataplexy*

Analysis of safety data from trial 1 indicate that the adverse events reported more frequently than with placebo were dizziness (23%), headache (20%), nausea (16%), pain (12%), somnolence (9%), sleep disorder (9%), confusion (7%), infection (7%), vomiting (6%) and urinary incontinence (5%).[18] The long-term, open-label trials showed a similar safety profile.[9,17] Data from trial 2 suggest the incidence of dizziness, nausea, urinary incontinence (enuresis) and vomiting may be dose related. Importantly, there was no evidence of tolerance or dependence in patients taking sodium oxybate for up to 12 months.[19]

Of 136 patients who entered trial 1, ten withdrew from the study because of adverse events, including one patient on placebo.[18] There were no deaths; however, there was one serious adverse event described as an acute confusional state. Similarly,

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there were no deaths in trial 2 and one serious adverse event consisting of a fall, which resulted in a fractured wrist in a patient who was taking placebo.[19] All 55 patients who were enrolled completed the trial.

#### 3.1.3 Xyrem® (Sodium Oxybate) Oral Solution

Xyrem® (sodium oxybate) is provided as an aqueous solution containing sodium oxybate at a 500 mg/mL concentration. Each millilitre of the product contains sodium 91mg. To enhance safety of the product in the home, the bottle is secured with a child-resistant closure and a press-in bottle adaptor, to facilitate removal of drug with a measuring syringe and to prevent spillage. Because of the short duration of action, sodium oxybate is administered as two nightly doses. Both doses are prepared before bedtime and the first dose is taken while the patient is in bed and the second dose is taken while still in bed, 2.5–4 hours later. Sodium oxybate should not be taken with alcohol and must not be taken with other sedating medications. It is recommended that patients should not drive a car until 6 hours after the second dose of sodium oxybate.[20]

## 4. History of GHB Abuse

During the 1980s, GHB had been marketed in the US as a dietary supplement in health-food stores, training gyms and fitness centres. Anabolic benefits were allegedly produced by stimulating growth hormone release and it was used by body builders and for strength training. In addition, it was promoted as a 'natural' treatment for insomnia and to induce weight loss. Following reports of fatal overdoses among several body builders in California and Florida, all GHB sales were banned by the FDA in 1990.[21]

Unfortunately, these steps did little to curb the abuse of GHB. Restrictions placed on the sale of GHB by the FDA in 1990 and tighter state regulations led to an increase in illegally synthesised GHB and the use of so-called GHB analogues, such as GBL, 1,4-BD and most recently, gamma-valerolactone (GVL). Products containing these industrial compounds quickly became available through various sources including the internet. GBL was also sold over the counter in kit form with sodium hydroxide and instructions for the home synthesis of GHB.[22] As these analogues are converted to GHB *in vivo,*[23] the ingestion of GBL and 1,4-BD produces clinical manifestations similar to GHB ingestion although they may vary in potency and toxicokinetic properties.

By the mid-1990s, home-made and other illicit versions of GHB had already developed notoriety as a 'club drug' used at 'raves', or all-night dance parties.[24] Recreational users of the drug claimed to experience an alcohol-like euphoria, disinhibition and sexual arousal without unpleasant hang-over effects. Also, at this time, a number of GHB users were experiencing acute overdose, often a consequence of combining GHB with alcohol, which produces synergistic CNS depressant effects,[25] and other drugs.[26] Although direct comparisons between illicit GHB and sodium oxybate cannot be made, it is interesting to note that narcolepsy patients taking sodium oxybate immediately prior to retiring to sleep have not reported euphoric effects such as those seen with the abuse of GHB.

GHB was also being implicated in a number of sexual assault cases during this time and, like flunitrazepam (Rohypnol®, Roche), was being labelled as a 'date-rape' drug[27] in the US. Like many CNS depressants, GHB causes anterograde amnesia, especially when combined with alcohol, often leaving the victim unable to recall any details of the event.[22]

By the end of the decade, the serious consequences of chronic GHB abuse, including dependence and withdrawal, were being recognised.[28] Abuse over periods of time, ranging from 6 months to 2.5 years, has been reported, with some abusers allegedly escalating their daily GHB intake to approximately 150 g/day.[29,30] As a consequence of its short-half life, GHB dependence usually leads to almost continuous administration, with reported dosing frequency ranging from every 3 hours to every 30 minutes.

A distinct withdrawal syndrome following the abrupt cessation of illicit forms of GHB and its analogues has been reported, with symptoms of

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withdrawal occurring between 30 minutes and 3 hours following the last dose of GHB and persisting for 5–15 days. Symptoms have included nausea, vomiting, anxiety, confusion, tremor, insomnia, agitation, psychosis, auditory and visual hallucinations, tachycardia and hypertension. For these individuals, withdrawal symptoms may be severe and unresponsive to normally therapeutic amounts of benzodiazepines.[31] In contrast, the therapeutic administration of sodium oxybate for the treatment of cataplexy does not produce overt withdrawal symptoms after abrupt cessation following long-term use.[32]

By the late 1990s, there was a well established awareness of the scale and consequences of the abuse epidemic of GHB and related analogues. The increasing number of cases of surreptitious use, fatal overdose and drug-facilitated sexual assault prompted the Drug Enforcement Agency (DEA) to begin the formal rule-making process to control GHB as a schedule I controlled substance. In the US substances in schedule I are considered to have a high potential for abuse and no medical benefit (see table II).

A direct barrier to this proposal was the existence of an investigational new drug application for the use of sodium oxybate as a treatment of cataplexy in patients with narcolepsy, indicating a potential medical need. Thus, a solution was necessary that would permit the medical use of sodium oxybate while preventing GHB abuse.

**Table II.** Scheduling definitions established by the USC Controlled Substances Act of 1970 (modified from Section 812, Schedules of Controlled Substances[33])

| |
|---|
| **Schedule I** |
| The drug has a high potential for abuse, no currently accepted medical use or there is an unacceptable safety risk associated with the use of the drug |
| **Schedule II** |
| The drug has a high potential for abuse, but has a currently accepted medical use. Abuse may cause severe psychological or physical dependence |
| **Schedule III** |
| The drug has a currently accepted medical use and a potential of abuse less than drugs in schedules I and II. Abuse may lead to low to moderate physical dependence or high psychological dependence |
| **Schedule IV** |
| The drug has a currently accepted medical use and a low potential for abuse compared with drugs in schedule III. Abuse may cause limited physical dependence or psychological dependence compared with drugs in schedule III |
| **Schedule V** |
| The drug has a currently accepted medical use and a low potential for abuse compared with drugs in schedule IV. Abuse may cause limited physical dependence or psychological dependence compared with drugs in schedule IV |

## 5. Background for Risk Management

Coincident with the development of Xyrem® was the introduction and implementation of the risk management concept in the US.[34] Ultimately, the goal of risk management is to make certain that pharmaceutical products are being developed, tested, manufactured, labelled, prescribed, dispensed, and used in a way that maximises benefit and minimises risk. Risk management extends beyond the usual regulations on labelling, promotion and advertising to involve activities such as: mandated education to healthcare providers and patients; limited product distribution; post-marketing study requirements; a streamlined process for withdrawing the product from the market, if necessary; prescribing restrictions to specific patient populations; use of a physician registry; and/or establishment of a comprehensive method for overseeing the prescribing, dispensing, and use of the medication.[35]

To date, ten medications have been approved in the US with a risk management componant. Of these, thalidomide, transmucosal fentanyl citrate, mifepristone, alosetron, bosentan and sodium oxybate, have been granted marketing approval by the FDA that are contingent on the manufacturer engaging in required restricted distribution activities to assure safe use. Details about the risk-management components of these drugs are provided in table III.

Thus, the risk-management development model developed by the US FDA Task Force on Risk Management in 1999 (see figure 1) became a central element in the development of the Xyrem® Risk Management Program.

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**Table III.** US pharmaceuticals approved with risk-management components

| Trade name/manufacturer | Indication | Mandatory education | Patient agreement | Patient registry | Physician registry | Prescribing restrictions | Distribution restrictions | Mandatory monitoring | Post-marketing evaluation |
|---|---|---|---|---|---|---|---|---|---|
| Accutane® (isotretinoin) Hoffmann-La Roche, Inc. | Recalcitrant nodular acne | Yes | Yes | Yes | | | | Yes | Yes |
| Actiq®[a] (oral transmucosal fentanyl citrate) Cephalon, Inc. | Cancer pain | Yes | | | | Yes | | | |
| Clozaril® (clozapine) Novartis Pharmaceuticals | Schizophrenia | Yes | | | | | | Yes | Yes |
| Lotronex®[a] (alosetron) GlaxoSmithKline | Irritable bowel syndrome in women | Yes | Yes | | Yes | Yes | | | |
| Mifiprex®[a] (misfepristone) Danco Laboratories, LCC | Termination of early intrauterine pregnancy | Yes | Yes | Yes | | Yes | | | |
| Thalomid®[a] (thalidomide) Celgene Corporation | Erythema nodosum leprosum | Yes | Yes | Yes | | Yes | | | |
| Tikosyn® (trovafloxacin) Pfizer, Inc. | Cardiac dysrhythmias | Yes | | | | | | | |
| Tracleer®[a] (bosentan) Actelion Pharmaceuticals US, Inc. | Pulmonary arterial hypertension | Yes | | | | | Yes | Yes | |
| Trovan® (trovafloxacin mesylate or alatrofloxacin mesylate injection) Trovan, Ltd | Life-threatening infections | | | | | | Yes | | Yes |
| Xyrem®[a] (sodium oxybate) Orphan Medical, Inc. | Cataplexy in patients with narcolepsy | Yes | | Yes | Yes | | Yes | | Yes |

a Medications approved under subpart H, with restrictions to assure safe use ("Restricted") [21 CFR 314.520].

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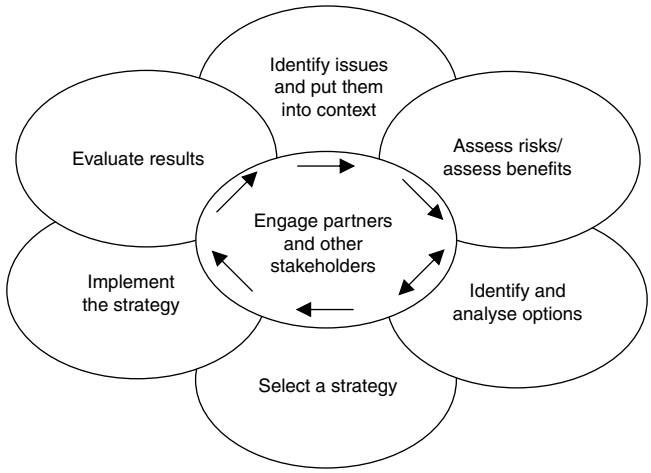


**Fig. 1.** The Risk Management Development Model proposed by the US FDA Task Force on Risk Management in 1999.

## 6. Identifying and Engaging the Stakeholders

It was clear that it was necessary to understand all of the concerns being expressed by those interested parties who represented the needs of patients as well as those committed to limiting drug diversion and abuse, including GHB. In 1998, company representatives began working closely with stakeholders (listed in table I) to learn about the evolution of GHB abuse and what tools would be needed to combat abuse. Although many stakeholders were concerned about the risk of drug diversion, leading to further misuse and abuse of the drug, the medical need for sodium oxybate was recognised. The company committed to help promote adoption of drug rape laws, analogue statutes and regulated chemical statutes whenever possible. Successful efforts in Congress and with the legislatures of Pennsylvania, New York and South Carolina helped allay apprehensions of early stakeholders and encouraged the later involvement of others.

As a result of these discussions, the following points were agreed upon:

- Sodium oxybate is a valuable medication, which should be made available for patients who need it; however, it must be handled responsibly by all parties involved.
- To manage the risks involved with the distribution of sodium oxybate, a comprehensive plan is needed that will require the co-operation of all stakeholders.
- The product manufacturer will collaborate with stakeholders around the country to help devise public policy to combat illicit use of all forms of GHB as club and date-rape drugs. Additionally, the company offered to provide its medical and scientific expertise to assist prosecutors and forensic scientists.

## 7. Components of Risk Management

### 7.1 Legislative Scheduling of GHB

A primary issue raised was the application of a drug schedule that would apply the harshest penalties possible for the illicit use of GHB and related chemicals, yet allow access to sodium oxybate for patients who need it. Initially, a schedule IV designation was proposed for sodium oxybate (see table II), which was in sharp contrast to the suggestion for schedule I status advocated by the DEA, which would preclude medical use. Therefore, members of congress were challenged to devise an acceptable legislative solution that addressed the urgent needs of law enforcement and patients with rare diseases. The resulting legislation was the Hillory J. Farias

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and Samantha Reid Date-Rape Drug Prohibition Act of 2000 (Public Law [PL] 106-172[HR2130]). This law stipulated a novel bifurcated scheduling and directed the US Attorney General to amend the Controlled Substances Act, making GHB a schedule I agent and any FDA-approved formulations of GHB a schedule III substance.[36] The listing of GHB as a schedule I drug automatically banned the use of GBL and 1,4-BD for human consumption. An additional provision to this act promoted continued evaluation of sodium oxybate as an orphan drug by permitting schedule III storage conditions for investigational drug products during clinical trials. The new law also made it clear that the use of any form of GHB to facilitate sexual assault was a federal crime and that illicit possession or distribution of any form of GHB would be subject to the severe penalties of schedule I.

Although each state has the option of imposing more restrictive scheduling than the Federal Guidelines, the groundbreaking schedule I/III status promoted by congress has been adopted by more than 40 states in the US thus far, with state rule makers and legislators in other states considering adoption in 2003.

### 7.2 Distribution

It was determined that the traditional (wholesale and retail) pharmaceutical distribution model lacked the controls deemed necessary to minimise diversion of sodium oxybate. These concerns were heightened by a diversion epidemic involving an opiate medication in the US, recently receiving widespread media attention.[37] It was agreed by the company and stakeholders that placing the responsibility for sodium oxybate dispensing and distribution solely on physicians or pharmacists was inappropriate and that a speciality distribution model was needed to address specific risk-management issues. The use of such a system would permit controls beyond those available in the traditional pharmaceutical distribution model and was being successfully employed by other manufacturers for products with specific safety concerns (see table III). In addition, it would avoid the need for putting sodium oxybate on the shelves of an estimated 63 000 retail pharmacies in the US, greatly reducing the potential for diversion.

It was concluded that a centralised system would be much better suited for minimising diversion and related risk issues. In the case of sodium oxybate, a centralised distribution system was especially well suited as narcolepsy affects a small patient populations (<200 000 patients in the US) and, as narcolepsy is a chronic, life-long illness, long-term drug use can be more carefully monitored.

### 7.3 Encouraging Appropriate Use

In addition to the fear of diversion and abuse, stakeholders also voiced concerns over inappropriate prescribing of sodium oxybate. To ensure that the medication is being used appropriately, it was suggested that the product manufacturer should be responsible for placing restrictions on sodium oxybate prescribing, based upon patient disease diagnosis or physician speciality. However, this was rejected as it would not only constitute an imposition on the practice of medicine, but it is illegal in most states.[3]

A more feasible suggestion was that the product manufacturer supports the responsible use of sodium oxybate by providing written information specifically addressing risk-management issues as well as other general medical issues. Such educational pieces could be written specifically for prescribers and patients. The physician material would stress the importance of patient education, key prescribing issues, such as dose titration, and heighten their awareness of the potential for drug diversion. Similarly, patient education materials could be used to emphasise proper use of the medication, the schedule III status of their prescription and warn about the possible schedule I legal consequences of sharing their sodium oxybate prescription with others.

**3** In the US, only federal agencies may impose such restrictions.

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With respect to off-label prescribing,[4] it was agreed that it is the responsibility of the product manufacturer to promote the medication in a manner consistent with the indication stated on the product label. However, in light of the many unapproved uses of GHB, a major stakeholder concern was the potential for inappropriate prescribing. In this regard, the speciality pharmacy is responsible for filling prescriptions according to the rules and regulations governing the practice of pharmacy in each state. Pharmacy ethics prohibit dispensing medications that are prescribed for inappropriate uses or in excessive quantities. Additionally, state medical boards would have access to a registry of sodium oxybate prescribers, should prescribing practices be questioned.

### 7.4 Ongoing Information Reporting

The manufacturer agreed to collect and share information about the abuse or addiction potential of sodium oxybate and pledged to support research efforts which evaluate the abuse and addictive properties of other GHB-related compounds even though they are not marketed by the company. To date, the manufacturer has shared its clinical research data with the National Institute on Drug Abuse (NIDA), the Department of Justice, forensic science groups, toxicologists and emergency medicine physicians. The company is currently supporting several studies designed to better understand the abuse of illicit forms of GHB.

## 8. Implementing the Best Strategy

Following a 5-year period of consultation with stakeholders, most of the major stakeholder concerns about the distribution and safe use of sodium oxybate were identified and resolved and a risk-management programme was designed and implemented. The primary goals of the Xyrem® Risk Management Program are to provide a system that ensures the responsible distribution of sodium oxybate to patients with narcolepsy and educational support to physicians and patients about the safe and responsible use of this medication. In an effort to address specific stakeholder concerns, the Xyrem® Risk Management Program was designed to include the following components:

- a single, centralised pharmacy located in a secure facility;
- a specialised prescription form with information required by the FDA which also serves to register patients and prescribers in the programme;
- state medical and DEA license verification;
- prescription shipment tracking requiring patient signature;
- a dedicated team of pharmacists available 24-hours a day, 7 days a week to provide physician and patient support regarding the safe and responsible use of sodium oxybate;
- physician and patient registries to monitor prescribing habits or excessive patient use;
- Xyrem® Success Program℠ educational materials for patients and physicians; and
- a defined post-marketing surveillance of adverse events resulting from the use of sodium oxybate.

### 8.1 The Centralised Pharmacy

The use of a centralised pharmacy, compliant with FDA schedule III regulations, eliminates the need to have the product distributed by several wholesalers and stocked by retail pharmacies, minimising the potential for theft and diversion. The design and function of a centralised pharmacy has several unique aspects designed to maximise product security.

The facility was specially designed to be the Xyrem® pharmacy and has security features that extend far beyond what is considered adequate for most pharmacies. The medication holding, dispensing and shipping areas are secured by restricted access and security measures that include locked, steel-reinforced concrete holding areas for the medication, and 24-hour security and surveillance including closed-circuit television monitoring of all areas and the use of motion detectors. The med-

**4** Off-label use refers to the use of a drug for a purpose other than the approved indication.

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ication stock is inspected and inventoried every 24 hours.

The responsibilities of the central pharmacy extend beyond dispensing medication and each step of the prescription-filling process is in itself a rigorous procedure, outlined in section 8.3, below. After careful personnel selection, each member of the pharmacy becomes part of a dedicated team whose sole responsibilities involve receiving, filling, shipping and tracking prescriptions. They receive extensive training about narcolepsy and the therapeutic application of sodium oxybate. Consequently, they are able to provide comprehensive drug information and drug counselling support for physicians and patients and are available around the clock.

In the traditional pharmaceutical distribution model, a single patient who obtains multiple prescriptions from several physicians may go undetected. In contrast, the staff of the central pharmacy is able to maintain a central registry of all physicians currently prescribing sodium oxybate and all patients currently receiving the medication. This feature enables pharmacists to verify state medical and DEA licenses, monitor for inappropriate prescribing practices in addition to preventing patients from receiving multiple prescriptions from several prescribers. In addition, pharmacists are specially trained to be alert for cash-paying customers, compliance problems or any suspicious questions or behaviours on the part of physicians or patients.

In the event of theft or suspected diversion of sodium oxybate, the pharmacy will instruct local law enforcement. In this regard, the central pharmacy can practice in all 50 states, and must abide by the laws of each state with respect to issues of patient confidentiality. It is recommended that law enforcement personnel requesting patient-specific information check with local authorities before attempting to obtain information of this type.

## 8.2 Physician and Patient Education

The Xyrem® Success Program℠ includes educational materials, aimed at two distinct audiences: the Physician Success Program℠ is designed specifically for the physician while the Patient Success Program℠ is tailored to meet the needs of the patient. These educational pieces have been approved by the FDA and are part of the product labelling.

### *8.2.1 The Physician Success Program℠*

The materials comprising the Physician Success Program℠ contain a comprehensive description of each component of the Xyrem® Risk Management Program, detailed information about prescribing sodium oxybate and the use of special prescription forms and the Xyrem® Post Marketing Evaluation Program. The materials also provide guidelines for physicians to consider when prescribing sodium oxybate. For example, physicians are encouraged to evaluate patients and re-write prescriptions every 3 months and to report all adverse events related to sodium oxybate using special forms.

Physicians are also advised that, in accordance with the US Controlled Substances Act, the central pharmacy will maintain records on each sodium oxybate prescriber, which may be made available to government agencies upon request. By completing the special prescription for each patient, the physician confirms that they:

- have read and understand the Physician Success Program℠ materials;
- have provided sodium oxybate dosing, preparation and administration counselling to their patient;
- understand that sodium oxybate is approved for the treatment of cataplexy in patients with narcolepsy;
- understand their responsibility regarding participation in the Xyrem® Post Marketing Evaluation Program.

### *8.2.2 The Patient Success Program℠*

The Xyrem® Patient Success Program℠ materials include written educational materials as well as an instructional videotape. These materials inform the patient about the role of the central pharmacy, receiving their prescriptions, how to order refills, the proper use, care and handling of the drug and consequences of diversion for illicit purposes. The important features regarding sodium oxybate use, such as

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dosing, administration and adverse events, are stressed to each patient.

### 8.3 The Xyrem® Prescription Process

The components of the Xyrem® Risk Management Program work together to ensure appropriate dispensing and use of sodium oxybate in the following manner.

- To prescribe sodium oxybate, the physician must first receive the Xyrem® Success Program℠ materials. They may receive these materials by telephoning the Xyrem® Success Program℠, on 1-866-XYREM88® (866-997-3688), or one of the company's speciality sales' consultants. After thoroughly reviewing the prescribing requirements, a completed prescription form is sent to the central pharmacy.
- Upon receipt of a sodium oxybate prescription, the pharmacy checks the credentials of the physician to ascertain they have controlled substance prescribing privileges and that there have been no disciplinary actions in their state. If the physician's credentials are approved, the patient is mailed the Xyrem® Patient Success Program℠ materials and the reimbursement process is started. If any relevant disciplinary actions against the physician are identified, the enrolment form is returned to the physician with a cover letter explaining why the prescription cannot be filled. The patient is also sent a letter instructing them to contact their physician.
- While reimbursement is being sought, the pharmacy contacts the patient to confirm that the educational materials were received and read by the patient and to address any patient questions. If a patient indicates that the Patient Success Program℠ has been read, the pharmacist will counsel the patient and schedule the prescription for delivery. If a patient indicates that the Patient Success Program℠ materials have not been reviewed, the importance of doing so is emphasised and another call is scheduled to complete the patient counselling process before the drug is shipped.
- The shipment must be sent by an overnight delivery service to the patient or patient designee, either of whom must be ≥18 years of age and who must sign for the package upon delivery. Each shipment is tracked from the time it leaves the pharmacy until it is received by the patient or designee. Following shipment, the patient is called to confirm that the prescription was received.
- No sooner than 8 days before the prescription is scheduled to be finished, the pharmacy contacts the patient to arrange for shipment of the next prescription refill. If the patient is not reached, they are left a message to return the call using a telephone number provided. The nature of the call is never disclosed in any messages left by the pharmacy. If the patient is reached, shipment of the prescription refill is scheduled.
- With each refill, the pharmacist evaluates the patient's compliance with therapy and any evidence of possible product diversion, misuse or over-use, such as calls for early refills or receipt of multiple prescriptions. When appropriate, the pharmacist contacts the prescribing physician to alert them of the situation and, in the case of early refills, confirm whether the physician approves of the early refill. If the physician does not approve, the patient must wait until the next scheduled refill date to receive additional medication. If drug diversion is suspected, local law enforcement is notified.
- Pharmacists contact the patient to ensure that prescriptions have been received, to provide ongoing communication to monitor patient safety, and to offer support as needed to maximise the benefits from their prescribed therapy.

### 8.4 The Xyrem® Postmarketing Evaluation Program

As a condition of FDA approval, in consideration of the relatively small safety database generated in clinical trials, the Xyrem® Post Marketing Evaluation Program was created. This programme provides to the FDA information regarding the initial 6 months of Xyrem® therapy for 1000 patients pre-

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scribed sodium oxybate. Each physician is requested to solicit the occurrence of adverse events of special interest with their patients at 3- and 6-month clinic visits. Of special interest are reports of potentially serious events, such as vomiting, urinary incontinence (enuresis), sleepwalking, confusion or convulsions. In addition, physicians may use these forms to record information about suspected patient abuse or misuse of sodium oxybate. All obtained information are recorded on evaluation forms, provided in the Physician Success Program[SM] materials, which are then faxed or mailed to an independent drug safety agency for data management.

### 8.5 Evaluating the Results

Evaluation of the Xyrem® Risk Management Program is ongoing. The programme has been operational for several months and, as expected with any medication, several reports of minor, expected adverse events have been received. At the present time, there have been no physician reports of suspected abuse or diversion, there have been no patient reports of loss or theft, and no premature refill requests have been received by the pharmacy.

## 9. Conclusion

During the clinical development of sodium oxybate, the need for a system that ensures the responsible distribution of sodium oxybate while educating patients and physicians about the unique aspects of the product was identified. Working with experts in drug diversion and abuse, the Xyrem® Risk Management Program was developed to satisfy the needs of patients, physicians and other stakeholders. The centralised distribution system, physician and patient registry, special educational materials for patients and physicians and a specially-trained pharmacy team contribute to the safe use of sodium oxybate while minimising diversion. The Xyrem® Risk Management Program appears to be a viable model for the responsible distribution of beneficial medications to small patient populations when they are associated with a significant element of risk for abuse, theft or diversion.

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