IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 21-691 (MN)
	)	
AVADEL PHARMACEUTICALS PLC, AVADEL US HOLDINGS, INC., AVADEL SPECIALTY PHARMACEUTICALS, LLC, AVADEL LEGACY PHARMACEUTICALS, LLC, AVADEL MANAGEMENT CORPORATION and AVADEL CNS PHARMACUEITCALS LLC,	)	
	)	
Defendants.	)	

PLAINTIFF'S ANSWERING BRIEF IN OPPOSITION TO DEFENDANTS' MOTION FOR PARTIAL JUDGMENT ON THE PLEADINGS

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I. NATURE AND STAGE OF THE PROCEEDINGS

In this patent infringement suit between Plaintiff Jazz Pharmaceuticals, Inc. ("Jazz") and the Avadel Defendants, four of the five patents cover sodium oxybate drug formulations. The other patent—U.S. Patent No. 8,731,963 (the "'963 patent")—claims methods of using a computer-implemented system to safely distribute sodium oxybate for treatment of a narcoleptic patient. Specifically, the independent claims recite a "computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion." Avadel seeks a judgment on the pleadings that the '963 patent is improperly listed in the FDA Orange Book and should be removed therefrom. This is Jazz's answering brief in opposition to that motion.

II. SUMMARY OF ARGUMENT

Avadel's motion fails for each of the following, independent reasons:

First, FDA regulations ***require*** listing the '963 patent in the Orange Book. Particularly, FDA regulations require innovator pharmaceutical companies that file a New Drug Application ("NDA")—like Jazz did—to submit for listing in the Orange Book any patent claiming a method of using the drug that is the subject of the NDA. The regulations explain that method-of-use patents include not only those that claim therapeutic indications, but also those that claim "other conditions of use for which approval is sought or has been granted in the NDA." 21 C.F.R. § 314.53(b)(1). When the FDA first approved Jazz's sodium oxybate drug product (Xyrem®), it expressly conditioned approval on Jazz marketing the drug in accordance with the specific restrictions on distribution and use that are claimed in the '963 patent. Thus, there can be no doubt that the '963 patent claims a condition of use for which approval was granted and that the patent was required to be listed in the Orange Book in connection with Xyrem®.

Second, Avadel's motion is premised entirely on a proposed claim construction that cannot be resolved on the pleadings. Indeed, Avadel's motion is based on its position that the '963 patent claims only a computerized "system" that is ineligible for Orange Book listing. Avadel ignores (and hardly even mentions) that the claims are directed to a "system for treatment." And Jazz pled that the '963 patent claims "methods" that require the use of a computer, which are eligible for listing. In short, the parties have a fundamental disagreement over the meaning of key claim terms, which cannot be decided on the pleadings.

Third and finally, Avadel's patent-delisting counterclaim is not ripe for adjudication because any alleged harm to Avadel is speculative in nature or uncertain to occur. Here, Avadel could only argue that it is affected by an improper listing if FDA approval of its sodium oxybate product were also affected as a result of that listing. But because Avadel has not filed any patent certifications against the '963 patent with the FDA, and because its CEO has publicly stated that the company has no current or future plans to do so, there is no indication that the presence of the '963 patent in the Orange Book has had or will have any impact whatsoever on Avadel or its pending drug application. Accordingly, the delisting counterclaim is not ripe for the Court's adjudication. Further, if Avadel's motion is merely directed to whether Jazz is entitled to relief under the Hatch-Waxman Act, as Avadel's counsel stated during the Rule 16 conference, then the Court need not reach this issue until after the trial scheduled for October 2023 (which will be after the June 2023 expiration of the '963 patent).[1]

[1] Although the '963 patent will expire before trial, Avadel has threatened (and continues to threaten) to launch its product before the patent expires.

III. STATEMENT OF FACTS

A. Xyrem® Was Approved With Mandatory Conditions of Use that Are Covered by the '963 Patent

Jazz developed and manufactures Xyrem®, an FDA-approved drug product for use in the treatment of both cataplexy and excessive daytime sleepiness, which are devastating symptoms associated with the sleep disorder narcolepsy. *See, e.g.*, D.I. 1, Ex. B at 2:51-53.

The active ingredient in Xyrem® is sodium oxybate, which is a specific salt form of gamma-hydroxybutyrate ("GHB"). *Id.* GHB has been recognized by Congress and federal agencies as a dangerous substance, frequently misused as a "date rape drug" in cases of drug-facilitated sexual assault. Because of its high potential for abuse and misuse involving third parties, GHB was classified as a Schedule I controlled substance under the Controlled Substances Act, a designation reserved for drugs with a high potential for abuse and no accepted medical use. *See* 21 U.S.C. § 812(b)(1); 21 C.F.R. § 1308.11(e)(1). At the same time, however, the FDA and Congress recognized that studies had established that GHB might be the basis for a unique treatment for certain symptoms of narcolepsy. *See, e.g.*, D.I. 1, Ex. B at 1:41-58. Thus, approved forms of GHB like Xyrem® were classified as Schedule III controlled substances, acknowledging their legitimate medical uses. *See* 21 U.S.C. § 812(b)(3); 21 C.F.R. § 1308.13(c)(6). In reaching this compromise, however, both Congress and the FDA noted that medical use of a GHB-based drug like Xyrem® must be strictly controlled to ensure that it cannot be illicitly obtained and misused.

Given its unique status, the FDA conditioned approval of Xyrem® on Jazz's development and implementation of a controlled distribution program. Specifically, upon FDA approval of Xyrem® in 2002, the FDA stated that the drug could only be "approved with a Risk Management

Program (RMP) that must include [several specified] components." Ex. A at 2.[2,3] In fact, the FDA stated in Xyrem's approval letter in no uncertain terms that the "[m]arketing of this drug product and related activities are to be in accordance with the substance and procedure of all FDA regulations ***and the specific restrictions on distribution and use described [in the Xyrem Risk Management Program] below***." *Id.* at 1 (emphasis added).

Following approval, the labeling for Xyrem® has specified that "Xyrem is available only through a restricted distribution program called the XYWAV and XYREM REMS because of the risks of central nervous system depression and abuse and misuse." *See, e.g.*, Ex. B at § 5.3.[4] Consequently, distributing and using Xyrem® according to the methods set forth in the FDA-required REMS (which, as explained below, are covered by the '963 patent) are conditions of using the drug.

B. The '963 Patent Covers the Method of Use Required by the Xyrem® REMS

The claims of the '963 patent address the unique problem that the Xyrem® REMS was invented to solve: using GHB for legitimate medical purposes while avoiding the potential for misuse, abuse, or diversion of GHB by or against others. *See* D.I. 1, Ex. A at 1:32-45. The

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[2] A REMS is a form of Risk Management Plan that the FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. *See, e.g.*, https://www.fda.gov/files/drugs/published/Risk-Evaluation-and-Mitigation-Strategies--Modifications-and-Revisions-Guidance-for-Industry.pdf at 2.

[3] The Court may take judicial notice of the FDA Approval Letter for Xyrem®, as well as the other exhibits cited herein, which are publicly available on the FDA's website. *See, e.g.*, *Desai v. Sorin CRM USA, Inc.*, No. 12-2995, 2013 WL 163298, at *4 (D.N.J. Jan. 15, 2013) (explaining, in context of deciding Rule 12(c) motion, that "[t]his Court takes judicial notice of the FDA's website"); *Freed v. St. Jude Med., Inc.*, No. 17-1128, 2017 WL 4102583, at *2 (D. Del. Sept. 15, 2017) (taking judicial notice of documents "publically available on the FDA's website and [which] are indisputably authentic").

[4] Xywav® is an oxybate product marketed by Jazz that contains 92% less sodium than Xyrem® and is distributed and used according to the methods set forth in the '963 patent. For simplicity's sake, the XYWAV and XYREM REMS is referred to hereafter as the "Xyrem® REMS."

claims cover methods of using a computer-implemented system to safely distribute GHB for treatment of a narcoleptic patient. Specifically, the independent claims recite a "computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion." *See, e.g.*, *id.* at Claim 1. The claimed methods make use of the computerized system to confirm, among other things, that the patient and prescriber are authorized to receive and prescribe the drug, and to identify whether the physician or patient is potentially misusing the drug. *Id.* Claim 6 of the '963 patent is specifically limited to GHB. *Id.* at Claim 6.

As set forth in the table below, the steps of the claimed methods are each required steps of the FDA-approved Xyrem® REMS, and thus are required for the "treatment of a narcoleptic patient" using GHB, as set forth in the claims:

FDA-Approved REMS	**Claimed Method Steps**
"Verify in the Central Database that the patient and prescriber are enrolled." Ex. C at 5.	Identifying "a physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug." *See* claim 1.
"Track and verify receipt of each shipment of [Xyrem®] through the processes and procedures established as a requirement of the REMS." *Id.* at 6.	Reconciling "inventory of the prescription drug before the shipments for a day or other time period are sent." *Id.*
"Monitor for all instances of patient and prescriber behavior that give rise to a reasonable suspicion of abuse, misuse, and diversion." *Id.*	Identifying any "indicator of a potential misuse, abuse or diversion by the narcoleptic patient." *Id.*
"Notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion." *Id.* at 1.	Notifying "the physician that is interrelated with the narcoleptic patient" if any indicators of misuse are detected. *Id.*
"For patients who request an early refill or if abuse, misuse or diversion is suspected: Discuss the request or concern with the prescriber." *Id.* at 5.	"Selectively block[ing] shipment of the prescription drug to the patient" based upon identification of abuse potential. *See* claim 2.

FDA-Approved REMS	Claimed Method Steps
"Ship … XYREM directly to each patient or a patient-authorized adult designee through the processes and procedures established as a requirement of the REMS." *Id.*	"Shipp[ing] to the narcoleptic patient if no potential misuse, abuse or diversion is found." *See* claim 3.
"Contact the patient's insurance provider to verify … XYREM prescription benefits." *Id.* at 21.	Identifying "an insurer to be contacted for payment for prescription drugs of an associated patient." *See* claim 13.
"Assess the patient for … signs of abuse and misuse including an increase in dose or frequency of dosing, reports of lost, stolen, or spilled medication, and drug-seeking behavior." *Id.* at 2.	Identifying "a current pattern or an anticipated pattern of abuse of the prescription drug." *See* claim 14.

Put simply, the '963 patent claims the FDA-required conditions of using Xyrem® according to its approved labeling, including its REMS. Accordingly, the '963 patent is properly listed in the Orange Book.

C. Avadel's NDA and this Litigation

Avadel describes its infringing sodium oxybate drug product as "an innovative new drug product," which makes this action "[u]nlike the typical pharmaceutical patent infringement case involving a defendant seeking to market a generic version of a brand-name drug." Avadel Br. at 2.[5] To make its argument, Avadel compares its once-nightly sodium oxybate formulation (which it calls "FT218") to Xyrem®, which is currently dosed twice-nightly. *See id.* at 2-3. Avadel omits, however, that although Jazz has yet to bring a once-nightly sodium oxybate formulation to market, it has been developing a once-nightly formulation for years and has obtained several patents that cover its innovations. In fact, four of the five patents-in-suit claim once-nightly sodium oxybate formulations, and Avadel's FT218 infringes them all. *See* D.I. 1, Exs. B-E.

[5] As used herein, "Avadel Br." refers to "Opening Brief in Support of Avadel's Motion for Partial Judgment on the Pleadings" (D.I. 21).

Moreover, despite its claims of innovation, the NDA that Avadel filed with the FDA to seek approval for FT218 largely relies on the clinical studies that Jazz carried out for Xyrem®. Indeed, Avadel did not file a typical NDA but instead submitted a 505(b)(2) NDA. *See, e.g.*, D.I. 1, Ex. F at 13. A 505(b)(2) NDA sponsor is permitted to "rely on clinical studies that were previously submitted to [the] FDA in support of another drug and that were not conducted or licensed by the 505(b)(2) [sponsor]." *Veloxis Pharms., Inc. v. U.S. Food & Drug Admin.*, 109 F. Supp. 3d 104, 108-09 (D.D.C. 2015). In this case, Xyrem® is the Reference Listed Drug ("RLD") for Avadel's 505(b)(2) NDA. *See, e.g.*, D.I. 1, Ex. F at 12; *id.*, Ex. I at 7. The RLD-related clinical studies that a Section 505(b)(2) NDA sponsor relies upon may be submitted to satisfy the sponsor's "entire burden of proving safety and effectiveness" to the FDA. *Veloxis*, 109 F. Supp. 3d at 109. To that end, the 505(b)(2) NDA pathway is "often used when the new drug differs only slightly from the pioneer [or reference listed] drug." *Id.*

And although Avadel filed a 505(b)(2) NDA that relied upon Xyrem® as the RLD, it has refused to file ***any*** patent certification with respect to the Orange Book-listed '963 patent. In fact, Avadel has publicly stated that the company has "not been asked by the agency to certify Paragraph IV against any [Xyrem] Orange Book-listed patents, and we don't believe based on the data and regulatory filing strategy of our FT218 NDA submission, there is any basis to request such a certification." D.I. 1, Ex. F at 3; *see also* D.I. 1, Ex. I at 13. Indeed, Jazz has not received any notice from Avadel of a Paragraph IV certification.

IV. LEGAL STANDARD

Under Federal Rule of Civil Procedure 12(c), a judgment on the pleadings "will not be granted unless the movant clearly establishes that no material issue of fact remains to be resolved and that he is entitled to judgment as a matter of law." *Rosenau v. Unifund Corp.*, 539 F.3d 218, 221 (3d Cir. 2008) (internal quotations and citations omitted). The court "must view the facts

presented in the pleadings and the inferences to be drawn therefrom in the light most favorable to the nonmoving party." *Id*; *see also, e.g.*, *Aqua Connect, Inc. v. TeamViewer US, LLC*, No. 18-1572 (MN), 2020 WL 5549086, at *1 (D. Del. Sept. 16, 2020) ("In ruling on a Rule 12(c) motion, the Court must accept as true all well-pleaded allegations in the non-movant's pleadings and draw all reasonable inferences in favor of the non-movant").

V. ARGUMENT

A. FDA Regulations Required Jazz to List the '963 Patent in the Orange Book

Under the Hatch-Waxman Act, NDA holders are ***required*** to file with the FDA "the patent number and expiration date of each patent for which a claim of patent infringement could reasonably be asserted . . . and that . . . claims a method of using such drug for which approval is sought or has been granted in the [NDA]." 21 U.S.C. § 355(b)(1)(A)(viii). The FDA identifies these patents in the "Orange Book" (*Approved Drug Products with Therapeutic Equivalence Evaluations*). The FDA's Orange Book listing rules specify that, among other things, "[f]or patents that claim a method of use, the applicant must submit information only on those patents that claim indications or other conditions of use for which approval is sought or has been granted in the NDA." 21 C.F.R. § 314.53(b)(1). The FDA has also explained that, "if a method of use is described in the labeling for the drug product, and there is a patent claiming that method of use, the patent must be submitted for listing in the Orange Book." *See* 68 Fed. Reg. 36680 (June 18, 2003).

Pursuant to the statute and its attendant regulations, Jazz was required to submit the '963 patent for listing in the Orange Book. As set forth above, the FDA-approved labeling for Xyrem® states that "Xyrem is available ***only*** through a restricted distribution program called the XYWAV and XYREM REMS because of the risks of central nervous system depression and abuse and misuse." Ex. B at § 5.3 (emphasis added). Moreover, the FDA only approved

Xyrem® on the express condition that the drug would be used according to the "specific restrictions on distribution and use described [in the Xyrem Risk Management Program]." *See* Ex. A at 1; *see also id.* at 2 (describing such restrictions on distribution and use). The '963 patent claims the methods "for treatment of a narcoleptic patient" that comprise the FDA-required conditions of use for Xyrem®, which are described in the Xyrem® REMS. *See supra* at § II(B). Accordingly, the method of using Xyrem® according to its approved REMS is not only a "condition of use" as required by the FDA (*see* 21 C.F.R. § 314.53(b)(1)), but also is "described in the labeling for the drug product" (*see* 68 Fed. Reg. 36680). As such, the '963 patent claims "an approved method of using the drug" under both the relevant statute and FDA Rule. *See* 21 U.S.C. § 355(b)(1)(A)(viii); 21 C.F.R. § 314.53(b) (requiring listing of "patents that claim indications or other conditions of use"). Thus, far from this being a case of improper listing, Jazz was legally ***required*** to list the '963 patent in the Orange Book.

Moreover, although FDA regulations expressly set forth the categories of patents that are ***ineligible*** for Orange Book listing, the '963 patent does not fall into any such category. Instead, the FDA makes clear that patents that "must not be submitted to FDA" for listing in the Orange Book are those that are: "[p]rocess patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates … ." 21 C.F.R. § 314.53(b)(1). Avadel does not and cannot contend that the '963 patent falls within any of these prohibited categories.

On this basis alone, Avadel's motion should be denied.

B. Avadel's Motion is Based on a Flawed Claim Construction Argument That Cannot Be Adjudicated At This Early Stage of the Case

Avadel's delisting argument is premised entirely on its theory that the '963 patent claims a "system" as opposed to a "method." *See, e.g.*, Avadel Br. at 5. This is, plain and simple, claim construction. As explained below, Avadel's claim construction argument is incorrect, and at the

very least, it cannot be adjudicated on the current record. This is another, independent reason why Avadel's motion should be denied.

Avadel does not dispute that Jazz has pled that the '963 patent claims a method. *See* Avadel Br. at 5 (arguing that "Jazz has incorrectly asserted" that the patent claims recite a "method"); *see also, e.g.*, D.I. 1 at ¶ 27 ("The claims of the patents-in-suit cover, *inter alia*, methods of use and administration of sodium oxybate…"). And yet, at this preliminary stage in the case—and on a motion for judgment on the pleadings—Avadel would have the Court disregard the pleadings and decide the meaning of claim terms based on nothing but six pages of attorney argument. This is improper.

To accept Avadel's arguments and to find that the '963 patent is improperly listed in the Orange Book, the Court would have to construe the claims and hold that the '963 patent covers no methods at all. Such a determination cannot be made on the pleadings. The Federal Circuit has explained that "it would be inappropriate for a district court to engage in 'claim construction at the pleading stage—with no claim construction processes undertaken.'" *Gestion Proche, Inc. v. Dialight Corp.*, No. 16-00407, 2017 WL 1551606, at *3 (E.D. Tex. May 1, 2017) (quoting *In re Bill of Lading Transmission & Processing Sys. Pat. Litig.*, 681 F.3d 1323, 1343 n.13 (Fed. Cir. 2012)). Accordingly, as this Court recently explained in denying a motion to dismiss, where the moving party's arguments "seem to require claim construction…. [the Court] cannot resolve the claim construction issues on the record [at this early stage of the case]." *Blackbird Tech v. Uber Techs., Inc.*, No. 19-561 (MN), 2020 WL 58535, at *8 (D. Del. Jan. 6, 2020). And other courts within this district routinely decline to resolve claim construction disputes at the outset of a case, well before *Markman* proceedings. *See, e.g., Walker Digital, LLC v. Facebook, Inc.*, 852 F. Supp. 2d 559, 563 (D. Del. 2012) ("The court is not prepared to engage in a claim

construction exercise at this stage of the proceedings, with no context whatsoever provided by discovery or a motion practice."); *Tech. Innovations, LLC v. Amazon.com*, No. 11-690, 2012 WL 1441300, at *2 (D. Del. Apr. 25, 2012).

Avadel nonetheless suggests that the Court need not engage in any sort of claim construction analysis because "Jazz itself" has supposedly "characterized the '963 patent claims as 'system' claims in proceedings before the Patent Trial and Appeal Board." Avadel Br. at 6. Avadel is mistaken. Avadel's argument rests on a selectively (and improperly) cropped quote from a PTAB proceeding involving the '963 patent. There, Jazz described the claims as follows: "computer-implemented systems ***for treating a narcoleptic patient*** with a prescription drug that has a potential for misuse, abuse, or diversion, while preventing that misuse, abuse, and diversion ***by means of various controls***." Avadel Br., Ex. B at 2 (emphasis added); *see also id.* (explaining that "FDA would not have approved Xyrem without a ***method*** of restricting access to the drug that could ensure that its benefits would outweigh the risks to patients and third parties."). In other words, Jazz has consistently described the claims of the '963 patent as covering a method of safely using GHB that relies on the use of a specific, computerized system. And, notably, the PTAB proceeding concerned the alleged obviousness of the claims-at-issue and, thus, had nothing to do with whether the claims were directed towards methods or systems.

To be sure, there is no dispute that the preambles of the independent claims of the '963 patent refer to "a computer-implemented system." But Avadel goes to great lengths throughout its brief to ignore that the claims cover "a computer-implemented system ***for treatment of a narcoleptic patient***." In other words, the '963 patent does not simply claim a computerized system. Rather, the claims describe a method of using GHB through a computer-implemented system "for the treatment of a narcoleptic patient."

Determining whether a patent claims a system, a method, or both is fundamentally a question of claim construction, and so the court should not limit its analysis to the words in the preamble. Instead, the court must consider whether the body of each claim sets forth method steps, regardless of how the preamble may describe the invention. *See, e.g.*, *Lyda v. CBS Corp.*, 838 F.3d 1331, 1339 (Fed. Cir. 2016) (holding that "the purported system claims asserted in this case are, in fact, method claims because the body of the claims require the performance of particular method steps."). Avadel would have the court stop its analysis at the fourth word of the preamble of claim 1, glossing over the fact that the patent claims "[a] computer-implemented system ***for treatment of a narcoleptic patient*** with a prescription drug that has a potential for misuse, abuse or diversion."

The body of claim 1 (and the additional method steps set forth in the dependent claims) illustrate that the claims recite methods. The claimed methods are carried out—and misuse, abuse, and diversion of GHB are avoided—by requiring that, before the drug is dispensed, numerous pieces of information about both the patient and the prescriber are entered into (and analyzed by) the computerized system. For instance and by way of example, the methods comprise:

- Identifying "a physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug." *See* claim 1.
- Reconciling "inventory of the prescription drug before the shipments for a day or other time period are sent." *Id.*
- Identifying any "indicator of a potential misuse, abuse or diversion by the narcoleptic patient." *Id.*
- Identifying "an insurer to be contacted for payment for prescription drugs of an associated patient." *See* claim 13.
- Using the computer database to identify "a current pattern or an anticipated pattern of abuse of the prescription drug." *See* claim 14.

- Selecting "one or more controls for distribution … based on the identified pattern." *See* claim 15.

Only if the answers to all inquiries are satisfactory will the methods allow the computer to be "used to notify the physician that is interrelated with the narcoleptic patient through the schema of the single computer database" that the drug may be dispensed. *See* claim 1.[6]

In any event, the pleadings stage is not the appropriate time to resolve this claim construction dispute. *Celgene Corporation v. Lotus Pharmaceutical Company* is instructive. There, a generic drug applicant moved for judgment on the pleadings against several patents that covered aspects of a REMS for a different FDA-approved drug product. No. 17-6842, 2018 WL 6584888, at *1 (D.N.J. Dec. 14, 2018). The court there denied the motion because it could not "determine whether these patents are invalid under [the relevant standard] without construing [several] terms," further explaining that "[j]udgment may only be granted if 'the movant clearly establishes that no material issue of fact remains to be resolved and that he is entitled to judgment as a matter of law.'" *Id.* at *1-2.

The same result is warranted here. In order to give credence to Avadel's theory, the Court must: (1) ignore the fact that Jazz pled that the '963 patent claims a method, and (2) construe each claim as covering only systems (Avadel's position), and not methods that must

[6] Contrary to Avadel's suggestion (*see* Avadel Br. at 6), the claims of the '963 patent do not improperly claim both a system and a method. Instead, and as "[b]oth common sense and a cursory inspection of relevant authorities demonstrate," a claimed method may be "limited to performance on a particular type of apparatus." *Collaboration Props., Inc. v. Tandberg ASA*, No. 05-1940, 2006 WL 1752140, at *3 (N.D. Cal. June 23, 2006). Accordingly, the Federal Circuit has since "made it clear" that the prohibition on hybrid claiming identified in *IPXL Holdings* (on which Avadel relies) "is not implicated where a method claim 'recite[s] the physical structures of a system in which the claimed method is practiced.'" *Steuben Foods, Inc. v. Oystar USA, Inc.*, No. 10-780, 2021 WL 630906, at *13 (W.D.N.Y. Feb. 18, 2021) (quoting *Microprocessor Enhancement Corp. v. Texas Instruments, Inc.*, 520 F.3d 1367, 1374 (Fed. Cir. 2008)). That is the situation here.

be carried out using a system (Jazz's position). Claim construction determinations cannot be made at the pleadings stage. Instead, where, like here, "the parties vigorously dispute the basic character and meaning of the claims," the court should not attempt "to conjure up all plausible claim constructions at th[e] pleadings stage in the absence of stipulated constructions." *Id.* at *3.

C. Avadel's Delisting Motion Is Not Ripe For Adjudication

In addition to the substantive reasons to deny Avadel's motion set forth above, the Court should also deny the motion for the independent reason that the motion is not ripe for adjudication.

Subject matter jurisdiction in the federal courts requires an Article III case or controversy. *See, e.g.*, *Caraco Pharm. Labs, Ltd. v. Forest Labs., Inc.*, 527 F.3d 1278, 1290 (Fed. Cir. 2008). "A justiciable Article III controversy requires the party instituting the action to have standing and the issue presented to the court to be ripe." *Teva Pharms. USA, Inc. v. Novartis Pharms. Corp.*, 482 F.3d 1330, 1337 (Fed. Cir. 2007). The "ripeness analysis considers whether further factual development would significantly advance [the court's] ability to deal with the legal issues presented, and whether the complained-of conduct has an immediate and substantial impact on the plaintiff." *Sandoz Inc. v. Amgen Inc.*, 773 F.3d 1274, 1278 (Fed. Cir. 2014) (internal citations and quotations omitted).

Because Avadel has not filed any patent certification against the '963 patent, the listing of that patent in the Orange Book has no impact on Avadel and no Article III controversy exists. Avadel can only be affected by the alleged improper listing if it files a patent certification against the '963 patent. For instance, if the FDA requires Avadel to file a patent certification vis-a-vis the '963 patent, Avadel would have two choices—it could file a Paragraph III or a Paragraph IV certification. If Avadel files a Paragraph III certification, it cannot sell FT218 until the '963 patent expires in June 2023, and if it files a Paragraph IV certification, then the FDA would

have to stay approval of Avadel's NDA for 30-months while this lawsuit is resolved. But unless and until Avadel actually files a patent certification against the '963 patent, the patent's presence in the Orange Book is not immediately or substantially harming Avadel. To the contrary, without any patent certification, the Orange Book listing of the '963 patent has no impact on Avadel whatsoever.

Avadel has made clear in its recent public statements that it has no intention of filing any patent certification against the '963 patent. In fact, the company's CEO recently stated that, "as we sit here today through the [FDA] review process, we've not been asked to certify against any Orange Book-listed patents, and we do not believe there's a reason to do so." D.I. 1, Ex. I at 13; *see also* D.I. 1, Ex. F at 3 ("[W]e still have not been asked by the agency to certify Paragraph IV against any Orange Book-listed patents, and we don't believe based on the data and regulatory filing strategy of our FT218 NDA submission, there is any basis to request such a certification.").

It is well-established that a "claim is not ripe for adjudication if it rests upon contingent ***future*** events that may not occur as anticipated, or indeed may not occur at all." *Texas v. United States*, 523 U.S. 296, 300 (1998) (emphasis added and internal quotations omitted). Therefore, because the '963 patent's presence in the Orange Book is not currently affecting (let alone harming) Avadel in any way, Avadel's counterclaim is not ripe for adjudication.

In addition, during the Rule 16 conference with the Court, Avadel's counsel remarked that Avadel's motion related to Jazz's "claim that they're entitled to an automatic injunction under the Hatch-Waxman Act." D.I. 28 at 16:8-11. But to plead a case under the Hatch-Waxman Act, and thus be entitled to a Hatch-Waxman injunction, Jazz only has to allege that the filing of a 505(b)(2) application infringes one or more of its patents under 35 U.S.C. § 271(e)(2). *See AstraZeneca Pharms. v. Apotex Corp.*, 669 F.3d 1370, 1377 (Fed. Cir. 2012); *Vanda*

Pharms. Inc. v. West-Ward Pharms. Int'l Ltd., 887 F.3d 1117, 1124 (Fed. Cir. 2018). In other words, Jazz is entitled to a Hatch-Waxman injunction if it proves infringement of the '963 patent regardless of whether that patent is listed in the Orange Book. Thus, the purported basis that Avadel offered for its motion at the Rule 16 conference fails to create a ripe dispute for the Court. Further, even if Avadel's motion had merit (it does not), given that Avadel's claimed reason for filing its motion goes to Jazz's remedy, the Court will only need to decide the issue if Jazz prevails on the '963 patent after trial on the merits, which is currently scheduled for October 2023 (i.e., after the June 2023 expiration of the '963 patent).

In this case, given that Avadel has publicly and repeatedly stated that it has no intention of filing a patent certification against the '963 patent, and that Jazz may properly seek Hatch-Waxman relief regardless of whether the '963 patent is listed in the Orange Book, Avadel may never be harmed by any alleged improper listing. Accordingly, the claim is not ripe for adjudication and the motion should be denied on this additional, independent basis.

VI. CONCLUSION

For the foregoing reasons, the Court should deny Avadel's partial motion for judgment on the pleadings.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Jeremy A. Tigan

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August 20, 2021

CERTIFICATE OF SERVICE

I hereby certify that on August 20, 2021, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on August 20, 2021, upon the following in the manner indicated:

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Jeremy A. Tigan (#5239)

EXHIBIT A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-196

Orphan Medical
Attention: Dayton Reardan, Ph.D.
Vice President, Regulatory Affairs
13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305

Dear Dr. Reardan:

Please refer to your new drug application (NDA) dated September 30, 2000, received October 2, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xyrem® (sodium oxybate) Oral Solution.

We acknowledge receipt of your submissions dated May 8 and 28; June 6; July 1, 12 and 15, 2002. Your submission of May 16, 2002 constituted a complete response to our April 9, 2002 action letter.

This new drug application provides for the use of Xyrem® Oral Solution for the treatment of cataplexy associated with narcolepsy.

We also refer to your March 12, 2002, correspondence requesting review of Xyrem® Oral Solution under the provisions of Subpart H for restricted distribution. Therefore, as previously agreed, we have reviewed this application under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) to assure safe use of the product.

Finally, we refer to the July 17, 2002, teleconference between representatives of Orphan Medical Inc. and this division during which the final language of the labeling text was agreed upon.

We have completed the review of this application, including the Xyrem® Risk Management Program, as amended, and have concluded that adequate information has been presented to approve Xyrem® (sodium oxybate) Oral Solution under 21 CFR 314 Subpart H. Accordingly, the application is approved under the provisions of 21 CFR 314, Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of all FDA regulations and the specific restrictions on distribution and use described below.

Xyrem® Risk Management Program

We remind you that Xyrem is being approved with a Risk Management Program (RMP) that must include each of the following components:

1) Implementation of a restricted distribution program for Xyrem.
2) Implementation of a program to educate physicians and patients about the risks and benefits of Xyrem, including critical information necessary for the safe use and handling of the drug.
3) Filling of the initial prescription only after the prescriber and patient have received and read the educational materials.
4) Maintenance of a registry of all patients and a record of all prescribers.

The RMP, as described in the attached documents, adequately addresses each of these requirements. Any proposed change in the RMP must be discussed with FDA prior to its institution. FDA will determine whether the proposed change is subject to FDA approval before implementation. We expect your continued cooperation to resolve any problems regarding the RMP that may be identified following approval of this NDA.

Medication Guide

As previously communicated to you in our December 13, 2001, letter, we have determined that Xyrem® poses a serious and significant public health concern requiring distribution of a Medication Guide. This Medication Guide is necessary to help prevent serious adverse effects due to Xyrem® pursuant to 21 CFR Part 208.1 (c)(1).

In accordance with 21 CFR Part 208, Orphan Medical is responsible for ensuring that:

- A Medication Guide for Xyrem® is available for every patient who is dispensed a prescription for Xyrem®.
- The label of each carton container of Xyrem® include a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom Xyrem® is dispensed.
- The label of each container includes a statement about how the Medication Guide is dispensed.

Post Marketing Commitments

You have made a commitment to conduct the following post marketing studies, as specified in your submission dated July 1, 2002, and our telephone conversation of July 12, 2002:

1. *Description:* conduct a drug interaction study to evaluate the pharmacokinetics of Xyrem® when administered concomitantly with a proton pump inhibitor in normal human volunteers.

   Protocol Submission: within three months of FDA approval of the NDA
   Study Start: within three months of FDA approval of the protocol
   Final Report: within six months of study initiation

2. *Description:* conduct a clinical study in subjects with respiratory compromise.

   Protocol Submission: within three months of FDA approval of the NDA
   Study Start: within three months of FDA approval of the protocol
   Final Report: completion of the study within 12 months of initiation with the final report three months following completion of the study.

3. *Description:* assess the post marketing safety of Xyrem in a prospective cohort of one thousand (1,000) patients prescribed Xyrem by evaluating physician-filed adverse event data sheets; each patient will be assessed for at least 6 months.

   Submission of Plans: within one month of approval
   Start Date: immediately upon treatment of any patient
   Reports to FDA: every three months from time of approval

Clinical protocols should be submitted to your IND for this product and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a summary of the status of each commitment in your annual report to this NDA. The summary should include expected study completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies. The number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

The final printed labeling (FPL) must be identical to the enclosed agreed upon labeling text for the Product Information Insert and Medication Guide. The immediate container and carton labels must be identical to those submitted on January 8, 2002. Marketing the product with FPL text that is not identical to the agreed upon approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-196." Approval of this submission by FDA is not required before the labeling is used.

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must directly submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement to the Division of Drug Marketing, Advertising and Communications. Please submit all

proposed materials in draft or mock up form, not final print and send one copy to the Division of Neuropharmacological Drug Products. We acknowledge your agreement to submit the reprint with the citation Sleep 2002; 25:42-49, under 21 U.S.C. § 360aaa.

We have approved an expiration date of 36 months for this drug product.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80, 314.81, 314.520, 314.550 and 314.560.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Professional Labeling
Patient Medication Guide
Risk Management Plan
Post Marketing Evaluation Program
Physician and Patient Educational Programs

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple
7/17/02 04:57:49 PM

EXHIBIT B

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XYREM safely and effectively. See full prescribing information for XYREM.

XYREM® (sodium oxybate) oral solution, CIII
Initial U.S. Approval: 2002

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and ABUSE AND MISUSE.
See full prescribing information for complete boxed warning.

Central Nervous System Depression
- **Xyrem is a CNS depressant, and respiratory depression can occur with Xyrem use (5.1, 5.4)**

Abuse and Misuse
- **Xyrem is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death (5.2, 9.2)**

Xyrem is available only through a restricted program called the XYWAV and XYREM REMS (5.3)

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1, 2.2, 2.3, 2.5)	7/2020
Contraindications (4)	7/2020
Warnings and Precautions (5.1, 5.3, 5.5)	9/2020

----------INDICATIONS AND USAGE----------

Xyrem is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy (1)

----------DOSAGE AND ADMINISTRATION----------

Dosage for Adult Patients
- Initiate dosage at 4.5 g per night orally, divided into two doses (2.1).
- Titrate to effect in increments of 1.5 g per night at weekly intervals (0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) (2.1).
- Recommended dosage range: 6 g to 9 g per night orally (2.1).

Total Nightly Dose	Take at Bedtime	Take 2.5 to 4 Hours Later
4.5 g per night	2.25 g	2.25 g
6 g per night	3 g	3 g
7.5 g per night	3.75 g	3.75 g
9 g per night	4.5 g	4.5 g

Dosage for Pediatric Patients (7 years of Age and Older)
- The recommended starting dosage, titration regimen, and maximum total nightly dosage are based on body weight (2.2).

Important Administration Information
- Prepare both doses prior to bedtime; dilute each dose with approximately ¼ cup of water in pharmacy-provided containers (2.3).
- Allow 2 hours after eating before dosing (2.3).
- Take each dose while in bed and lie down after dosing (2.3).

Patients with Hepatic Impairment
Recommended starting dosage is one-half of the original dosage per night administered orally, divided into two doses (2.4).

----------DOSAGE FORMS AND STRENGTHS----------

Oral solution, 0.5 g per mL (3)

----------CONTRAINDICATIONS----------

- In combination with sedative hypnotics or alcohol (4)
- Succinic semialdehyde dehydrogenase deficiency (4)

----------WARNINGS AND PRECAUTIONS----------

- CNS depression: Use caution when considering the concurrent use of Xyrem with other CNS depressants (5.1).
- Caution patients against hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that Xyrem does not affect them adversely (5.1).
- Depression and suicidality: Monitor patients for emergent or increased depression and suicidality (5.5).
- Confusion/Anxiety: Monitor for impaired motor/cognitive function (5.6).
- Parasomnias: Evaluate episodes of sleepwalking (5.7).
- High sodium content in Xyrem: Monitor patients with heart failure, hypertension, or impaired renal function (5.8).

----------ADVERSE REACTIONS----------

Most common adverse reactions in adults (≥5% and at least twice the incidence with placebo) were nausea, dizziness, vomiting, somnolence, enuresis, and tremor (6.1).

Most common adverse reactions in pediatric patients (≥5%) were nausea, enuresis, vomiting, headache, weight decreased, decreased appetite, dizziness, and sleepwalking (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals, Inc. at 1-800-520-5568, or FDA at 1-800-FDA-1088 or www.fda.gov/Medwatch.

----------DRUG INTERACTIONS----------

- Concomitant use with divalproex sodium: An initial reduction in Xyrem dose of at least 20% is recommended (2.5, 7.2).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Geriatric patients: Monitor for impaired motor and/or cognitive function when taking Xyrem (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

- **Central Nervous System Depression**
  Xyrem (sodium oxybate) is a CNS depressant. In clinical trials at recommended doses, obtundation and clinically significant respiratory depression occurred in adult patients treated with Xyrem *[see Warnings and Precautions (5.1)]*. Many patients who received Xyrem during clinical trials in narcolepsy were receiving central nervous system stimulants *[see Clinical Trials (14)]*.
- **Abuse and Misuse**
  Xyrem® (sodium oxybate) is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death *[see Warnings and Precautions (5.2)]*.

  Because of the risks of CNS depression and abuse and misuse, Xyrem is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XYWAV and XYREM REMS *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

Xyrem is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosing Information

The recommended starting dosage is 4.5 grams (g) per night administered orally, divided into two doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (see Table 1). Increase the dosage by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dosage range of 6 g to 9 g per night orally. The dosage may be gradually titrated based on efficacy and tolerability. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

Table 1: Recommended Adult Xyrem Dose Regimen (g = grams)

If A Patient's Total Nightly Dose is:	Take at Bedtime:	Take 2.5 to 4 Hours Later:
4.5 g per night	2.25 g	2.25 g
6 g per night	3 g	3 g
7.5 g per night	3.75 g	3.75 g
9 g per night	4.5 g	4.5 g

2.2 Pediatric Dosing Information

Xyrem is administered orally twice nightly. The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight, as specified in Table 2. The dosage may be gradually titrated based on efficacy and tolerability.

Table 2: Recommended Pediatric Xyrem Dosage for Patients 7 Years of Age and Older*

Patient Weight	Initial Dosage		Maximum Weekly Dosage Increase		Maximum Recommended Dosage	
	Take at Bedtime:	Take 2.5 to 4 Hours Later:	Take at Bedtime:	Take 2.5 to 4 Hours Later:	Take at Bedtime:	Take 2.5 to 4 Hours Later:
<20 kg**	There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.					
20 kg to <30 kg	≤1 g	≤1 g	0.5 g	0.5 g	3 g	3 g
30 kg to <45 kg	≤1.5 g	≤1.5 g	0.5 g	0.5 g	3.75 g	3.75 g
≥45 kg	≤2.25 g	≤2.25 g	0.75 g	0.75 g	4.5 g	4.5 g

* For patients who sleep more than 8 hours per night, the first dose of Xyrem may be given at bedtime or after an initial period of sleep.

**If Xyrem is used in patients 7 years of age and older who weigh less than 20 kg, a lower starting dosage, lower maximum weekly dosage increases, and lower total maximum nightly dosage should be considered.
Note: Some patients may achieve better responses with unequal doses at bedtime and 2.5 to 4 hours later.

2.3 Important Administration Instructions for All Patients

The total nightly dosage of Xyrem is divided into two doses. Prepare both doses of Xyrem prior to bedtime. Prior to ingestion, each dose of Xyrem should be diluted with approximately ¼ cup (approximately 60 mL) of water in the empty pharmacy containers provided.

Take the first nightly dose of Xyrem at least 2 hours after eating *[see Clinical Pharmacology (12.3)]*. Take the second nightly dose 2.5 to 4 hours after the first dose.

Patients should take both doses of Xyrem while in bed and lie down immediately after dosing, and remain in bed following ingestion of each dose. Xyrem may cause patients to fall asleep abruptly without first feeling drowsy *[see Adverse Reactions (6.2)]*. Patients will often fall asleep within 5 minutes of taking Xyrem, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night. Patients may need to set an alarm to awaken for the second dose. Rarely, patients may take up to 2 hours to fall asleep.

If the second dose is missed, that dose should be skipped and Xyrem should not be taken again until the next night. Both Xyrem doses should never be taken at one time.

2.4 Dosage Modification in Patients with Hepatic Impairment

The recommended starting dosage in patients with hepatic impairment is one-half of the original dosage per night, administered orally divided into two doses *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.5 Dose Adjustment with Co-administration of Divalproex Sodium

When initiating divalproex sodium in patients taking a stable dosage of Xyrem, a reduction of the Xyrem dosage by at least 20% is recommended with initial concomitant use *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. When initiating Xyrem in patients already taking divalproex sodium, a lower starting dosage of Xyrem is recommended. Subsequently, the dosage of Xyrem can be adjusted based on individual clinical response and tolerability.

3 DOSAGE FORMS AND STRENGTHS

Xyrem is a clear to slightly opalescent oral solution, in a concentration of 0.5 g per mL (0.5 g/mL of sodium oxybate equivalent to 0.413 g/mL of oxybate).

4 CONTRAINDICATIONS

Xyrem is contraindicated for use in:

- combination with sedative hypnotics *[see Warnings and Precautions (5.1)]*.
- combination with alcohol *[see Warnings and Precautions (5.1)]*.
- patients with succinic semialdehyde dehydrogenase deficiency *[see Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Depression

Xyrem is a central nervous system (CNS) depressant. In adult clinical trials at recommended doses, obtundation and clinically significant respiratory depression occurred in patients treated with Xyrem. Xyrem is contraindicated in combination with alcohol and sedative hypnotics. The concurrent use of Xyrem with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with Xyrem is required, dose reduction or discontinuation of one or more CNS depressants (including Xyrem) should be considered. In addition, if short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with Xyrem should be considered.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that Xyrem does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking Xyrem. Patients should be queried about CNS depression-related events upon initiation of Xyrem therapy and periodically thereafter.

Xyrem is available only through a restricted program under a REMS *[see Warnings and Precautions (5.3)]*.

5.2 Abuse and Misuse

Xyrem is a Schedule III controlled substance. The active ingredient of Xyrem, sodium oxybate or gamma-hydroxybutyrate (GHB), is a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with the amnestic features of Xyrem, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim). Because illicit use and abuse of GHB have been reported, 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 (e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy) *[see Drug Abuse and Dependence (9.2)]*.

Xyrem is available only through a restricted program under a REMS *[see Warnings and Precautions (5.3)]*.

5.3 XYWAV and XYREM REMS

Xyrem is available only through a restricted distribution program called the XYWAV and XYREM REMS because of the risks of central nervous system depression and abuse and misuse *[see Warnings and Precautions (5.1, 5.2)]*.

Notable requirements of the XYWAV and XYREM REMS include the following:

- Healthcare Providers who prescribe Xyrem are specially certified
- Xyrem will be dispensed only by the central pharmacy that is specially certified
- Xyrem will be dispensed and shipped only to patients who are enrolled in the XYWAV and XYREM REMS with documentation of safe use

Further information is available at www.XYWAVXYREMREMS.com or 1-866-997-3688.

5.4 Respiratory Depression and Sleep-Disordered Breathing

Xyrem may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported *[see Overdosage (10)]*.

In an adult study assessing the respiratory-depressant effects of Xyrem at doses up to 9 g per night in 21 patients with narcolepsy, no dose-related changes in oxygen saturation were demonstrated in the group as a whole. One of the four patients with preexisting, moderate-to-severe sleep apnea had significant worsening of the apnea/hypopnea index during treatment.

In an adult study assessing the effects of Xyrem 9 g per night in 50 patients with obstructive sleep apnea, Xyrem did not increase the severity of sleep-disordered breathing and did not adversely affect the average duration and severity of oxygen desaturation overall. However, there was a significant increase in the number of central apneas in patients taking Xyrem, and clinically significant oxygen desaturation (≤55%) was measured in three patients (6%) after Xyrem administration, with one patient withdrawing from the study and two continuing after single brief instances of desaturation.

During polysomnographic evaluation (PSG), central sleep apnea and oxygen desaturation were observed in pediatric patients with narcolepsy treated with Xyrem.

Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with Xyrem administration in adult and pediatric patients.

In adult clinical trials in 128 patients with narcolepsy, two subjects had profound CNS depression, which resolved after supportive respiratory intervention. Two other patients discontinued sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea. In two controlled trials assessing PSG measures in adult patients with narcolepsy, 40 of 477 patients were included with a baseline apnea/hypopnea index of 16 to 67 events per hour, indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a clinically significant worsening of respiratory function as measured by apnea/hypopnea index and pulse oximetry at doses of 4.5 g to 9 g per night.

Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not on hormone replacement therapy and among patients with narcolepsy.

5.5 Depression and Suicidality

In adult clinical trials in patients with narcolepsy (n=781), there were two suicides and two attempted suicides in patients treated with Xyrem, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used Xyrem in conjunction with other drugs. Xyrem was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 patients treated with Xyrem, with four patients (<1%) discontinuing because of depression. In most cases, no change in Xyrem treatment was required.

In a controlled adult trial, with patients randomized to fixed doses of 3 g, 6 g, or 9 g per night Xyrem or placebo, there was a single event of depression at the 3 g per night dose. In another adult controlled trial, with patients titrated from an initial 4.5 g per night starting dose, the incidences of depression were 1 (1.7%), 1 (1.5%), 2 (3.2%), and 2 (3.6%) for the placebo, 4.5 g, 6 g, and 9 g per night doses, respectively.

In the pediatric clinical trial in patients with narcolepsy (n=104), one patient experienced suicidal ideation and two patients reported depression while taking Xyrem.

The emergence of depression in patients treated with Xyrem requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking Xyrem.

5.6 Other Behavioral or Psychiatric Adverse Reactions

During adult clinical trials in patients with narcolepsy, 3% of 781 patients treated with Xyrem experienced confusion, with incidence generally increasing with dose.

Less than 1% of patients discontinued the drug because of confusion. Confusion was reported at all recommended doses from 6 g to 9 g per night. In a controlled trial in adults where patients were randomized to fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose-response relationship for confusion was demonstrated, with 17% of patients at 9 g per night experiencing confusion. In all cases in that controlled trial, the confusion resolved soon after termination of treatment. In Trial 3 where sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in one patient at the 9 g per night dose. In the majority of cases in all adult clinical trials in patients with narcolepsy, confusion resolved either soon after termination of dosing or with continued treatment.

Anxiety occurred in 5.8% of the 874 patients receiving Xyrem in adult clinical trials in another population.

Other neuropsychiatric reactions reported in adult clinical trials in patients with narcolepsy and the post-marketing setting included hallucinations, paranoia, psychosis, aggression, and agitation.

In the pediatric clinical trial in patients with narcolepsy, neuropsychiatric reactions, including acute psychosis, confusion, and anxiety, were reported while taking Xyrem.

The emergence or increase in the occurrence of behavioral or psychiatric events in adult and pediatric patients taking Xyrem should be carefully monitored.

5.7 Parasomnias

Sleepwalking, defined as confused behavior occurring at night and at times associated with wandering, was reported in 6% of 781 patients with narcolepsy treated with Xyrem in adult controlled trials and long-term open-label studies, with <1% of patients discontinuing due to sleepwalking. Rates of sleepwalking were similar for patients taking placebo and patients taking Xyrem in controlled trials. It is unclear if some or all of the reported sleepwalking episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Five instances of sleepwalking with potential injury or significant injury were reported during a clinical trial of Xyrem in patients with narcolepsy.

Parasomnias, including sleepwalking, also have been reported in the pediatric clinical trial and in postmarketing experience with Xyrem. Therefore, episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

5.8 Use in Patients Sensitive to High Sodium Intake

Xyrem has a high salt content. In patients sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment), consider the amount of daily sodium intake in each dose of Xyrem. Table 3 provides the approximate sodium content per Xyrem dose.

Table 3
Approximate Sodium Content per Total Nightly Dose of Xyrem (g = grams)

Xyrem Dose	Sodium Content/Total Nightly Exposure
3 g per night	550 mg
4.5 g per night	820 mg
6 g per night	1100 mg
7.5 g per night	1400 mg
9 g per night	1640 mg

6 ADVERSE REACTIONS

The following clinically significant adverse reactions appear in other sections of the labeling:

- CNS depression *[see Warnings and Precautions (5.1)]*
- Abuse and Misuse *[see Warnings and Precautions (5.2)]*
- Respiratory Depression and Sleep-Disordered Breathing *[see Warnings and Precautions (5.4)]*
- Depression and Suicidality *[see Warnings and Precautions (5.5)]*
- Other Behavioral or Psychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Parasomnias *[see Warnings and Precautions (5.7)]*
- Use in Patients Sensitive to High Sodium Intake *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adult Patients

Xyrem was studied in three placebo-controlled clinical trials (Trials N1, N3, and N4, described in Sections 14.1 and 14.2) in 611 patients with narcolepsy (398 subjects treated with Xyrem, and 213 with placebo). A total of 781 patients with narcolepsy were treated with Xyrem in controlled and uncontrolled clinical trials.

Section 6.1 and Table 4 present adverse reactions from three pooled, controlled trials (N1, N3, N4) in patients with narcolepsy.

Adverse Reactions Leading to Treatment Discontinuation:

Of the 398 patients with narcolepsy treated with Xyrem, 10.3% of patients discontinued because of adverse reactions compared with 2.8% of patients receiving placebo. The most common adverse reaction leading to discontinuation was nausea (2.8%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.

Commonly Observed Adverse Reactions in Controlled Clinical Trials:

The most common adverse reactions (incidence ≥5% and twice the rate seen with placebo) in patients treated with Xyrem were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.

Adverse Reactions Occurring at an Incidence of 2% or Greater:

Table 4 lists adverse reactions that occurred at a frequency of 2% or more in any treatment group for three controlled trials and were more frequent in any Xyrem treatment group than with placebo. Adverse reactions are summarized by dose at onset. Nearly all patients in these studies initiated treatment at 4.5 g per night. In patients who remained on treatment, adverse reactions tended to occur early and to diminish over time.

Table 4
Adverse Reactions Occurring in ≥2% of Adult Patients and More Frequently with Xyrem than Placebo in Three Controlled Trials (N1, N3, N4) by Body System and Dose at Onset

Adverse Reaction	Placebo (n=213) %	Xyrem 4.5g (n=185) %	Xyrem 6g (n=258) %	Xyrem 9g (n=178) %
ANY ADVERSE REACTION	62	45	55	70
GASTROINTESTINAL DISORDERS				
Nausea	3	8	13	20
Vomiting	1	2	4	11
Diarrhea	2	4	3	4
Abdominal pain upper	2	3	1	2
Dry mouth	2	1	2	1
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS				
Pain	1	1	<1	3
Feeling drunk	1	0	<1	3
Edema peripheral	1	3	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Cataplexy	1	1	1	2
Muscle spasms	2	2	<1	2
Pain in extremity	1	3	1	1
NERVOUS SYSTEM DISORDERS				
Dizziness	4	9	11	15
Somnolence	4	1	3	8
Tremor	0	0	2	5
Disturbance in attention	0	1	0	4
Paresthesia	1	2	1	3
Sleep paralysis	1	0	1	3
PSYCHIATRIC DISORDERS				
Disorientation	1	1	2	3
Irritability	1	0	<1	3
Sleepwalking	0	0	0	3
Anxiety	1	1	1	2
RENAL AND URINARY DISORDERS				
Enuresis	1	3	3	7
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Hyperhidrosis	0	1	1	3

Dose-Response Information

In clinical trials in narcolepsy, a dose-response relationship was observed for nausea, vomiting, paresthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking, and enuresis. The incidence of all these reactions was notably higher at 9 g per night.

In controlled trials in narcolepsy, discontinuations of treatment due to adverse reactions were greater at higher doses of Xyrem.

Pediatric Patients (7 Years of Age and Older)

In the pediatric clinical trial (Trial N5), 104 patients aged 7 to 17 years (37 patients aged 7 to 11 years; 67 patients aged 12 to 17 years) with narcolepsy received Xyrem for up to one year. This study included an open-label safety continuation period in which eligible patients

received Xyrem for up to an additional 2 years. The median and maximum exposure across the entire study were 371 and 987 days, respectively.

Adverse Reactions Leading to Treatment Discontinuation

In the pediatric clinical trial, 7 of 104 patients reported adverse reactions that led to withdrawal from the study (hallucination, tactile; suicidal ideation; weight decreased; sleep apnea syndrome; affect lability; anger, anxiety, depression; and headache).

Adverse Reactions in the Pediatric Clinical Trial

The most common adverse reactions (≥5%) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%), and sleepwalking (6%).

Additional information regarding safety in pediatric patients appears in the following sections:

- Respiratory Depression and Sleep-Disordered Breathing *[see Warnings and Precautions (5.4)]*
- Depression and Suicidality *[see Warnings and Precautions (5.5)]*
- Other Behavioral or Psychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Parasomnias *[see Warnings and Precautions (5.7)]*

The overall adverse reaction profile of Xyrem in the pediatric clinical trial was similar to that seen in the adult clinical trial program.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Xyrem. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

arthralgia, decreased appetite, fall*, fluid retention, hangover, headache, hypersensitivity, hypertension, memory impairment, nocturia, panic attack, vision blurred, and weight decreased.

*The sudden onset of sleep in patients taking sodium oxybate, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization.

7 DRUG INTERACTIONS

7.1 Alcohol, Sedative Hypnotics, and CNS Depressants

Xyrem is contraindicated for use in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of Xyrem *[see Warnings and Precautions (5.1)]*.

7.2 Divalproex Sodium

Concomitant use of Xyrem with divalproex sodium results in an increase in systemic exposure to GHB, which was shown to cause a greater impairment on some tests of attention and working memory in a clinical study *[see Clinical Pharmacology (12.3)]*. An initial dose reduction of Xyrem is recommended when used concomitantly with divalproex sodium *[see Dosage and Administration (2.5)]*. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of Xyrem and divalproex sodium is warranted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of sodium oxybate in pregnant women. Oral administration of sodium oxybate to pregnant rats (150, 350, or 1,000 mg/kg/day) or rabbits (300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity; however, oral administration to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and growth, at a clinically relevant dose *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Labor or Delivery

Xyrem has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate, newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid and gamma-hydroxybutyrate (GHB) has been detected in newborns at delivery after intravenous administration of GHB to mothers. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

Data

Animal Data

Oral administration of sodium oxybate to pregnant rats (150, 350, or 1,000 mg/kg/day) or rabbits (300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity. The highest doses tested in rats and rabbits were approximately 1 and 3 times, respectively, the maximum recommended human dose (MRHD) of 9 g per night on a body surface area (mg/m^2) basis.

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and body weight gain at the highest dose tested. The no-effect dose for pre- and post-natal developmental toxicity in rats is less than the MRHD on a mg/m^2 basis.

8.2 Lactation

Risk Summary

GHB is excreted in human milk after oral administration of sodium oxybate. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Xyrem and any potential adverse effects on the breastfed infant from Xyrem or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of Xyrem in the treatment of cataplexy or excessive daytime sleepiness in pediatric patients (7 years of age and older) with narcolepsy have been

established in a double-blind, placebo-controlled, randomized-withdrawal study *[see Adverse Reactions (6.1) and Clinical Studies (14.3)]*.

In the pediatric clinical trial with Xyrem administration in patients with narcolepsy, serious adverse reactions of central sleep apnea and oxygen desaturation documented by polysomnography evaluation; depression; suicidal ideation; neuropsychiatric reactions including acute psychosis, confusion, and anxiety; and parasomnias, including sleepwalking, have been reported *[see Warnings and Precautions (5.4, 5.5, 5.6, 5.7) and Adverse Reactions (6.1)]*.

Safety and effectiveness of Xyrem in pediatric patients below the age of 7 years have not been established.

Juvenile Animal Toxicity Data

In a study in which sodium oxybate (0, 100, 300, or 900 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 21 through 90), mortality was observed at the two highest doses tested. Deaths occurred during the first week of dosing and were associated with clinical signs (including decreased activity and respiratory rate) consistent with the pharmacological effects of the drug. Reduced body weight gain in males and females and delayed sexual maturation in males were observed at the highest dose tested. The no-effect dose for adverse effects in juvenile rats is associated with plasma exposures (AUC) less than that at the maximum recommended human dose (9 g/night).

8.5 Geriatric Use

Clinical studies of Xyrem in patients with narcolepsy did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects. In controlled trials in another population, 39 (5%) of 874 patients were 65 years or older. Discontinuations of treatment due to adverse reactions were increased in the elderly compared to younger adults (21% vs. 19%). Frequency of headaches was markedly increased in the elderly (39% vs. 19%). The most common adverse reactions were similar in both age categories. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Because of an increase in exposure to Xyrem, the starting dose should be reduced by half in patients with hepatic impairment *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Xyrem is a Schedule III controlled substance under the Federal Controlled Substances Act. Non-medical use of Xyrem could lead to penalties assessed under the higher Schedule I controls.

9.2 Abuse

Xyrem (sodium oxybate), the sodium salt of GHB, produces dose-dependent central nervous system effects, including hypnotic and positive subjective reinforcing effects. The onset of effect is rapid, enhancing its potential for abuse or misuse.

Drug abuse is the intentional non-therapeutic use of a drug product or substance, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug misuse and abuse may occur with or without

progression to addiction. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).

Illicit GHB is abused in social settings primarily by young adults. Some of the doses estimated to be abused are in a similar dosage range to that used for treatment of patients with cataplexy. GHB has some commonalities with ethanol over a limited dose range, and some cross tolerance with ethanol has been reported as well. Cases of severe dependence and craving for GHB have been reported when the drug is taken around the clock. Patterns of abuse indicative of dependence include: 1) the use of increasingly large doses, 2) increased frequency of use, and 3) continued use despite adverse consequences.

Because illicit use and abuse of GHB have been reported, 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 (e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy). Dispose of Xyrem according to state and federal regulations. It is safe to dispose of Xyrem down the sanitary sewer.

9.3 Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the recommended dosage range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required. The discontinuation effects of Xyrem have not been systematically evaluated in controlled clinical trials. In the clinical trial experience with Xyrem in narcolepsy/cataplexy patients at recommended doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time.

Tolerance

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to Xyrem has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended Xyrem dosage regimen. Clinical studies of sodium oxybate in the treatment of alcohol withdrawal suggest a potential cross-tolerance with alcohol. The safety and effectiveness of Xyrem in the treatment of alcohol withdrawal have not been established.

10 OVERDOSAGE

10.1 Human Experience

Information regarding overdose with Xyrem is derived largely from reports in the medical literature that describe symptoms and signs in individuals who have ingested GHB illicitly. In these circumstances the co-ingestion of other drugs and alcohol was common, and may have influenced the presentation and severity of clinical manifestations of overdose.

In adult clinical trials two cases of overdose with Xyrem were reported. In the first case, an estimated dose of 150 g, more than 15 times the maximum recommended dose, caused a patient to be unresponsive with brief periods of apnea and to be incontinent of urine and feces. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of Xyrem and numerous other drugs.

10.2 Signs and Symptoms

Information about signs and symptoms associated with overdosage with Xyrem derives from reports of illicit use of GHB. Patient presentation following overdose is influenced by the dose ingested, the time since ingestion, the co-ingestion of other drugs and alcohol, and the fed or fasted state. Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even when obtunded), diaphoresis, headache, and impaired psychomotor skills have been observed. No typical pupillary changes have been described to assist in diagnosis; pupillary reactivity to light is maintained. Blurred vision has been reported. An increasing depth of coma has been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported. Respiration may be unaffected or compromised in rate and depth. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact.

10.3 Recommended Treatment of Overdose

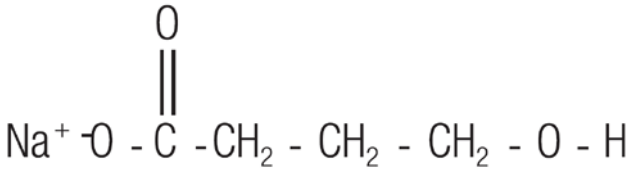
General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with GHB overdose has been responsive to atropine intravenous administration. No reversal of the central depressant effects of Xyrem can be expected from naloxone or flumazenil administration. The use of hemodialysis and other forms of extracorporeal drug removal have not been studied in GHB overdose. However, due to the rapid metabolism of sodium oxybate, these measures are not warranted.

10.4 Poison Control Center

As with the management of all cases of drug overdosage, the possibility of multiple drug ingestion should be considered. The healthcare provider is encouraged to collect urine and blood samples for routine toxicologic screening, and to consult with a regional poison control center (1-800-222-1222) for current treatment recommendations.

11 DESCRIPTION

Sodium oxybate, a CNS depressant, is the active ingredient in Xyrem. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $C_4H_7NaO_3$, and the molecular weight is 126.09 g/mole. The chemical structure is:



Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. Each mL of Xyrem contains 0.5 g of sodium oxybate (equivalent to 0.413 g/mL of oxybate) in USP Purified Water, neutralized to pH 7.5 with malic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Xyrem is a CNS depressant. The mechanism of action of Xyrem in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous compound and metabolite of the neurotransmitter GABA. It is hypothesized that the therapeutic effects of Xyrem on cataplexy and excessive daytime sleepiness are mediated through $GABA_B$ actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.

12.3 Pharmacokinetics

Pharmacokinetics of GHB are nonlinear and are similar following single or repeat dosing of Xyrem.

Absorption

Following oral administration of Xyrem, GHB is absorbed rapidly across the clinical dose range, with an absolute bioavailability of about 88%. The average peak plasma concentrations (C_{max}) following administration of each of the two 2.25 g doses given under fasting conditions 4 hours apart were similar. The average time to peak plasma concentration (T_{max}) ranged from 0.5 to 1.25 hours. Following oral administration of Xyrem, the plasma levels of GHB increased more than dose-proportionally, with blood levels increasing 3.7-fold as total daily dose is doubled from 4.5 g to 9 g. Single doses greater than 4.5 g have not been studied.

Effect of Food

Administration of Xyrem immediately after a high-fat meal resulted in delayed absorption (average T_{max} increased from 0.75 hr to 2 hr) and a reduction in C_{max} of GHB by a mean of 59% and of systemic exposure (AUC) by 37%.

Distribution

GHB is a hydrophilic compound with an apparent volume of distribution averaging 190 mL/kg to 384 mL/kg. At GHB concentrations ranging from 3 mcg/mL to 300 mcg/mL, less than 1% is bound to plasma proteins.

Elimination

Metabolism

Animal studies indicate that metabolism is the major elimination pathway for GHB, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. The primary pathway involves a cytosolic $NADP^+$-linked enzyme, GHB dehydrogenase, that catalyzes the conversion of GHB to succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle where it is metabolized to carbon dioxide and water. A second mitochondrial oxidoreductase enzyme, a transhydrogenase, also catalyzes the conversion to succinic semialdehyde in the presence of α-ketoglutarate. An alternate pathway of

biotransformation involves β-oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

Excretion

The clearance of GHB is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible. GHB has an elimination half-life of 0.5 to 1 hour.

Specific Populations

Geriatric Patients

There is limited experience with Xyrem in the elderly. Results from a pharmacokinetic study (n=20) in another studied population indicate that the pharmacokinetic characteristics of GHB are consistent among younger (age 48 to 64 years) and older (age 65 to 75 years) adults.

Pediatric Patients

The pharmacokinetics of sodium oxybate were evaluated in pediatric patients from 7 to 17 years of age (n=29). The pharmacokinetic characteristics of sodium oxybate were shown to be similar in adults and pediatric patients. Body weight was found to be the major intrinsic factor affecting oxybate pharmacokinetics.

Male and Female Patients

In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of GHB following a single Xyrem oral dose of 4.5 g.

Racial or Ethnic Groups

There are insufficient data to evaluate any pharmacokinetic differences among races.

Patients with Renal Impairment

No pharmacokinetic study in patients with renal impairment has been conducted.

Patients with Hepatic Impairment

The pharmacokinetics of GHB in 16 cirrhotic patients, half without ascites (Child's Class A) and half with ascites (Child's Class C), were compared to the kinetics in 8 subjects with normal hepatic function after a single Xyrem oral dose of 25 mg/kg. AUC values were double in the cirrhotic patients, with apparent oral clearance reduced from 9.1 mL/min/kg in healthy adults to 4.5 and 4.1 mL/min/kg in Class A and Class C patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control patients (mean $t_{1/2}$ of 59 and 32 minutes, respectively, versus 22 minutes). The starting dose of Xyrem should be reduced in patients with liver impairment *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

Drug Interactions Studies

Studies *in vitro* with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A up to the concentration of 3 mM (378 mcg/mL), a level considerably higher than levels achieved with recommended doses.

Drug interaction studies in healthy adults (age 18 to 50 years) were conducted with Xyrem and divalproex sodium, diclofenac, and ibuprofen:

- Divalproex sodium: Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with divalproex sodium (valproic acid, 1250 mg per day) increased mean systemic exposure to GHB as shown by AUC by approximately 25%

(AUC ratio range of 0.8 to 1.7), while C_{max} was comparable. Co-administration did not appear to affect the pharmacokinetics of valproic acid. A greater impairment on some tests of attention and working memory was observed with co-administration of both drugs than with either drug alone *[see Drug Interactions (7.2) and Dosage and Administration (2.5)]*.

- Diclofenac: Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with diclofenac (50 mg/dose twice per day) showed no significant differences in systemic exposure to GHB. Co-administration did not appear to affect the pharmacokinetics of diclofenac.
- Ibuprofen: Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with ibuprofen (800 mg/dose four times per day also dosed four hours apart) resulted in comparable systemic exposure to GHB as shown by plasma C_{max} and AUC values. Co-administration did not affect the pharmacokinetics of ibuprofen.

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between Xyrem and protriptyline hydrochloride, zolpidem tartrate, and modafinil. Also, there were no pharmacokinetic interactions with the alcohol dehydrogenase inhibitor fomepizole. However, pharmacodynamic interactions with these drugs cannot be ruled out. Alteration of gastric pH with omeprazole produced no significant change in the pharmacokinetics of GHB. In addition, drug interaction studies in healthy adults demonstrated no pharmacokinetic or clinically significant pharmacodynamic interactions between Xyrem and duloxetine HCl.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Administration of sodium oxybate to rats at oral doses of up to 1,000 mg/kg/day for 83 (males) or 104 (females) weeks resulted in no increase in tumors. Plasma exposure (AUC) at the highest dose tested was 2 times that in humans at the maximum recommended human dose (MRHD) of 9 g per night.

The results of 2-year carcinogenicity studies in mouse and rat with gamma-butyrolactone, a compound that is metabolized to sodium oxybate *in vivo*, showed no clear evidence of carcinogenic activity. The plasma AUCs of sodium oxybate achieved at the highest doses tested in these studies were less than that in humans at the MRHD.

Mutagenesis

Sodium oxybate was negative in the *in vitro* bacterial gene mutation assay, an *in vitro* chromosomal aberration assay in mammalian cells, and in an *in vivo* rat micronucleus assay.

Impairment of Fertility

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females through early gestation resulted in no adverse effects on fertility. The highest dose tested is approximately equal to the MRHD on a mg/m^2 basis.

14 CLINICAL STUDIES

The efficacy of Xyrem for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy has been established in the following adequate and well-controlled trials:

- Cataplexy in adult narcolepsy in Trials N1 and N2 *[see Clinical Studies (14.1)]*

- Excessive Daytime Sleepiness (EDS) in adult narcolepsy in Trials N3 and N4 *[see Clinical Studies (14.2)]*
- Cataplexy and EDS in pediatric narcolepsy in Trial N5 *[see Clinical Studies (14.3)]*

14.1 Cataplexy in Adult Narcolepsy

The effectiveness of Xyrem in the treatment of cataplexy was established in two randomized, double-blind, placebo-controlled, multicenter, parallel-group trials (Trials N1 and N2) in patients with narcolepsy (see Table 5). In Trials N1 and N2, 85% and 80% of patients, respectively, were also being treated with CNS stimulants. The high percentages of concomitant stimulant use make it impossible to assess the efficacy and safety of Xyrem independent of stimulant use. In each trial, the treatment period was 4 weeks and the total nightly Xyrem doses ranged from 3 g to 9 g, with the total nightly dose administered as two equal doses. The first dose each night was taken at bedtime and the second dose was taken 2.5 to 4 hours later. There were no restrictions on the time between food consumption and dosing.

Trial N1 enrolled 136 narcoleptic patients with moderate to severe cataplexy (median of 21 cataplexy attacks per week) at baseline. Prior to randomization, medications with possible effects on cataplexy were withdrawn, but stimulants were continued at stable doses. Patients were randomized to receive placebo, Xyrem 3 g per night, Xyrem 6 g per night, or Xyrem 9 g per night.

Trial N2 was a randomized-withdrawal trial with 55 narcoleptic patients who had been taking open-label Xyrem for 7 to 44 months prior to study entry. To be included, patients were required to have a history of at least 5 cataplexy attacks per week prior to any treatment for cataplexy. Patients were randomized to continued treatment with Xyrem at their stable dose (ranging from 3 g to 9 g per night) or to placebo for 2 weeks. Trial N2 was designed specifically to evaluate the continued efficacy of sodium oxybate after long-term use.

The primary efficacy measure in Trials N1 and N2 was the frequency of cataplexy attacks.

Table 5
Median Number of Cataplexy Attacks in Trials N1 and N2

Trial/Dosage Group	Baseline	Median Change from Baseline	Comparison to Placebo (p-value)
Trial N1 (Prospective, Randomized, Parallel Group Trial)			
		(median attacks/week)	
Placebo (n=33)	20.5	-4	–
Xyrem 6 g per night (n=31)	23.0	-10	0.0451
Xyrem 9 g per night (n=33)	23.5	-16	0.0016
Trial N2 (Randomized-Withdrawal Trial)			
		(median attacks/2 weeks)	
Placebo (n=29)	4.0	21	–
Xyrem (n=26)	1.9	0	<0.001

In Trial N1, both the 6 g and 9 g per night Xyrem doses resulted in statistically significant reductions in the frequency of cataplexy attacks. The 3 g per night dose had little effect. In Trial N2, patients randomized to placebo after discontinuing long-term open-label Xyrem therapy experienced a significant increase in cataplexy attacks ($p<0.001$), providing evidence of long-term efficacy of Xyrem. In Trial N2, the response was numerically similar for patients treated

with doses of 6 g to 9 g per night, but there was no effect seen in patients treated with doses less than 6 g per night, suggesting little effect at these doses.

14.2 Excessive Daytime Sleepiness in Adult Narcolepsy

The effectiveness of Xyrem in the treatment of excessive daytime sleepiness in patients with narcolepsy was established in two randomized, double-blind, placebo-controlled trials (Trials N3 and N4) (see Tables 6 to 8). Seventy-eight percent of patients in Trial N3 were also being treated with CNS stimulants.

Trial N3 was a multicenter randomized, double-blind, placebo-controlled, parallel-group trial that evaluated 228 patients with moderate to severe symptoms at entry into the study including a median Epworth Sleepiness Scale (see below) score of 18, and a Maintenance of Wakefulness Test (see below) score of 8.3 minutes. Patients were randomized to one of 4 treatment groups: placebo, Xyrem 4.5 g per night, Xyrem 6 g per night, or Xyrem 9 g per night. The period of double-blind treatment in this trial was 8 weeks. Antidepressants were withdrawn prior to randomization; stimulants were continued at stable doses.

The primary efficacy measures in Trial N3 were the Epworth Sleepiness Scale and the Clinical Global Impression of Change. The Epworth Sleepiness Scale is intended to evaluate the extent of sleepiness in everyday situations by asking the patient a series of questions. In these questions, patients were asked to rate their chances of dozing during each of 8 activities on a scale from 0-3 (0=never; 1=slight; 2=moderate; 3=high). Higher total scores indicate a greater tendency to sleepiness. The Clinical Global Impression of Change is evaluated on a 7-point scale, centered at *No Change*, and ranging from *Very Much Worse* to *Very Much Improved*. In Trial N3, patients were rated by evaluators who based their assessments on the severity of narcolepsy at baseline.

In Trial N3, statistically significant improvements were seen on the Epworth Sleepiness Scale score at Week 8 and on the Clinical Global Impression of Change score at Week 8 with the 6 g and 9 g per night doses of Xyrem compared to the placebo group.

Table 6
Change from Baseline in Daytime Sleepiness Score (Epworth Sleepiness Scale) at Week 8 in Trial N3 (Range 0-24)

Treatment Group	Baseline	Week 8	Median Change from Baseline at Week 8	p-value
Placebo (n=59)	17.5	17.0	-0.5	-
Xyrem 6 g per night (n=58)	19.0	16.0	-2.0	<0.001
Xyrem 9 g per night (n=47)	19.0	12.0	-5.0	<0.001

Table 7
Proportion of Patients with a Very Much or Much Improved Clinical Global Impression of Change in Daytime and Nighttime Symptoms in Trial N3

Treatment Group	Percentages of Responders (Very Much Improved or Much Improved)	Change from Baseline Significance Compared to Placebo (p-value)
Placebo (n=59)	22%	-
Xyrem 6 g per night (n=58)	52%	<0.001
Xyrem 9 g per night (n=47)	64%	<0.001

Trial N4 was a multicenter randomized, double-blind, placebo-controlled, parallel-group trial that evaluated 222 patients with moderate to severe symptoms at entry into the study including a median Epworth Sleepiness Scale score of 15, and a Maintenance of Wakefulness Test (see below) score of 10.3 minutes. At entry, patients had to be taking modafinil at stable doses of 200 mg, 400 mg, or 600 mg daily for at least 1 month prior to randomization. The patients enrolled in the study were randomized to one of 4 treatment groups: placebo, Xyrem, modafinil, or Xyrem plus modafinil. Xyrem was administered in a dose of 6 g per night for 4 weeks, followed by 9 g per night for 4 weeks. Modafinil was continued in the modafinil alone and the Xyrem plus modafinil treatment groups at the patient's prior dose. Trial N4 was not designed to compare the effects of Xyrem to modafinil because patients receiving modafinil were not titrated to a maximal dose. Patients randomized to placebo or to Xyrem treatment were withdrawn from their stable dose of modafinil. Patients taking antidepressants could continue these medications at stable doses.

The primary efficacy measure in Trial N4 was the Maintenance of Wakefulness Test. The Maintenance of Wakefulness Test measures latency to sleep onset (in minutes) averaged over 4 sessions at 2-hour intervals following nocturnal polysomnography. For each test session, the subject was asked to remain awake without using extraordinary measures. Each test session is terminated after 20 minutes if no sleep occurs, or after 10 minutes, if sleep occurs. The overall score is the mean sleep latency for the 4 sessions.

In Trial N4, a statistically significant improvement in the change in the Maintenance of Wakefulness Test score from baseline at Week 8 was seen in the Xyrem and Xyrem plus modafinil groups compared to the placebo group.

This trial was not designed to compare the effects of Xyrem to modafinil, because patients receiving modafinil were not titrated to a maximally effective dose.

Table 8
Change in Baseline in the Maintenance of Wakefulness Test Score (in minutes) at Week 8 in Trial N4

Treatment Group	Baseline	Week 8	Mean Change from Baseline at Week 8	p-value
Placebo (modafinil withdrawn) (n=55)	9.7	6.9	-2.7	-
Xyrem (modafinil withdrawn) (n=50)	11.3	12.0	0.6	<0.001
Xyrem plus modafinil (n=54)	10.4	13.2	2.7	<0.001

14.3 Cataplexy and Excessive Daytime Sleepiness in Pediatric Narcolepsy

The effectiveness of Xyrem in the treatment of cataplexy and excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy was established in a double-blind, placebo-controlled, randomized-withdrawal study (Trial N5) (NCT02221869). The study was conducted in 106 pediatric patients (median age: 12 years; range: 7 to 17 years) with a baseline history of at least 14 cataplexy attacks in a typical 2-week period prior to any treatment for narcolepsy symptoms. Of the 106 patients, 2 did not receive study drug and 63 patients were randomized 1:1 either to continued treatment with Xyrem or to placebo. Randomization to placebo was stopped early as the efficacy criterion was met at the pre-planned interim analysis.

Patients entered the study either taking a stable dose of Xyrem or were Xyrem-naïve. CNS stimulants were allowed at entry, and approximately 50% of patients used a stable dose of stimulant throughout the stable-dose and double-blind periods. Xyrem-naïve patients were initiated and titrated based on body weight over a period of up to 10 weeks. The total nightly dose was administered in two divided doses, with the first dose given at nighttime and the second given 2.5 to 4 hours later *[see Dosage and Administration (2.2)]*. Once a stable dose of Xyrem had been achieved, these patients entered the 2-week stable-dose period; patients taking a stable dose of Xyrem at study entry remained taking this dose for 3 weeks, prior to randomization. Efficacy was established at doses ranging from 3 g to 9 g of Xyrem per night.

The primary efficacy measure was the change in frequency of cataplexy attacks. In addition, change in cataplexy severity was evaluated with the Clinical Global Impression of Change for cataplexy severity *[see Clinical Studies (14.2) for description of scale]*. The efficacy of Xyrem in the treatment of excessive daytime sleepiness in pediatric patients with narcolepsy was evaluated with the change in the Epworth Sleepiness Scale (Child and Adolescent) score. The Epworth Sleepiness Scale (Child and Adolescent) is a modified version of the scale used in adult clinical trials described above *[see Clinical Studies (14.2) for description and scoring]*. The overall change in narcolepsy condition was assessed by the Clinical Global Impression of Change for narcolepsy overall. Efficacy was assessed during or at the end of the 2-week double-blind treatment period, relative to the last 2 weeks or end of the stable-dose period (see Tables 9 and 10).

Pediatric patients taking stable doses of Xyrem who were withdrawn from Xyrem treatment and randomized to placebo during the double-blind treatment period experienced a statistically

significant increase in weekly cataplexy attacks compared with patients who were randomized to continue treatment with Xyrem. Patients randomized to receive placebo during the double-blind treatment period experienced a statistically significant worsening of EDS compared with patients randomized to continue receiving Xyrem (see Table 9).

Table 9
Number of Weekly Cataplexy Attacks and Epworth Sleepiness Scale (Child and Adolescent) Score (Trial N5)

Treatment Group	Baseline[*,†]	Double-blind Treatment Period[‡,§]	Median Change from Baseline	Comparison to Placebo (p-value[¶])
Median Number of Cataplexy Attacks (attacks/week)				
Placebo (n=32)	4.7	21.3	12.7	-
Xyrem (n=31)	3.5	3.8	0.3	<0.0001
Median Epworth Sleepiness Scale (Child and Adolescent) Score				
Placebo (n=31**)	11	12	3	-
Xyrem (n=30**)	8	9	0	0.0004

[*] For weekly number of cataplexy attacks, baseline value is calculated from the last 14 days of the stable-dose period.
[†] For Epworth Sleepiness Scale score, baseline value is collected at the end of stable-dose period.
[‡] Weekly number of cataplexy attacks is calculated from all days within the double-blind treatment period.
[§] For Epworth Sleepiness Scale, value is collected at the end of the double-blind treatment period.
[¶] P-value from rank-based analysis of covariance (ANCOVA) with treatment as a factor and rank baseline value as a covariate.
** One patient in each of the treatment groups did not have baseline ESS score available and were not included in this analysis.

Patients randomized to receive placebo during the double-blind treatment period experienced a statistically significant worsening of cataplexy severity and narcolepsy overall according to the clinician's assessment compared with patients randomized to continue receiving Xyrem (see Table 10).

Table 10
Clinical Global Impression of Change (CGIc) for Cataplexy Severity and Narcolepsy Overall (Trial N5)

	CGIc Cataplexy Severity[*]		CGIc Narcolepsy Overall[*]	
Worsened, %[†]	Placebo (n=32)	Xyrem (n=29)[‡]	Placebo (n=32)	Xyrem (n=29)[‡]
Much worse or very much worse	66%	17%	59%	10%
p-value[§]	0.0001		<0.0001	

[*] Responses indicate change of severity or symptoms relative to receiving Xyrem treatment at baseline.
[†] Percentages based on total number of observed values.
[‡] Two patients randomized to Xyrem did not have the CGIc assessments completed and were excluded from the analysis.
[§] P-value from Pearson's chi-square test.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Xyrem is a clear to slightly opalescent oral solution. Each prescription includes one bottle of Xyrem with attached press in bottle adaptor, an oral measuring device (plastic syringe), and a Medication Guide. The pharmacy provides two empty containers with child-resistant caps with each Xyrem shipment.

Each amber bottle contains Xyrem oral solution at a concentration of 0.5 g per mL (0.5 g/mL of sodium oxybate equivalent to 0.413 g/mL of oxybate) and has a child-resistant cap.

One 180 mL bottle NDC 68727-100-01

16.2 Storage

Keep out of reach of children.

Xyrem should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

Dispense in tight containers.

Solutions prepared following dilution should be consumed within 24 hours.

16.3 Handling and Disposal

Xyrem is a Schedule III drug under the Controlled Substances Act. Xyrem should be handled according to state and federal regulations. It is safe to dispose of Xyrem down the sanitary sewer.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Central Nervous System Depression

Inform patients and/or caregivers that Xyrem can cause central nervous system depression, including respiratory depression, hypotension, profound sedation, syncope, and death. Instruct patients to not engage in activities requiring mental alertness or motor coordination, including operating hazardous machinery, for at least 6 hours after taking Xyrem. Instruct patients and/or their caregivers to inform their healthcare providers of all the medications they take *[see Warnings and Precautions (5.1)]*.

Abuse and Misuse

Inform patients and/or caregivers that the active ingredient of Xyrem is gamma-hydroxybutyrate (GHB), which is associated with serious adverse reactions with illicit use and abuse *[see Warnings and Precautions (5.2)]*.

XYWAV and XYREM REMS

Xyrem is available only through a restricted program called the XYWAV and XYREM REMS *[see Warnings and Precautions (5.3)]*. Inform the patient and/or caregiver of the following notable requirements:

- Xyrem is dispensed only by the central pharmacy
- Xyrem will be dispensed and shipped only to patients enrolled in the XYWAV and XYREM REMS

Xyrem is available only from the central pharmacy participating in the program. Therefore, provide patients and/or caregivers with the telephone number and website for information on how to obtain the product.

Alcohol or Sedative Hypnotics

Advise patients and/or caregivers that alcohol and other sedative hypnotics should not be taken with Xyrem.

Sedation

Inform patients and/or caregivers that the patient is likely to fall asleep quickly after taking Xyrem (often within 5 and usually within 15 minutes), but the time it takes to fall asleep can vary from night to night. The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization *[see Adverse Reactions (6.2)]*. Instruct patients and/or caregivers that the patient should remain in bed following ingestion of the first and second nightly doses. Instruct patients and/or caregivers that the patient should not take their second nightly dose until 2.5 to 4 hours after the first dose *[see Dosage and Administration (2.3)]*.

Food Effects on Xyrem

Inform patients and/or caregivers that the first nightly dose should be taken at least 2 hours after eating.

Respiratory Depression and Sleep-Disordered Breathing

Inform patients that Xyrem may impair respiratory drive, especially in patients with compromised respiratory function, and may cause apnea *[see Warnings and Precautions (5.4)]*.

Depression and Suicidality

Instruct patients and/or caregivers to contact a healthcare provider immediately if the patient develops depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or suicidal ideation *[see Warnings and Precautions (5.5)]*.

Other Behavioral or Psychiatric Adverse Reactions

Inform patients and/or caregivers that Xyrem can cause behavioral or psychiatric adverse reactions, including confusion, anxiety, and psychosis. Instruct them to notify their healthcare provider if any of these types of symptoms occur *[see Warnings and Precautions (5.6)]*.

Sleepwalking

Instruct patients and/or caregivers that Xyrem has been associated with sleepwalking and other behaviors during sleep, and to contact their healthcare provider if this occurs *[see Warnings and Precautions (5.7)]*.

Sodium Intake

Instruct patients and/or caregivers that Xyrem contains a significant amount of sodium and patients who are sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment) should limit their sodium intake *[see Warnings and Precautions (5.8)]*.

Distributed By:

Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

Protected by U.S. Patent Nos. 8,731,963; 8,772,306; 9,050,302; 9,486,426; and 10,213,400.

MEDICATION GUIDE
XYREM® (ZĪE-rem)
(sodium oxybate)
oral solution, CIII

Read this Medication Guide carefully before you start or your child starts taking XYREM and each time you get or your child gets a refill. There may be new information. This information does not take the place of talking to your doctor about your or your child's medical condition or treatment.

What is the most important information I should know about XYREM?

- XYREM is a central nervous system (CNS) depressant. Taking XYREM with other CNS depressants such as medicines used to make you or your child fall asleep, including opioid analgesics, benzodiazepines, sedating antidepressants, antipsychotics, sedating anti-epileptic medicines, general anesthetics, muscle relaxants, alcohol, or street drugs, may cause serious medical problems, including:
  - o trouble breathing (respiratory depression)
  - o low blood pressure (hypotension)
  - o changes in alertness (drowsiness)
  - o fainting (syncope)
  - o death

  Ask your doctor if you are not sure if you are, or your child is, taking a medicine listed above.
- XYREM is a federal controlled substance (CIII). The active ingredient of XYREM is a form of gamma-hydroxybutyrate (GHB) that is also a federal controlled substance (CI). Abuse of illegal GHB, either alone or with other CNS depressants may cause serious medical problems, including:
  - o seizure
  - o trouble breathing (respiratory depression)
  - o changes in alertness (drowsiness)
  - o coma
  - o death

  Call your doctor right away if you have or your child has any of these serious side effects.
- Anyone who takes XYREM should not do anything that requires them to be fully awake or is dangerous, including driving a car, using heavy machinery, or flying an airplane, for at least 6 hours after taking XYREM. Those activities should not be done until you know how XYREM affects you or your child.
- Keep XYREM in a safe place to prevent abuse and misuse. Selling or giving away XYREM may harm others, and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
- Because of the risk of CNS depression, abuse, and misuse, XYREM is available only by prescription, and filled through the central pharmacy in the XYWAV and XYREM REMS. You or your child must be enrolled in the XYWAV and XYREM REMS to receive XYREM. For information on how to receive XYREM visit www.XYWAVXYREMREMS.COM. Before you receive or your child receives XYREM, your doctor or pharmacist will make sure that you understand how to take XYREM safely and effectively. If you have any questions about XYREM, ask your doctor or call the XYWAV and XYREM REMS at 1-866-997-3688.

What is XYREM?

XYREM is a prescription medicine used to treat the following symptoms in people 7 years of age or older with narcolepsy:

- sudden onset of weak or paralyzed muscles (cataplexy), or
- excessive daytime sleepiness (EDS)

It is not known if XYREM is safe and effective in children less than 7 years of age.

Do not take XYREM if you or your child:

- takes other sleep medicines or sedatives (medicines that cause sleepiness)
- drinks alcohol
- has a rare problem called succinic semialdehyde dehydrogenase deficiency

Before taking XYREM, tell your doctor about all medical conditions, including if you or your child:

- have a history of drug abuse.
- have short periods of not breathing while sleeping (sleep apnea)
- has trouble breathing or has lung problems. You or your child may have a higher chance of having serious breathing problems when taking XYREM.

- have or had depression or has tried to harm yourself or themselves. You or your child should be watched carefully for new symptoms of depression.
- has or had behavior or other psychiatric problems such as**:**

o anxiety	o seeing or hearing things that are not real (hallucinations)
o feeling more suspicious (paranoia)	o being out of touch with reality (psychosis)
o acting aggressive	o agitation

- have liver problems
- are on a salt-restricted diet. XYREM contains a lot of sodium (salt) and may not be right for you or your child.
- have high blood pressure
- have heart failure
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if XYREM can harm your unborn baby.
- are breastfeeding or plan to breastfeed. XYREM passes into breast milk. You and your doctor should decide if you or your child will take XYREM or breastfeed.

Tell your doctor about all the medicines you take or your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially, tell your doctor if you take or your child takes other medicines to help you or your child sleep (sedatives). Know the medicines you take or your child takes. Keep a list of them to show your doctor and pharmacist when you get or your child gets a new medicine.

How should I take or give XYREM?

- Read the **Instructions for Use** at the end of this Medication Guide for detailed instructions on how to take XYREM.
- Take or give XYREM exactly as your doctor tells you to take or give it.
- XYREM can cause physical dependence and craving for the medicine when it is not taken as directed.
- Never change the XYREM dose without talking to your doctor.
- XYREM can cause sleep very quickly without feeling drowsy. Some people fall asleep within 5 minutes and most fall asleep within 15 minutes. The time it takes to fall asleep might be different from night to night.
- Falling asleep quickly, including while standing or while getting up from the bed, has led to falls with injuries that have required some people to be hospitalized.
- XYREM is taken at night divided into 2 doses.
  - **Adults:** Take the first XYREM dose at bedtime while you are in bed and lie down immediately. Take the second XYREM dose 2½ to 4 hours after the first XYREM dose. You may want to set an alarm clock to make sure you wake up to take the second XYREM dose. You should remain in bed after taking the first and second doses of XYREM.
  - **Children:** Give the first XYREM dose at bedtime or after an initial period of sleep, while your child is in bed and have them lie down immediately. Give the second XYREM dose 2½ to 4 hours after the first XYREM dose. You may want to set an alarm clock to make sure you wake up to give the second XYREM dose. Your child should remain in bed after taking the first and second doses of XYREM.
- If you miss or your child misses the second XYREM dose, skip that dose and do not take or give XYREM again until the next night. Never take or give 2 XYREM doses at 1 time.
- Wait at least 2 hours after eating before taking XYREM.
- If you take or your child takes too much XYREM, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of XYREM?
XYREM can cause serious side effects, including:

- See **"What is the most important information I should know about XYREM?"**
- **breathing problems, including:**
  - slower breathing
  - trouble breathing
  - short periods of not breathing while sleeping (sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they take XYREM.
- **mental health problems, including:**
  - confusion
  - seeing or hearing things that are not real (hallucinations)
  - unusual or disturbing thoughts (abnormal thinking)
  - feeling anxious or upset
  - depression
  - thoughts of killing yourself or trying to kill yourself
  - increased tiredness
  - feelings of guilt or worthlessness
  - difficulty concentrating

  Call your doctor right away if you have or your child has symptoms of mental health problems, or a change in weight or appetite.
- **sleepwalking.** Sleepwalking can cause injuries. Call your doctor if you start or your child starts sleepwalking. Your doctor should check you or your child.

The most common side effects of XYREM in adults include:

- nausea
- sleepiness
- dizziness
- vomiting
- bedwetting
- tremor

The most common side effects of XYREM in children include:

- nausea
- bedwetting
- vomiting
- headache
- weight decreased
- decreased appetite
- dizziness
- sleepwalking

Side effects may increase when taking higher doses of XYREM.
These are not all the possible side effects of XYREM. **For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

How should I store XYREM?

- Store XYREM in the original bottle prior to mixing with water. After mixing with water, store XYREM in pharmacy containers with child-resistant caps provided by the pharmacy.
- Store XYREM at room temperature between 68°F to 77°F (20°C to 25°C).
- XYREM solution prepared after mixing with water should be taken within 24 hours.
- When you have finished using a XYREM bottle:
  - empty any unused XYREM down the sink drain
  - cross out the label on the XYREM bottle with a marker
  - place the empty XYREM bottle in the trash

XYREM comes in a child-resistant package. **Keep XYREM and all medicines out of the reach of children and pets.**

General information about the safe and effective use of XYREM.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XYREM for a condition for which it was not prescribed. Do not give XYREM to other people, even if they have the same symptoms. It may harm them.
You can ask your pharmacist or doctor for information about XYREM that is written for health professionals.

What are the ingredients in XYREM?
Active ingredients: sodium oxybate
Inactive ingredients: purified water and malic acid
Distributed By:
Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

For more information, go to www.XYWAVXYREMREMS.com or call the XYWAV and XYREM REMS at 1-866-997-3688.

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 9/2020

Instructions for Use
XYREM® (ZĪE-rem)
(sodium oxybate)
oral solution, CIII

Read this Instructions for Use carefully before you (or your child) start taking XYREM and each time you (or your child) get a refill. There may be new information. This information does not take the place of talking to your doctor about your (or your child's) medical condition or treatment.

Important Information:

- **You will need to split your (or your child's) prescribed XYREM dose into 2 separate pharmacy containers for mixing.**
- **You will need to mix XYREM with water before you take or give your child the dose.**
- **Safely store the prepared XYREM doses and take within 24 hours after mixing. If the prepared dose was not taken within this time, throw the mixture away. See "Throwing away (disposing of) XYREM" section below for instructions about how to safely throw away XYREM.**
- **Both XYREM doses should be taken while in bed.**
- **The pharmacy containers may be rinsed out with water and emptied into the sink drain.**

Supplies you will need for mixing and taking (or giving your child) XYREM. See Figure A:

- Bottle of XYREM medicine
- Dosing syringe for measuring and dispensing the XYREM dose
- Measuring cup that is able to measure about ¼ cup of water (not provided with the XYREM shipment)
- 2 **empty** pharmacy containers with child-resistant caps for mixing, storing, and taking the XYREM doses
- Alarm clock (not pictured which may be included in the first shipment)
- Medication Guide

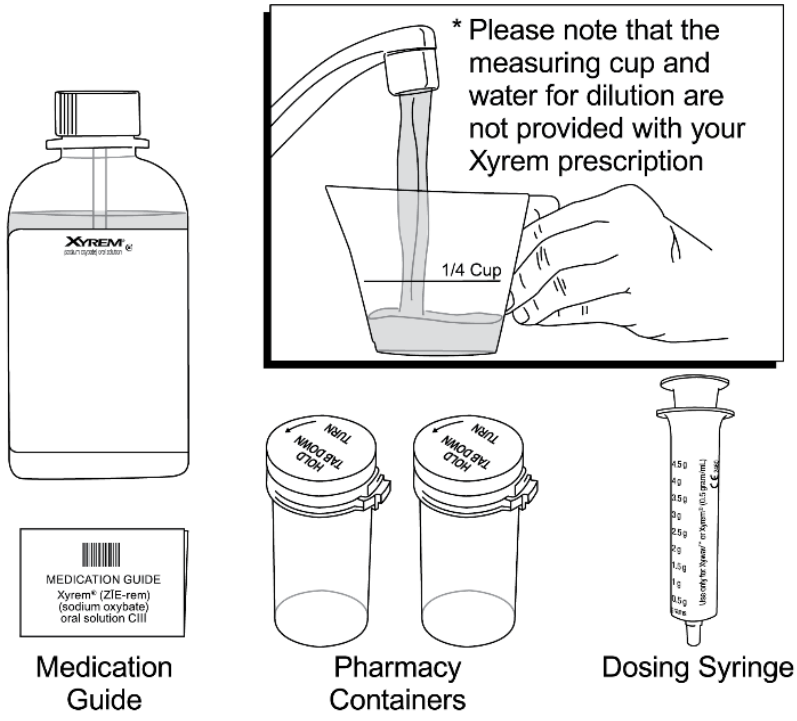


Figure A

Step 1: Setup

- Take the XYREM bottle, syringe, and pharmacy containers out of the shipping box.
- Take the syringe out of the plastic wrapper. Use only the syringe provided with the XYREM prescription.
- Fill a measuring cup (not provided) with about ¼ cup of water available for mixing your dose.
- **Make sure the pharmacy containers are empty.**
- Open both pharmacy containers by holding the tab under the cap and turning counterclockwise (to the left). See Figure B.

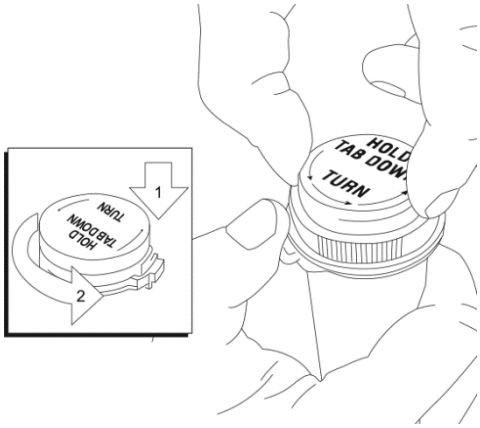


Figure B

Remove the tamper evident band by pulling at the perforations and then remove the bottle cap from the XYREM bottle by pushing down while turning the cap counterclockwise. See Figure C.

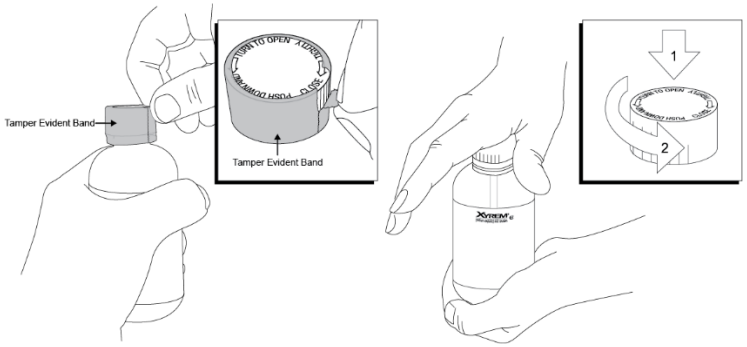


Figure C

Step 2. Prepare the first XYREM dose (prepare before bedtime)
Place the XYREM bottle on a hard, flat surface and grip the bottle with one hand and firmly press the syringe into the center opening of the bottle with the other hand. See Figure D.

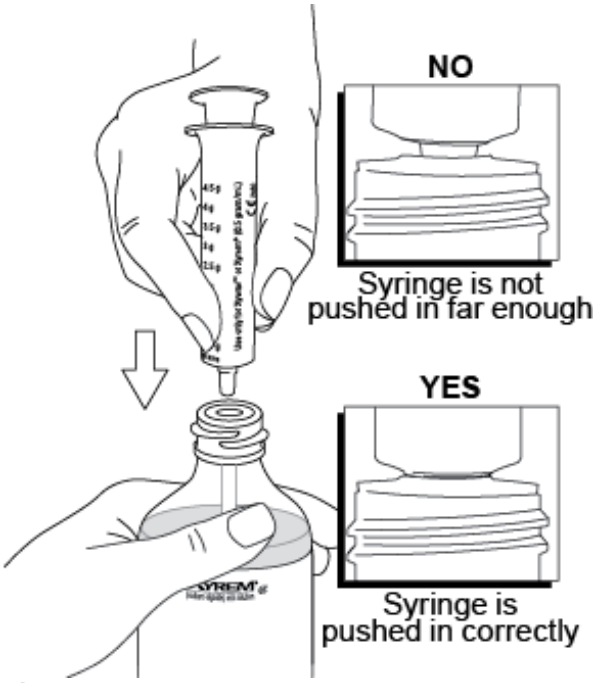


Figure D

Pull back on the plunger until the medicine flows into the syringe and the liquid level is lined up with the marking on the syringe that matches you or your child's dose. See Figure E.

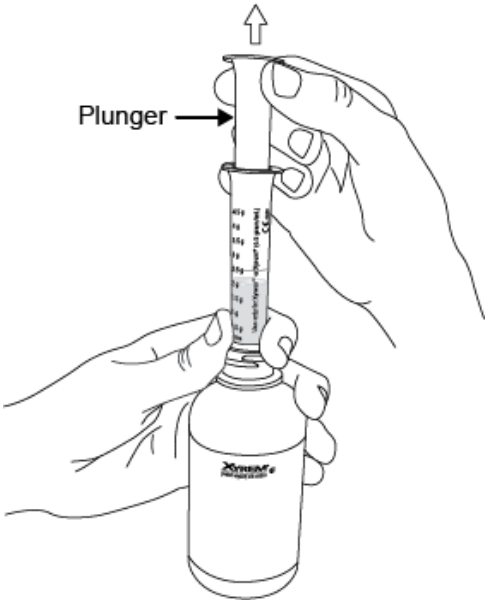


Figure E

Note: The XYREM medicine will not flow into the syringe unless you keep the bottle upright.

Figure F shows an example of drawing up a XYREM dose of 2.25 g. Figure G shows an example if an air space forms when drawing up the dose.

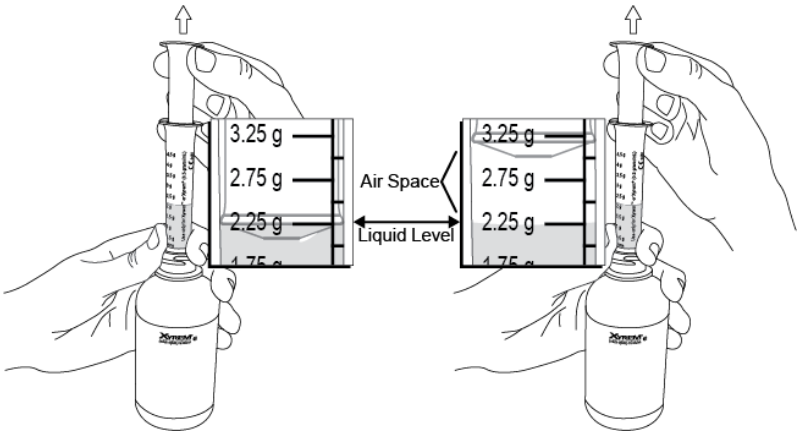


Figure F **Figure G**

Note: If an air space forms between the plunger and the liquid when drawing up the medicine, line up the liquid level with the marking on the syringe that matches your or your child's dose. See Figure G above.

- After you draw up the first divided XYREM dose, remove the syringe from the opening of the XYREM bottle.
- Empty all of the medicine from the syringe into one of the provided **empty** pharmacy containers by pushing down on the plunger until it stops. See Figure H.

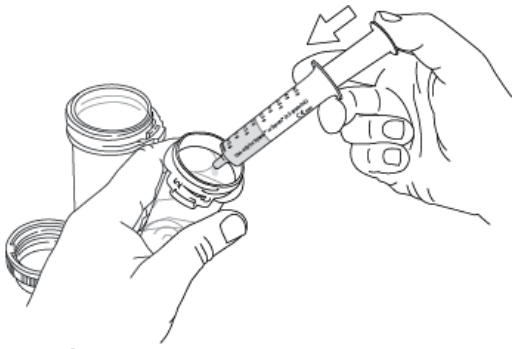


Figure H

- Using a measuring cup, pour about ¼ cup of water into the pharmacy container. **Be careful to add only water to the pharmacy container and not more XYREM.**
- **All shipped bottles of XYREM contain the concentrated medicine. Water for mixing the medicine is not provided in the shipment.**

- Place the child-resistant cap provided on the filled pharmacy container on the pharmacy container and turn the cap clockwise (to the right) until it clicks and locks into its child-resistant position. See Figure I.

Figure I

Step 3. Prepare the second XYREM dose (prepare before bedtime)

- Repeat Step 2 drawing up the amount of medicine prescribed for your (or your child's) second dose:
  - emptying the syringe into the second pharmacy container
  - adding about ¼ cup of water and
  - closing the pharmacy container

Step 4. Store the prepared XYREM doses

- Put the cap back on the XYREM bottle and store the XYREM bottle and both prepared doses in a safe and secure place. Store in a locked place if needed.
- Keep the XYREM bottle and both prepared XYREM doses out of the reach of children and pets.
- Rinse the syringe out with water and squirt the liquid into the sink drain by pushing down on the plunger until it stops.

Step 5. Take or give the first XYREM dose

- At bedtime, and before you take (or give) the first XYREM dose, put the second XYREM dose in a safe place. Caregivers should make sure all XYREM doses are kept in a safe place until given. You may want to set an alarm clock for 2½ to 4 hours later to make sure you wake up to take (or give) the second dose.
- When it is time to take (or give) the first XYREM dose, remove the cap from the pharmacy container by pressing down on the child-resistant locking tab and turning the cap counterclockwise.
- Drink (or have your child drink) all of the first XYREM dose while sitting in bed. Put the cap back on the first pharmacy container and immediately lie down to sleep (or have your child lie down to sleep).
- You (or your child) should fall asleep soon. Some people fall asleep within 5 minutes and most fall asleep within 15 minutes. Some patients take less time to fall asleep, and some take more time. The time it takes you (or your child) to fall asleep might be different from night to night.

Step 6. Take or give the second XYREM dose

- When you wake up 2½ to 4 hours later for your (or your child's) second dose of XYREM, take the cap off the second pharmacy container.
- If you (or your child) wake up before the alarm and it has been at least 2½ hours since the first XYREM dose, turn off the alarm and take (or give your child) the second XYREM dose.
- Drink (or have your child drink) all of the second XYREM dose while sitting in bed. Put the cap back on the second pharmacy container and immediately lie down (or have your child lie down) to continue sleeping.

How should I store XYREM?

- Store XYREM in the original bottle prior to mixing with water. After mixing, store XYREM in the pharmacy containers provided by the pharmacy. The caps on the original bottle and pharmacy containers are child-resistant.
- Store XYREM at room temperature between 68°F to 77°F (20°C to 25°C).
- XYREM solution prepared after mixing with water should be taken within 24 hours or emptied down the sink drain.

Throwing away (disposing of) XYREM

- When you have finished using a XYREM bottle:
  - empty any unused XYREM down the sink drain
  - cross out the label on the XYREM bottle with a marker (not provided with the XYREM shipment)
  - place the empty XYREM bottle in the trash
- **Keep XYREM and all medicines out of the reach of children and pets.**

Distributed By:
Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304
These Instructions for Use have been approved by the U.S. Food and Drug Administration. Approved: 7/2020

EXHIBIT C

Risk Evaluation and Mitigation Strategy (REMS) Document

XYWAV (calcium, magnesium, potassium, and sodium oxybates) and XYREM[1] (sodium oxybate) REMS Program

I. Administrative Information

Application Numbers: NDA 21196 (and Authorized Generic); NDA 212690
Application Holder: Jazz Pharmaceuticals, Inc (NDA 21196); Jazz Pharmaceuticals Ireland, Ltd. (NDA 212690)
Initial REMS Approval: 02/2015
Most Recent REMS Update: [01/2021]

II. REMS Goal

The goal of the XYWAV and XYREM REMS is to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of XYWAV and XYREM by:

1. Informing prescribers, pharmacists, and patients of:
    a. The risk of significant CNS and respiratory depression associated with XYWAV and XYREM
    b. The contraindication of use of XYWAV and XYREM with sedative hypnotics and alcohol
    c. The potential for abuse, misuse, and overdose associated with XYWAV and XYREM
    d. The safe use, handling, and storage of XYWAV and XYREM
2. Ensuring that pharmacy controls exist prior to filling prescriptions for XYWAV and XYREM that:
    a. Screen for concomitant use of sedative hypnotics and other potentially interacting agents
    b. Monitor for inappropriate prescribing, misuse, abuse, and diversion of XYWAV and XYREM
    c. Notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion

III. REMS Requirements

Jazz Pharmaceuticals must ensure that healthcare providers, patients, and the pharmacy comply with the following requirements:

1. Healthcare providers who prescribe XYWAV and XYREM must:	
To become certified to prescribe	1. Review the XYWAV and XYREM Prescribing Information. 2. Review the following: Prescriber Brochure. 3. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS Program.

[1] Includes XYREM (sodium oxybate) oral solution and authorized generic sodium oxybate oral solution

1. Healthcare providers who prescribe XYWAV and XYREM must:	
Before treatment initiation (first dose)	4. Assess the patient's health status to determine if XYWAV or XYREM is medically appropriate by screening for history of alcohol or substance abuse, sleep-related breathing disorders, compromised respiratory function, and depression or suicidality. 5. Assess the patient's health status to determine if XYWAV or XYREM is medically appropriate by screening for concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents. Document and submit to the REMS Program using the product-specific Prescription Form. 6. Counsel the patient on the serious risks associated with XYWAV and XYREM safe use, handling, and storage using the XYWAV Patient Quick Start Guide, XYREM Patient Quick Start Guide, XYWAV Brochure for Pediatric Patients and their Caregivers, or XYREM Brochure for Pediatric Patients and their Caregivers. 7. Enroll the patient by completing and submitting the Patient Enrollment Form to the REMS Program. 8. Order the prescription using either the XYWAV Prescription Form or XYREM Prescription Form and submit it to the REMS Program.
Before treatment re-initiation	9. For patients dis-enrolled for suspicion of abuse, misuse or diversion: communicate with the pharmacy and agree it is appropriate to re-enroll the patient. 10. For patients with a lapse in treatment of 6 months or longer: order the prescription using either the XYWAV Prescription Form or XYREM Prescription Form and submit it to the REMS program.
During treatment; within the first 3 months of starting treatment and recommended every 3 months thereafter	11. Assess the patient for: concomitant use of sedative hypnotics, other CNS depressants, or potentially interacting agents; serious adverse events; and signs of abuse and misuse including an increase in dose or frequency of dosing, reports of lost, stolen, or spilled medication, and drug-seeking behavior.
At all times	12. Report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death, and any cases of suspected abuse, misuse, or diversion to Jazz Pharmaceuticals.

2. Patients who are prescribed XYWAV and XYREM:

Before treatment initiation	1. Review the XYWAV Patient Quick Start Guide, XYREM Patient Quick Start Guide, XYWAV Brochure for Pediatric Patients and their Caregivers, or XYREM Brochure for Pediatric Patients and their Caregivers. 2. Receive counseling from the prescriber on the serious risks associated with XYWAV and XYREM and safe use, handling, and storage of XYWAV and XYREM using the XYWAV Patient Quick Start Guide, XYREM Patient Quick Start Guide, XYWAV Brochure for Pediatric Patients and their Caregivers, or XYREM Brochure for Pediatric Patients and their Caregivers. 3. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program. 4. Complete the Patient Counseling Checklist with the pharmacist.
During treatment	5. Adhere to the safe use conditions described in the XYWAV Patient Quick Start Guide, XYREM Patient Quick Start Guide, XYWAV Brochure for Pediatric Patients and their Caregivers, or XYREM Brochure for Pediatric Patients and their Caregivers. 6. Complete the Patient Counseling Checklist with the pharmacist based on changes in your medication and/or medical history.
During treatment; within the first 3 months of starting treatment and recommended every 3 months thereafter	7. Be monitored for concomitant use of sedative hypnotics, other CNS depressants, or potentially interacting agents; serious adverse events; signs of abuse and misuse including an increase in dose or frequency of dosing; reports of lost, stolen, or spilled medication; and drug-seeking behavior.
Before treatment re-initiation, after lapse in treatment for 6 months or longer	8. Complete the Patient Counseling Checklist with the pharmacist.
At all times	9. Inform your prescriber and the pharmacy about any new medications you may be taking or medical conditions you may have.

3.The pharmacy that dispenses XYWAV and XYREM must:

To become certified to dispense	1. For all relevant staff involved in dispensing: review the Pharmacy Training Program – Module A. 2. For all relevant staff involved in dispensing: successfully complete the Module A Knowledge Assessment and submit it to the REMS Program. 3. For all pharmacists involved in dispensing: review the Pharmacy Training Program – Module A and B. 4. For all pharmacists involved in dispensing: successfully complete the Module A Knowledge Assessment and Module B Knowledge Assessment and submit it to the REMS Program. 5. Train all pharmacists involved in dispensing per the requirements of the Pharmacy Training Program – Module B. 6. Establish processes and procedures to verify the following: the patient and prescriber are enrolled, the patient has no other active XYWAV or XYREM prescriptions. 7. Establish processes and procedures to verify all the prescription information including patient name and two additional identifiers, prescriber name and information, dose, titration information (if applicable), number of refills, dosing directions, total quantity (days' supply), and concomitant medications. 8. Establish processes and procedures to assess the patient's concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents that either are unknown to the prescriber or pose a high risk of serious interaction. 9. Establish processes and procedures to provide 24-7 toll-free access to a XYWAV and XYREM REMS Program pharmacist; to dispense no more than a one-month supply for the initial shipment and no more than a three-month supply for subsequent shipments; and to ship, track, and verify receipt of XYWAV and XYREM to the patient or patient-authorized adult designee using an overnight service.

Before dispensing	10.	For new patients and existing patients who restart treatment after not receiving XYWAV or XYREM for 6 months or longer: Counsel the patient using the Patient Counseling Checklist. Document and submit to the REMS Program using the Central Database.
	11.	For patients who report a change in their medication use or medical history: document and submit to the REMS Program using the Central Database.
	12.	Assess the patient's concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents that either are unknown to the prescriber or pose a high risk of serious interaction using the processes and procedures established as a requirement of the REMS Program.
	13.	Verify in the Central Database that the patient and prescriber are enrolled and that the patient has no other active XYWAV or XYREM prescriptions through the processes and procedures established as a requirement of the REMS Program.
	14.	For patients previously dis-enrolled for suspicion of abuse, misuse or diversion: communicate all relevant patient history to the prescriber and re-enroll the patient if the prescriber and pharmacist agree.
	15.	Verify the patient's prescription information, including patient name and two additional identifiers, prescriber name and information, dose, titration information (if applicable), number of refills, dosing directions, total quantity (days' supply), and concomitant medications through the processes and procedures established as a requirement of the REMS Program.
	16.	Assess the patient's potential for abuse, misuse, and diversion by reviewing the alerts and Risk Management Report history in the Central Database.
	17.	For patients who request an early refill or if abuse, misuse or diversion is suspected: Discuss the request or concern with the prescriber.
	18.	Dispense no more than a one months' supply for the initial shipment.
	19.	Dispense no more than a three months' supply for subsequent shipments.
Before Shipping	20.	Verify the patient's shipping address and that the patient or patient-authorized adult designee will be available to receive the shipment through the processes and procedures established as a requirement of the REMS.
	21.	Ship XYWAV and XYREM directly to each patient or a patient-authorized adult designee through the processes and procedures established as a requirement of the REMS.
	22.	Provide the patient with the XYWAV Patient Quick Start Guide, XYREM Patient Quick Start Guide, XYWAV Brochure for Pediatric Patients and their Caregivers, or XYREM Brochure for Pediatric Patients and their Caregivers with the first shipment.

After Shipping	23.	Track and verify receipt of each shipment of XYWAV and XYREM through the processes and procedures established as a requirement of the REMS.
	24.	Document and submit the shipment and receipt dates to the Central Database.
To Maintain Certification to Dispense, Every Year	25.	For all relevant staff involved in dispensing: review the Pharmacy Training Program – Module A.
	26.	For all relevant staff involved in dispensing: successfully complete the Module A Knowledge Assessment and submit it to the REMS Program.
	27.	For all pharmacists involved in dispensing: review the Pharmacy Training Program – Modules A and B.
	28.	For all pharmacists involved in dispensing: successfully complete the Module A Knowledge Assessment and Module B Knowledge Assessment and submit it to the REMS Program.
	29.	Train all pharmacists involved in dispensing on the requirements of the REMS Program using Pharmacy Training Program – Module B.
At all times	30.	Provide 24-7 toll-free access to a XYWAV and XYREM REMS Program pharmacist.
	31.	Ship XYWAV or XYREM directly to the patient or a patient-authorized adult designee using an overnight service.
	32.	Document and report all potential adverse events reported by all sources, including any CNS depression, respiratory depression, loss of consciousness, coma, and death to Jazz Pharmaceuticals.
	33.	Report lost, stolen, destroyed, or spilled drug to the Central Database using the Risk Management Report.
	34.	Monitor for all instances of patient and prescriber behavior that give rise to a reasonable suspicion of abuse, misuse, and diversion, including all requests for early refills, and all reports of lost, stolen, destroyed, or spilled drug. Report to Jazz Pharmaceuticals by documenting into the Central Database using the Risk Management Report.
	35.	Not distribute, transfer, loan, or sell XYWAV or XYREM.
	36.	Not stock XYWAV or XYREM in retail pharmacies.
	37.	Maintain records documenting staff's completion of the Pharmacy Training Program.
	38.	Comply with audits carried out by Jazz Pharmaceuticals or a third party acting on behalf of Jazz Pharmaceuticals to ensure that all processes and procedures are in place and are being followed.

Jazz Pharmaceuticals must provide training to healthcare providers who prescribe XYWAV and XYREM.
The training includes the following educational material: Prescriber Brochure. The training must be available on a website or delivered by Jazz Pharmaceuticals.

Jazz Pharmaceuticals must provide training to the pharmacy that dispenses XYWAV and XYREM.
The training includes the following educational materials: Certified Pharmacy Training Program-Module A and B, Module A Knowledge Assessment, and Module B Knowledge Assessment. The training must be available on a website or delivered by Jazz Pharmaceuticals.

To support REMS Program operations, Jazz Pharmaceuticals must:

1. Certify a pharmacy through a contract and distribute XYWAV and XYREM only to the certified pharmacy for dispensing.

2. Not stock XYWAV or XYREM in retail pharmacies.

3. Establish and maintain a REMS Program website, www.XYWAVXYREMREMS.com. The REMS Program website must include the capability to complete prescriber certification and patient enrollment, and the option to print the Prescribing Information and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS Program website must not link back to the promotional product website(s).

4. Make the REMS Program website fully operational and all REMS materials available through the website or call center within 180 calendar days of REMS modification (07/21/2020).

5. Establish and maintain a REMS Program call center for REMS participants at 1-866-997-3688.

6. Establish and maintain a validated, secure database, called the Central Database, of all REMS participants who have been or are enrolled and/or certified in the XYWAV and XYREM REMS Program. The database must include the following information: prescriber and patient enrollment status, all completed forms, prescription and shipment data as well as dosing, concomitant medications, behavior that raises suspicion of abuse, misuse, or diversion including all alerts and risk management reports.

7. Ensure prescribers are able to submit the Prescriber Enrollment Form by facsimile, mail, email, and online.

8. Ensure prescribers are able to submit the Patient Enrollment Form by facsimile, mail, and online.

9. Ensure prescribers are able to submit the Prescription Form by facsimile and mail.

10. Ensure prescribers are able to add refills and renew prescriptions by phone, facsimile, mail, and electronically

11. Ensure pediatric patients are able to change caregivers provided that the new caregiver has been counseled by the pharmacy on the serious risks and safe use of XYWAV and XYREM and acknowledges that he/she had any questions about XYWAV and XYREM answered before drug product is dispensed and shipped.

12. Ensure patients are able to change prescribers.

13. Ensure that the pharmacy is able to report lost, stolen, destroyed or spilled drug by completing a Risk Management Report in the Central Database.

14. Ensure that the pharmacy is able to report repeated incidents of lost, stolen, destroyed, or spilled drug by creating an alert on the patient's profile in the Central Database.

15. Ensure that the pharmacy is able to disenroll patients, in consultation with the prescriber and/or Jazz Pharmaceuticals, after review of incidents suggestive of abuse, misuse, or diversion by changing the patient's enrollment status in the Central Database.

16. Notify Prescribers within 2 business days after they become certified in the REMS Program.

17. Provide the certified pharmacy access to the database of certified prescribers and enrolled patients.

To ensure REMS participants' compliance with the REMS Program, Jazz Pharmaceuticals must:

18. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: XYREM distribution and dispensing; XYWAV distribution and dispensing, certification of prescribers, and the certified pharmacy; enrolled patients; and audits of REMS participants. These records must be readily available for FDA inspections.
19. Ensure that a prescriber is enrolled in the REMS Program only after verification that the Prescriber Enrollment Form is complete and all enrollment requirements are met.
20. Establish a plan for addressing noncompliance with REMS Program requirements.
21. Monitor prescribers and the certified pharmacy on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
22. Monitor the certified pharmacy for timely reporting to Jazz Pharmaceuticals of all potential adverse events and any behavior by patients or prescribers enrolled in the REMS Program that raises suspicion of abuse, misuse or diversion.
23. Monitor the Central Database on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified.
24. Audit the certified pharmacy at least annually.
25. Take reasonable steps to improve implementation of and compliance with the requirements in the XYWAV and XYREM REMS Program based on monitoring and evaluation of the XYWAV and XYREM REMS Program.

IV. REMS Assessment Timetable

Jazz Pharmaceuticals must submit REMS Assessments every 6 months from the date of the REMS approval (02/2015) for the first year, and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Jazz Pharmaceuticals must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the XYWAV and XYREM REMS:

Enrollment Forms

Prescriber:

1. Prescriber Enrollment Form

Patient:

2. Patient Enrollment Form

Training and Educational Materials

Prescriber:

3. Prescriber Brochure

Patient:

4. XYREM Patient Quick Start Guide
5. XYREM Brochure for Pediatric Patients and their Caregivers
6. XYWAV Patient Quick Start Guide
7. XYWAV Brochure for Pediatric Patients and their Caregivers

Pharmacy

8. Certified Pharmacy Training Program
9. Module A Knowledge Assessment
10. Module B Knowledge Assessment

Patient Care Forms

11. XYREM Prescription Form
12. XYWAV Prescription Form
13. Patient Counseling Checklist

Other Materials

14. Risk Management Report
15. REMS Program website

XYWAV and XYREM REMS

XYWAV and XYREM REMS PRESCRIBER ENROLLMENT FORM

XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL
XYREM® (sodium oxybate) oral solution 0.5 g/mL

Complete and submit form online at www.XYWAVXYREMREMS.com, OR scan and e-mail to ESSDSPrescribers@express-scripts.com, OR fax to XYWAV and XYREM REMS at 1-866-470-1744
(toll free), OR mail to XYWAV and XYREM REMS, PO Box 66589, St. Louis, MO 63166-6589.
For more information, please call the XYWAV and XYREM REMS at 1-866-997-3688 (toll free).
Note: Completion of this form and enrollment in the REMS allows you to prescribe both XYWAV and XYREM.

Step 1: ALL BOXES BELOW MUST BE CHECKED (☑) IN ORDER FOR THE ENROLLMENT PROCESS TO BE COMPLETE AND BEFORE YOU CAN ENROLL PATIENTS AND PRESCRIBE XYWAV or XYREM.

☐ I understand that XYWAV and XYREM are indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

☐ I have read the Prescribing Information (PI) and the XYWAV and XYREM REMS Prescriber Brochure and understand that:

- XYWAV and XYREM are Schedule III CNS depressants and can cause obtundation and clinically significant respiratory depression at recommended doses
- The use of XYWAV or XYREM in combination with alcohol or sedative hypnotics is contraindicated.
- Concurrent use of XYWAV or XYREM with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptics, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death
- Patients who have sleep apnea or compromised respiratory function (e.g., asthma, COPD, etc.) may be at higher risk of developing respiratory depression, loss of consciousness, coma, and death with XYWAV or XYREM use

☐ I agree to:

- Enroll each patient in the XYWAV and XYREM REMS
- Screen each patient for history of alcohol or substance abuse, sleep-related breathing disorders, compromised respiratory function, depression, suicidality, and concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
- Counsel each patient and/or caregiver prior to initiating therapy on the serious risks and safe use, handling, and storage of XYWAV or XYREM
- Evaluate patients within the first 3 months of starting XYWAV or XYREM. It is recommended that patients be re-evaluated every 3 months thereafter while taking XYWAV or XYREM
- Report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death, and any cases of suspected abuse, misuse, or diversion to Jazz Pharmaceuticals

Step 2: To help expedite the enrollment process, please PRINT clearly (*denotes required field).

Prescriber Information

*First Name: _____ M.I.: _____ *Last Name: _____ Prof. Designation (MD, DO, PA, NP): _____

*DEA No.: _____ *State License No.: _____ *NPI no.: _____

Facility/Practice Name: _____

*Street Address: _____

*City: _____ *State: _____ *Zip Code: _____

*Phone: _____ *Fax: _____ E-mail: _____

Office Contact: _____ Office Contact Phone: _____

Additional office locations and contacts can be entered online at XYWAVXYREMREMS.com.

Step 3: Prescriber signature is required below for enrollment in the XYWAV and XYREM REMS.

By signing below, I acknowledge the above attestations, and I understand that my personally identifiable information provided above will be shared with Jazz Pharmaceuticals, Inc., its agents, contractors, and affiliates and entered into a prescriber database for the XYWAV and XYREM REMS. I agree that I may be contacted in the future by mail, e-mail, fax, and/or telephone concerning XYWAV, XYREM, and the XYWAV and XYREM REMS.

*Prescriber Signature: _____ *Date: _____

Report SERIOUS ADVERSE EVENTS by contacting Jazz Pharmaceuticals at 1-800-520-5568 or AEReporting@jazzpharma.com.

XYWAV and XYREM REMS

XYWAV and XYREM REMS PATIENT ENROLLMENT FORM

XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL
XYREM® (sodium oxybate) oral solution 0.5 g/mL

Complete and submit form online at www.XYWAVXYREMREMS.com, OR scan and e-mail to ESSDSPrescribers@express-scripts.com, OR fax to XYWAV and XYREM REMS at 1-866-470-1744 (toll free), OR mail to: XYWAV and XYREM REMS, PO Box 66589, St. Louis, MO 63166-6589.
For more information, call the XYWAV and XYREM REMS at 1-866-997-3688 (toll free).

Note: Use this form to enroll patients in the XYWAV and XYREM REMS for either product.

Please Print (*denotes required field)

Prescriber Information

*First Name: _____ M.I.: _____ *Last Name: _____ *DEA No.: _____

*Street Address: _____ *Phone: _____

*City: _____ *State: _____ *Zip Code: _____ *Fax: _____

Office Contact: _____ Office Contact Phone: _____ *NPI No.: _____

Patient Information

*First Name: _____ M.I.: ____ *Last Name: _____ *Primary Phone: _____

*Date of Birth (MM/DD/YYYY): _____ *Gender: ☐ M ☐ F Cell Phone: _____

*Address: _____ Work Phone: _____

*City: _____ *State: _____ *Zip Code: _____ E-mail: _____

Caregiver Name: _____ Relationship to Patient: _____ Caregiver Phone (if different than above): _____

Insurance Information

Does Patient Have Prescription Coverage? ☐ Yes (provide photocopy of both sides of insurance identification card with this form) ☐ No

Policy Holder's Name: _____ Policy Holder's Date of Birth (MM/DD/YYYY): _____

Insurance Company Name: _____ Relationship to Patient: _____

Insurance Phone: _____ RxID No.: _____ RxGrp No.: _____

RxBIN No.: _____ RxPCN No.: _____

Patient/Caregiver: Form must be signed before enrollment can be processed.

By signing below, I acknowledge that:

- My doctor/prescriber has counseled me on the serious risks and safe use of XYWAV and XYREM
- I have asked my doctor/prescriber any questions I have about XYWAV and XYREM

*Patient/Caregiver Signature: _____ *Date: _____

*Printed Caregiver Name (if applicable): _____

Prescriber: Form must be signed before enrollment can be processed.

By signing below, I acknowledge that:

- I have counseled the patient and/or caregiver about the serious risks associated with the use of XYWAV and XYREM and the safe use conditions as described in the XYWAV or XYREM Patient Quick Start Guide (for adult patients) or the XYWAV or XYREM Brochure for Pediatric Patients and their Caregivers (for pediatric patients)

☐ I have provided the patient and/or caregiver with the appropriate educational material [XYWAV or XYREM Patient Quick Start Guide (for adult patients) and XYWAV or XYREM Brochure for Pediatric Patients and their Caregivers (for pediatric patients) (optional)]

*Prescriber Signature: _____ *Date: _____

xywav™ (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL

XYREM® (sodium oxybate) oral solution

XYWAV and XYREM REMS

PRESCRIBER BROCHURE

Includes important prescribing information for adult and pediatric patients

xywav™ (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL

XYREM® (sodium oxybate) oral solution

XYWAV and XYREM REMS

Dear Prescriber,

Welcome to the XYWAV and XYREM REMS, which was developed in collaboration with the Food and Drug Administration (FDA) as a Risk Evaluation and Mitigation Strategy (REMS). A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure that the benefits of the drug outweigh its risks.

This brochure provides information about the XYWAV and XYREM REMS that includes important prescribing information, educational and counseling requirements, and materials necessary for program enrollment and prescribing XYWAV™ (calcium, magnesium, potassium, and sodium oxybate) oral solution, and XYREM® (sodium oxybate) oral solution, including:

- **Prescriber Enrollment Form**—a one-time enrollment is required for all prescribers of XYWAV and XYREM.
- **Patient Enrollment Form**—a one-time patient enrollment in the XYWAV and XYREM REMS is required for each new patient for whom XYWAV or XYREM will be prescribed.
- **XYWAV and XYREM Prescription Forms**—required for prescribing XYWAV and XYREM. These forms must be used for initial prescriptions and may also be used for refills and renewals of XYWAV and XYREM prescriptions.
- **XYWAV and XYREM Patient Quick Start Guides**—these guides answer important questions for adult patients about how to get XYWAV and XYREM, how to use XYWAV and XYREM properly, and how to store them safely. It also gives important information about the risks associated with XYWAV and XYREM.
- **XYWAV and XYREM Brochures for Pediatric Patients and their Caregivers**—these guides answer important questions for caregivers of pediatric patients and pediatric patients about how to use XYWAV and XYREM properly, how to store them safely, and how to get XYWAV and XYREM. It also gives important information about the risks associated with XYWAV and XYREM.

The REMS Prescriber Enrollment Form, Patient Enrollment Form, and **XYWAV Prescription Form** or **XYREM Prescription Form** must be completed in full and sent to the XYWAV and XYREM REMS. For your convenience, all these forms are available online at www.XYWAVXYREMREMS.com, and can be requested by calling the XYWAV and XYREM REMS toll-free at 1-866-997-3688. The Certified Pharmacy with the XYWAV and XYREM REMS is responsible for processing all prescriptions for XYWAV and XYREM. Continue reading this brochure to learn more about the XYWAV and XYREM REMS and your responsibilities as a prescriber of XYWAV and XYREM.

Please review the Prescribing Information for XYWAV and XYREM.

XYWAV and XYREM may be dispensed only to patients enrolled in the XYWAV and XYREM REMS.

XYWAV and XYREM are indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with Narcolepsy

If you require any additional assistance or information, please call the XYWAV and XYREM REMS at 1-866-997-3688 or visit www.XYWAVXYREMREMS.com.

Sincerely,
Jazz Pharmaceuticals

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- The use of XYWAV or XYREM in combination with sedative hypnotics is contraindicated.
- The use of XYWAV or XYREM in combination with alcohol is contraindicated.
- XYWAV and XYREM are contraindicated in patients with succinic semialdehyde dehydrogenase deficiency.

WARNINGS AND PRECAUTIONS

CNS Depression

- XYWAV and XYREM are CNS depressants. Concurrent use of XYWAV or XYREM with other CNS depressants, including but not limited to opioid analgesics; benzodiazepines; sedating antidepressants, antipsychotics, or anti-epileptics; general anesthetics; muscle relaxants; and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.
  - If use of these CNS depressants in combination with XYWAV or XYREM is required, dose reduction or discontinuation of one or more CNS depressants (including XYWAV or XYREM) should be considered.
  - If short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with XYWAV or XYREM should be considered.
- Patients who have sleep apnea or compromised respiratory function may be at a higher risk of developing respiratory depression, loss of consciousness, coma, and death with XYWAV or XYREM use.

Healthcare providers should caution patients/caregivers against hazardous activities requiring complete mental alertness or motor coordination (e.g., driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYWAV or XYREM do not affect the patient adversely.

Abuse and Misuse

- XYWAV and XYREM are Schedule III controlled substances.
- The active moiety of XYWAV and XYREM is oxybate, also known as gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse events, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. Illicit GHB has also been associated with drug-facilitated sexual assault.
- The rapid onset of sedation, coupled with the amnestic features of XYWAV and XYREM, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).
- You should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of XYWAV or XYREM (e.g., increase in size or frequency of dosing; reports of lost, stolen, or spilled medication; drug-seeking behavior; feigned cataplexy).

XYWAV and XYREM REMS

- XYWAV and XYREM are to be prescribed only to patients enrolled in the XYWAV and XYREM REMS. XYWAV and XYREM are available only through a restricted distribution program called the XYWAV and XYREM REMS. Required components of the XYWAV and XYREM REMS are:
  - Healthcare providers who prescribe XYWAV or XYREM must be specially certified. To be certified, prescribers must complete the REMS Enrollment Forms and comply with the REMS requirements.
  - XYWAV and XYREM will be dispensed only by the central pharmacy that is specially certified.
  - XYWAV and XYREM will be shipped only to enrolled patients with documentation of safe use conditions. For a patient to be enrolled, patients or caregivers must sign the REMS Patient Enrollment Form and acknowledge that they have been counseled on the serious risks and safe use of XYWAV and XYREM.

Further information is available at **www.XYWAVXYREMREMS.com** or 1-866-997-3688.

Depression, Suicidality, and Other Behavioral/Neuropsychiatric Adverse Events

- Depression and suicidal ideation and behavior can occur in patients treated with XYWAV or XYREM
- The emergence of depression in patients treated with XYWAV and XYREM was seen in clinical trials and requires careful and immediate attention. 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 XYWAV or XYREM. XYWAV and XYREM can cause the emergence of neuropsychiatric adverse events (psychosis, paranoia, hallucination, aggression, and agitation), confusion, and sleepwalking. Patients should be instructed to call their healthcare provider if they experience any of these events.
- Anxiety can also occur in patients treated with XYWAV and XYREM.

Use in Patients Sensitive to High Sodium Intake

- XYREM has a high sodium content. Administration of the maximum recommended dose of XYREM (9g/night) delivers 1,640mg of sodium, corresponding to 71% of the recommended maximum daily intake of sodium (2,300 mg/day).
- Daily sodium intake should be considered in patients, particularly those on salt-restricted diets or with heart failure, hypertension, or compromised renal function.

Most Common Adverse Events

- In three controlled clinical trials with adult patients, the most common adverse reactions (incidence ≥5% and twice the rate seen with placebo) in XYREM-treated patients were nausea (20%), dizziness (15%), vomiting (11%), somnolence (8%), enuresis (7%), and tremor (5%).
- Of the 398 XYREM-treated adult patients with narcolepsy, 10.3% of patients discontinued because of adverse reactions compared with 2.8% of patients receiving placebo. The most common adverse reaction leading to discontinuation was nausea (2.8%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.
- The overall adverse reaction profile of XYREM (same active moiety as XYWAV) in pediatric patients (7 years of age and older) is similar to that in adult patients. The most common adverse reactions (>5%) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%), and sleepwalking (6%).
- In a 16-week double-blind placebo-controlled randomized withdrawal study in 201 patients with narcolepsy with cataplexy the most common adverse reactions (incidence ≥ 5% of XYWAV-treated patients) were headache (20%), nausea (13%), dizziness (10%), decreased appetite (8%), parasomnia (6%), diarrhea (6%), hyperhidrosis (6%), anxiety (5%), and vomiting (5%). 9 out of 201 patients (4%) reported adverse reactions that led to withdrawal from the study (anxiety, decreased appetite, depressed mood, depression, fatigue, headache, irritability, nausea, pain in extremity, parasomnia, somnolence, and vomiting). The most common adverse reaction leading to discontinuation was nausea (1.5%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.

Please see Prescribing Information for XYWAV and XYREM.

TABLE OF CONTENTS

Prescribing Information is also included

Prescribing XYWAV and XYREM – A Brief Guide

The XYWAV and XYREM REMS applies to XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL, and XYREM® (sodium oxybate) oral solution, 0.5 g/mL. XYWAV and XYREM are both aqueous solutions with the active moiety of oxybate. These products are subject to a REMS because they both contain oxybate, or gamma-hydroxybutyrate (GHB), a CNS depressant and a known drug of abuse. In order to prescribe either of these products, you will need to comply with the prescribing requirements outlined in the XYWAV and XYREM REMS, which are the same for both drugs. **The procedures for writing and dispensing prescriptions for XYWAV and XYREM are outlined below.**

PRESCRIBERS OF XYWAV and XYREM

PRESCRIBER ENROLLMENT

Prescribing XYWAV and XYREM requires a one-time enrollment.

- **If you are prescribing XYWAV or XYREM for the first time**, complete the **REMS Prescriber Enrollment Form**, found either accompanying this Prescriber Brochure or online at www.XYWAVXYREMREMS.com. Please:
  - Submit the form online at www.XYWAVXYREMREMS.com or
  - Scan and send via e-mail to ESSDSPrescribers@express-scripts.com or
  - Mail to **XYWAV and XYREM REMS, PO Box 66589, St. Louis, MO 63166-6589** or
  - Fax to **1-866-470-1744** (toll free).
- On the **REMS Prescriber Enrollment Form**, please confirm that:
  - You understand that **XYWAV** and **XYREM** are indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy
  - You have read and understand the Prescribing Information and this Prescriber Brochure

SCREEN

- You agree to screen each patient for:
  - History of alcohol or substance abuse
  - History of sleep-related breathing disorders
  - History of compromised respiratory function
  - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
  - History of depression or suicidality

COUNSEL

- You agree to counsel your patients and/or caregivers (for pediatric patients) on:
  - The serious risks associated with XYWAV and XYREM
  - Contraindications (alcohol and sedative hypnotics)
  - Risks of concomitant use of XYWAV or XYREM with alcohol and/or other CNS depressants, including sedating antidepressants, antipsychotics, or anti-epileptics; opioids; benzodiazepines; muscle relaxants; and general anesthetics
  - Risk of engaging in hazardous activities requiring complete mental alertness or motor coordination (e.g., driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYWAV or XYREM does not affect the patient adversely
  - Preparation and dosing instructions for XYWAV and XYREM
  - The risk of abuse and misuse associated with use of XYWAV and XYREM
  - Safe use, handling, and storage of XYWAV and XYREM

ENROLL

- You will enroll each patient in the XYWAV and XYREM REMS by completing the one-time REMS Patient

Enrollment Form and submitting the form to the XYWAV and XYREM REMS. A pediatric patient must have a caregiver

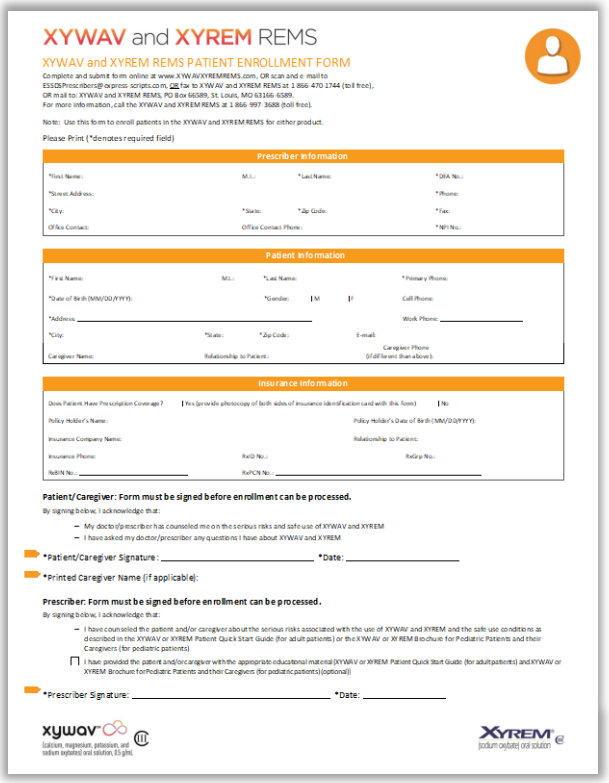
- You will evaluate each patient within the first 3 months of starting XYWAV or XYREM, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while on XYWAV or XYREM therapy:
  - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
  - Serious adverse events
  - Signs of abuse and misuse such as an increase in dose or frequency of dosing; reports of lost, stolen, or spilled medication; and/or drug-seeking behavior

REPORT

- You will report all potential serious adverse events, including CNS depression, respiratory depression, loss of consciousness, coma, and death, and any cases of suspected abuse, misuse, or diversion to Jazz Pharmaceuticals

PATIENT ENROLLMENT

- All patients must be enrolled one time in the XYWAV and XYREM REMS, using the **REMS Patient Enrollment Form**. A pediatric patient must have a caregiver.
- On the **REMS Patient Enrollment Form**:
  - For adult patients, verify that you have provided counseling to the patient about the serious risks associated with the use of the medication and its safe use as described in the XYWAV or XYREM Patient Quick Start Guides
  - For pediatric patients, verify that you have provided counseling to the caregiver about the serious risks associated with the use of the medication and its safe use as described in the XYWAV or XYREM Brochures for Pediatric Patients and their Caregivers
  - Obtain mandatory patient or caregiver signature acknowledging that he/she has been counseled on the serious risks and safe use conditions of XYWAV or XYREM and has had the opportunity to ask you any questions he/she may have about XYWAV or XYREM
  - Fax the completed **REMS Patient Enrollment Form** to the XYWAV and XYREM REMS at 1-866-470-1744 (toll free) or mail to **XYWAV and XYREM REMS, PO Box 66589, St. Louis, MO 63166-6589**. The form can also be completed online at **www.XYWAVXYREMREMS.com.**



XYWAV and XYREM REMS

XYWAV and XYREM REMS PATIENT ENROLLMENT FORM

Complete and submit form online at www.XYWAVXYREMREMS.com, OR scan and e-mail to ESSDSPrescribers@express-scripts.com, OR fax to XYWAV and XYREM REMS at 1 866 470 1744 (toll free), OR mail to: XYWAV and XYREM REMS, PO Box 66589, St. Louis, MO 63166-6589.
For more information, call the XYWAV and XYREM REMS at 1 866 997 3688 (toll free).

Note: Use this form to enroll patients in the XYWAV and XYREM REMS for either product.

Please Print (*denotes required field)

Prescriber Information

*First Name: M.I.: *Last Name: *DEA No.:
*Street Address: *Phone:
*City: *State: *Zip Code: *Fax:
Office Contact: Office Contact Phone: *NPI No.:

Patient Information

*First Name: M.I.: *Last Name: *Primary Phone:
*Date of Birth (MM/DD/YYYY): *Gender: | M | F Cell Phone:
*Address: Work Phone:
*City: *State: *Zip Code: E-mail:
Caregiver Name: Relationship to Patient: Caregiver Phone (if different than above):

Insurance Information

Does Patient Have Prescription Coverage? | Yes (provide photocopy of both sides of insurance identification card with this form) | No
Policy Holder's Name: Policy Holder's Date of Birth (MM/DD/YYYY):
Insurance Company Name: Relationship to Patient:
Insurance Phone: RxID No.: RxGrp No.:
RxBIN No.: RxPCN No.:

Patient/Caregiver: Form must be signed before enrollment can be processed.

By signing below, I acknowledge that:
- My doctor/prescriber has counseled me on the serious risks and safe use of XYWAV and XYREM
- I have asked my doctor/prescriber any questions I have about XYWAV and XYREM

*Patient/Caregiver Signature: _____ *Date: _____

*Printed Caregiver Name (if applicable):

Prescriber: Form must be signed before enrollment can be processed.

By signing below, I acknowledge that:
- I have counseled the patient and/or caregiver about the serious risks associated with the use of XYWAV and XYREM and the safe use conditions as described in the XYWAV or XYREM Patient Quick Start Guide (for adult patients) or the XYWAV or XYREM Brochure for Pediatric Patients and their Caregivers (for pediatric patients)

☐ I have provided the patient and/or caregiver with the appropriate educational material (XYWAV or XYREM Patient Quick Start Guide (for adult patients) and XYWAV or XYREM Brochure for Pediatric Patients and their Caregivers (for pediatric patients) (optional))

*Prescriber Signature: _____ *Date: _____

xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution

XYREM (sodium oxybate) oral solution

PRESCRIBING REQUIREMENTS

- Write prescriptions using either the **XYREM Prescription Form** or the **XYWAV Prescription Form** (general prescription forms will not be accepted) for the initial prescription of either product, and for patients who are reinitiating XYWAV or XYREM after a lapse in therapy of either XYWAV or XYREM for 6 months or longer. The prescription form may also be used for refills and renewals.
  - Fill out the form completely and clearly to ensure timely fulfillment of your patient's prescription
  - Verify that you have screened your patient for:
    - History of alcohol or substance abuse
    - History of sleep-related breathing disorders
    - History of compromised respiratory function
    - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
    - History of depression or suicidality
  - Verify that you have counseled the adult patient or caregiver (for pediatric patients) regarding the information below. Refer to pages 14 and 15 of this brochure for patient counseling information.
    - The serious risks associated with XYWAV or XYREM
    - Contraindications (alcohol and sedative hypnotics)
    - The risks of concomitant use of alcohol or other CNS depressants, including sedating antidepressants, antipsychotics, or anti-epileptics; opioids; benzodiazepines; muscle relaxants; and general anesthetics
    - The risks of engaging in hazardous activities requiring complete mental alertness or motor coordination (e.g. driving) within the first 6 hours of dosing or after first initiating treatment until certain that XYWAV or XYREM does not affect the patient adversely
    - Preparation and dosing instructions for XYWAV or XYREM
    - The risk of abuse and misuse associated with use of XYWAV or XYREM
    - Safe use, handling, and storage of XYWAV or XYREM (refer to pages 14 & 15 of this brochure for Patient Counseling Information)
  - Provide a list of all current prescription and non-prescription medications and dosages that the patient is currently taking, to the best of your knowledge. Additionally, indicate the presence of relevant comorbid medical conditions. This can be done by completing the appropriate fields on the **XYWAV** or **XYREM Prescription Form** or by faxing a separate page.
  - **NOTE:** Prior to dispensing each XYWAV or XYREM prescription (including refills), the Certified Pharmacy will complete an online Drug Utilization Review (DUR) and, during the patient counseling process, will ask the patient about the use of other medicines. If the pharmacist learns that the patient is taking a previously undisclosed contraindicated medication (sedative hypnotics), an opioid, or more than one CNS depressant, and the prescriber has not indicated awareness of the concomitant medication, the Certified Pharmacy will contact and inform the prescriber of the concomitant medication use prior to dispensing XYWAV or XYREM. The pharmacist may also contact the prescriber about other concomitant medications of concern. Verify that you have informed the patient and/or caregiver that the REMS will send him/her a copy of the appropriate educational material (the XYWAV or XYREM Patient Quick Start Guide for adult patients and the XYWAV or XYREM Brochure for Pediatric Patients and their Caregivers for caregivers of pediatric patients) prior to his/her first prescription fill, if you haven't provided one previously. These materials are available through Jazz Pharmaceuticals or may be downloaded at www.XYWAVXYREMREMS.com
  - Both the **XYWAV Prescription Form** and the **XYREM Prescription Form** are available online at www.XYWAVXYREMREMS.com. You can submit the prescription forms online directly to the XYWAV and XYREM REMS, or download the forms. Downloaded forms must be printed, signed, and either faxed to the XYWAV and XYREM REMS at **1-866-470-1744** (toll free), or mailed to the **XYWAV and XYREM REMS, PO Box 66589, St. Louis, MO 63166-6589**.

Please see Pediatric Patient Supplement for information on dosing for pediatric patients.

PATIENT EVALUATION

- Evaluate each patient within the first 3 months of starting XYWAV or XYREM therapy, including an evaluation of the following. It is recommended that patients be re-evaluated every 3 months thereafter while they are taking XYWAV or XYREM for:
  - Concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents
  - Serious adverse events
  - Signs of abuse and misuse, such as an increase in dose or frequency of dosing; reports of lost, stolen, or spilled medication; and/or drug-seeking behavior

Follow up frequently during titration to review symptom response and adverse reactions. A follow up of every three months is recommended.

REFILL PRESCRIPTIONS

- Prescription refills and renewals may be conveyed by phone, fax, mail, or through online submission at www.XYWAVXYREMREMS.com. In addition, the Certified Pharmacy with the XYWAV and XYREM REMS will send you the **XYWAV Prescription Form** or the **XYREM Prescription Form** upon your request. Prescription refills and renewals must be documented in the XYWAV and XYREM REMS Central Database.
- Complete refills or renewals by submitting the **XYWAV** or **XYREM Prescription Form** online at www.XYWAVXYREMSREMS.com
- To phone in refills or renewals for XYWAV or XYREM, call 1-866-997-3688
- To fax or mail refills or renewals for XYWAV or XYREM:
  - Fill out the XYWAV Prescription Form or the XYREM Prescription Form completely and clearly to ensure timely fulfillment of your patient's prescription
    - If downloading the XYWAV Prescription Form or XYREM Prescription Form online through www.XYWAVXYREMREMS.com, you must print and sign the form prior to submitting it to the XYWAV and XYREM REMS.
  - Fax the completed **XYWAV** or **XYREM Prescription Form** to the XYWAV and XYREM REMS at **1-866-470-1744** (toll free) or mail to **XYWAV** and **XYREM REMS, PO Box 66589, St. Louis, MO 63166-6589.**

Responsibilities of the XYWAV and XYREM REMS Certified Pharmacy

FOLLOWING RECEIPT OF A PATIENT'S PRESCRIPTION, THE CERTIFIED PHARMACY WILL:

- **Provide you with confirmation** of each new **XYWAV** or **XYREM Prescription Form** received from your office
- **Contact the patient's insurance provider** to verify XYWAV or XYREM prescription benefits
- **Prior to the first shipment, contact the patient or caregiver and complete the counseling checklist to:**
  - Confirm whether he/she has received a copy of the appropriate educational material (XYWAV or XYREM Patient Quick Start Guide for adult patients and XYWAV or XYREM Brochure for Pediatric Patients and their Caregivers for caregivers of pediatric patients). The Certified Pharmacy will send a copy of the appropriate educational material
  - Counsel the adult patient and/or caregiver on expectations from XYWAV or XYREM therapy and how to prepare and take XYWAV or XYREM doses safely and effectively
  - Review important XYWAV and XYREM safety information and precautions for XYWAV or XYREM use
  - Review XYWAV and XYREM safe handling and storage procedures
  - Review the adverse events associated with XYWAV and XYREM use
  - Review the patient's use of concomitant medications
    - Prior to dispensing each XYWAV or XYREM prescription (including refills), the Certified Pharmacy will complete an online Drug Utilization Review (DUR) and, during the patient counseling process, will ask the patient about the use of other medicines.
    - If the pharmacist learns that the patient is taking a previously undisclosed contraindicated medication (sedative hypnotics), an opioid, or more than one CNS depressant, and the prescriber has not indicated awareness of the concomitant medication, the Certified Pharmacy will contact and inform the prescriber of the concomitant medication use prior to dispensing XYWAV or XYREM.
    - The pharmacist may also contact the prescriber about other concomitant medications of concern.
  - Review the patient's comorbid medical conditions
  - You will be notified of any potential for drug interactions or relevant comorbid medical conditions based on patient counseling
  - Ask if the patient or caregiver has any questions about XYWAV or XYREM and answer the questions and/or refer the patient or caregiver back to the prescriber, as appropriate
- **Provide 24/7 toll-free telephone access to pharmacist support** for prescribers, office staff, patients, and caregivers by answering questions about safety, dosing, and patient care
- **Dispense and ship** XYWAV or XYREM by overnight service to the patient or his/her authorized adult designee
- **Remind** patients about monthly refills
- **Contact** the prescriber if a prescription refill or renewal is required

For your convenience, materials and information regarding the XYWAV and XYREM REMS are available online at www. XYWAVXYREMREMS.com.

Please be sure to review the Prescribing Information prior to prescribing XYWAV or XYREM for your patients.