
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

PRELIMINARY CLINICAL SAFETY REVIEW OF NDA

Brand Name: Xyrem
Generic Name: Sodium Oxybate
Sponsor: Orphan Medical, Inc.
Indication: Narcolepsy
NDA Number: 21196
Original Receipt Date: 10/3/00
Clinical Reviewer: Ranjit B. Mani, M.D.

Review Author: Ranjit B. Mani, M.D.
Review Completed: 5/3/01

Table of Contents

1. REVIEW SOURCES	7
1.1 MATERIALS FROM NDA	7
1.2 RELATED REVIEWS, CONSULTS	7
1.3 OTHER REVIEWS	7
2. BACKGROUND.....	8
2.1 INDICATION	8
2.2 IMPORTANT INFORMATION FROM PHARMACOLOGICALLY RELATED AGENTS	8
2.3 ADMINISTRATIVE HISTORY	8
2.4 PROPOSED LABELING	8
2.5 FOREIGN MARKETING	8
2.6 MISCELLANEOUS BACKGROUND INFORMATION.....	9
3. CHEMISTRY, MANUFACTURING AND CONTROLS	9
4. TOXICOLOGY	10
5. CLINICAL DATA SOURCES.....	10
5.1 SOURCES OF ALL DATA IN INTEGRATED SUMMARY OF SAFETY	10
5.1.1 <i>Study Type</i>	10
5.1.2 <i>Number Of Unique Narcoleptic Patients And Healthy Subjects In Integrated Summary Of Safety</i> 11	
5.1.3 <i>Demographics</i>	12
5.1.4 <i>Extent of Exposures</i>	13
5.2 CUT-OFF DATE FOR DATA IN INTEGRATED SUMMARY OF SAFETY	14
5.3 PRIMARY DATA SOURCES	14
5.3.1 <i>Efficacy And Long-Term Safety Studies</i>	14
5.3.2 <i>Pharmacokinetic Studies</i>	15
5.4 SECONDARY DATA SOURCES	15
5.5 OTHER DATA SOURCES	15
5.6 ADEQUACY OF HUMAN EXPERIENCE.....	16
5.7 DATA QUALITY AND COMPLETENESS.....	16
6. HUMAN PHARMACOKINETICS	16
7. TABULAR SUMMARY OF KEY EFFICACY STUDIES.....	17
7.1 STUDY OMC-GHB-2	17
7.2 SCRIMA STUDY.....	17
7.3 LAMMERS STUDY	18
7.4 STUDY OMC-SXB-21.....	18
8. INTEGRATED REVIEW OF SAFETY	18
8.1 BACKGROUND AND METHODOLOGY	18
8.2 DEATHS.....	19
8.2.1 <i>Tabular Summary Of Deaths</i>	19
8.2.2 <i>Conclusions Regarding Deaths</i>	19
8.3 SERIOUS ADVERSE EVENTS.....	19
8.3.1 <i>Serious Adverse Events In Integrated Clinical Trials</i>	20
8.3.2 <i>Serious Adverse Events In Scharf Study</i>	23
8.4 DROPOUTS AND “OTHER SIGNIFICANT ADVERSE EVENTS”	25
8.4.1 <i>Adverse Event Discontinuations In Integrated Clinical Trials</i>	26
8.4.2 <i>Adverse Event Discontinuations In Scharf Trial</i>	31

8.4.3 Adverse Event Discontinuations In Integrated Pharmacokinetic Trials	35
8.5 ADVERSE EVENTS INCIDENCE TABLES	35
8.5.1 Approach to Eliciting Adverse Events.....	35
8.5.2 Adverse Events Categorization and Preferred Terms.....	36
8.5.3 Key Adverse Events Tables	36
8.5.4 Common and Drug-Related Side Effects.....	41
8.5.5 Additional Analyses and Explorations	42
8.6 LABORATORY FINDINGS.....	56
8.6.1 Extent of Laboratory Testing During Development.....	56
8.6.2 Selection of Studies for Overall Drug-Control Comparisons And Other Analyses.....	57
8.6.3 Standard Analyses and Explorations of Laboratory Data	57
8.7 VITAL SIGNS	64
8.7.1 Extent of Vital Sign Testing During Development	64
8.7.2 Selection of Studies for Overall Drug-Control Comparisons And Other Analyses.....	65
8.7.3 Standard Analyses and Explorations of Vital Sign Data	65
8.8 ECG	67
8.8.1 Extent of Electrocardiogram Testing During Development.....	67
8.8.2 Selection of Studies for Overall Drug-Control Comparisons And Other Analyses.....	67
8.8.3 Standard Analyses and Explorations of Electrocardiogram Data.....	67
8.9 WITHDRAWAL PHENOMENON AND ABUSE POTENTIAL	70
8.9.1 Background.....	70
8.9.2 Purposes For Which GHB Is Misused Or Abused	70
8.9.3 Clinical Psychological And Physical Dependence In Humans	70
8.9.4 Rebound Symptoms With GHB Withdrawal.....	71
8.9.5 Extent Of GHB Abuse In The United States	72
8.9.6 Pre-Clinical Studies Of Drug Abuse Potential	72
8.10 HUMAN REPRODUCTION DATA.....	72
8.11 OVERDOSE.....	73
8.11.1 Background.....	73
8.11.2 Clinical Presentation	73
8.11.3 Treatment	74
9. STUDY OMC-SXB-20	74
9.1 OBJECTIVES.....	74
9.1.1 Primary	74
9.1.2 Secondary.....	74
9.2 DESIGN/SUMMARY OF INVESTIGATIONAL PLAN.....	75
9.2.1 Phase I	75
9.2.2 Phase II	75
9.3 DURATION.....	75
9.4 SAMPLE SIZE	75
9.5 KEY INCLUSION CRITERIA.....	75
9.6 KEY EXCLUSION CRITERIA.....	76
9.7 DOSAGE	76
9.8 OUTCOME MEASURES	76
9.8.1 Primary Efficacy Measures.....	76
9.8.2 Secondary Efficacy Measures	77
9.8.3 Safety Measures	77
9.9 ANALYSIS PLAN	77
9.10 RESULTS	78
9.10.1 Patient Disposition.....	78
9.10.2 Baseline And Demographic Characteristics	78
9.10.3 Tricyclic Antidepressants, Selective Serotonin Re-Uptake Inhibitors And Hypnotics At Baseline 78	
9.10.4 Protocol Deviations	78
9.10.5 Treatment Compliance.....	79

9.10.6 <i>Extent Of Exposure</i>	79
9.10.7 <i>Efficacy Results</i>	79
9.10.8 <i>Safety Results</i>	79
9.11 REVIEWER'S COMMENTS	81
10. SAFETY DATA FROM STUDY OMC-SXB-21	81
10.1 BRIEF SUMMARY OF STUDY PROTOCOL	81
10.1.1 <i>Objective</i>	81
10.1.2 <i>Design</i>	81
10.1.3 <i>Duration</i>	82
10.1.4 <i>Sample Size</i>	82
10.1.5 <i>Key Inclusion Criteria</i>	82
10.1.6 <i>Key Exclusion Criteria</i>	83
10.1.7 <i>Concomitant Medications</i>	83
10.1.8 <i>Dosage</i>	83
10.1.9 <i>Schedule</i>	83
10.1.10 <i>Outcome Measures</i>	84
10.1.11 <i>Analysis Plan</i>	84
10.2 PROTOCOL AMENDMENTS	85
10.3 ACTUAL ANALYSES PERFORMED	85
10.4 EFFICACY RESULTS	85
10.4.1 <i>Patient Disposition</i>	85
10.4.2 <i>Protocol Deviations</i>	86
10.4.3 <i>Medication Compliance</i>	86
10.4.4 <i>Baseline And Other Demographic Characteristics</i>	87
10.4.5 <i>Primary Efficacy Analysis</i>	87
10.4.6 <i>Analysis Of Secondary Efficacy Measures</i>	89
10.5 SAFETY RESULTS	89
10.5.1 <i>Exposure</i>	89
10.5.2 <i>Deaths, Serious Adverse Events And Adverse Event Discontinuations</i>	90
10.5.3 <i>Other Adverse Events</i>	90
10.5.4 <i>Laboratory Data</i>	92
10.5.5 <i>Vital Signs</i>	93
10.6 SPONSOR'S CONCLUSIONS REGARDING SAFETY	93
10.7 REVIEWER'S COMMENTS	93
11. KEY INFORMATION FROM INTEGRATED SUMMARY OF SAFETY AND OMC-SXB-21 SAFETY DATA	94
11.1 ALL ADVERSE EVENTS	94
11.2 DEATHS	94
11.3 SERIOUS ADVERSE EVENTS	94
11.4 ADVERSE EVENT DISCONTINUATIONS	95
11.5 LABORATORY DATA	95
11.6 ELECTROCARDIOGRAMS	96
11.7 VITAL SIGNS	96
11.8 WITHDRAWAL PHENOMENA	96
12. LITERATURE REVIEW	96
12.1 PUBLISHED STUDIES CONDUCTED IN HEALTHY INDIVIDUALS	96
12.2 PUBLISHED STUDIES CONDUCTED FOR SPECIFIC MEDICAL INDICATIONS	97
13. 120-DAY SAFETY UPDATE	98
13.1 CONTENTS	98
13.2 OUTLINE OF PROTOCOL FOR OMC-SXB-7	99
13.2.1 <i>Objectives</i>	99
13.2.2 <i>Design</i>	99

13.2.3 <i>Inclusion Criteria</i>	99
13.2.4 <i>Exclusion Criteria</i>	100
13.2.5 <i>Sample Size</i>	100
13.2.6 <i>Duration</i>	100
13.2.7 <i>Dosage</i>	100
13.2.8 <i>Concomitant Medication</i>	100
13.2.9 <i>Schedule</i>	101
13.2.10 <i>Statistical Considerations</i>	101
13.2.11 <i>Safety Monitoring</i>	101
13.3 PROTOCOL AMENDMENTS	101
13.4 PATIENT DISPOSITION.....	101
13.5 DEMOGRAPHICS.....	101
13.6 DOSAGE.....	102
13.7 PATIENT EXPOSURE.....	102
13.8 SAFETY RESULTS.....	103
13.8.1 <i>All Adverse Events</i>	103
13.8.2 <i>Adverse Event Tables</i>	103
13.9 DEATHS	104
13.10 SERIOUS ADVERSE EVENTS	105
13.10.1 <i>Patient # 0214</i>	105
13.10.2 <i>Patient # 0232</i>	106
13.10.3 <i>Patient # 0931</i>	106
13.10.4 <i>Patient # 1131</i>	106
13.10.5 <i>Patient # 14043</i>	106
13.10.6 <i>Patient # 2030</i>	107
13.11 ADVERSE EVENT DISCONTINUATIONS.....	107
13.11.1 <i>Patient 1305</i>	107
13.12 REVIEWER'S COMMENTS.....	108
14. RISK MANAGEMENT PROGRAM	108
14.1 STRUCTURE	108
14.1.1 <i>Closed-Loop Distribution System</i>	108
14.1.2 <i>Drug Product Kit</i>	110
14.1.3 <i>Xyrem® Physician Success Program</i>	111
14.1.4 <i>Xyrem® Patient Success Program</i>	113
14.2 OPDRA COMMENTS	114
14.3 COMMENTS OF CONTROLLED SUBSTANCES STAFF	115
14.4 ADDITIONAL RISK MANAGEMENT RECOMMENDATIONS	115
15. LABELING REVIEW	115
16. OVERALL COMMENTS	115
16.1 CLINICAL SAFETY	115
16.2 CLINICAL EFFICACY	116
16.3 WITHDRAWAL PHENOMENA AND ABUSE POTENTIAL	116
16.4 RISK MANAGEMENT PROGRAM	117
16.5 ADDITIONAL COMMENTS.....	117
17. STUDY SITE INSPECTIONS	117
18. FINANCIAL DISCLOSURE CERTIFICATION	118
18.1 COMPONENTS OF CERTIFICATION	118
18.1.1 <i>Certification Pertinent To Dr Lawrence Scrima</i>	118
18.1.2 <i>Certification Pertinent To Other Investigators</i>	118
18.2 REVIEWER'S COMMENT.....	119

Explore Litigation Insights



Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.