CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-196

MEDICAL REVIEW



Review and Evaluation of Clinical Data

NDA (Serial Number) 21196 Sponsor: Orphan Medical Inc. Xyrem® Drug: **Proposed Indication:** Narcolepsy **Material Submitted: Amendment To NDA Correspondence Date:** 5/16/02 Date Received / Agency: 5/17/02 **Date Review Completed** 6/13/02 Ranjit B. Mani, M.D. Reviewer:

TABLE OF CONTENTS

TAE	BLE OF CONTENTS	1
1.	BACKGROUND	5
2.	APPROVABLE LETTER OF APRIL 9, 2002	5
Asse	essment of Xyrem's Potential to Induce Respiratory Depression	6
Ade	quacy of the Safety Database	6
Pror	motional Materials	7
Post	marketing Issues	8
3.	LIST OF ALL CLINICAL STUDIES IN THIS APPLICATION	8
3.1	Efficacy And Safety Trials	8
3.2	Pharmacokinetic Trials	9
4.	CONTENTS OF SUBMISSION	9
5.	SCOPE OF REVIEW	10
6.	COVER LETTER	10
7. CO	ORGANIZATION OF REVIEW OF OMC-SXB-20 RESPIRATORY DATA NTAINED IN CURRENT SUBMISSION	14
8. EAF	RESPIRATORY DATA IN STUDY OMC-SXB-20 AS CONTAINED IN RLIER REVIEW COMPLETED 3/4/02	14



		-
8.1	Background	14
8.2	Outline Of Protocol For OMC-SXB-20 Study	15
8.3	Instruments For Measuring Respiratory Event Data	19
8.4	Respiratory Effect Measures	19
8.5	Methods Of Analyzing Respiratory Data	21
8.6	Results	21
8.7	Sponsor's Conclusions	38
8.8	Reviewer's Comments	39
	ADDENDUM TO REVIEW OF RESPIRATORY DATA IN STUDY OMC- 3-20 AS CONTAINED IN EARLIER REVIEW/ADDENDUM COMPLETED 3/02	
9.1	Background	40
9.2	Description Of Patients With Pre-Existing Moderate To Severe Sleep Apnea	41
9.3	Description Of A Single Patient With Mild Sleep Apnea At Baseline	47
9.4	Reviewer's Comments	48
	RESPONSE IN CURRENT SUBMISSION REGARDING RESPIRATORY	
10.1	Variability In Sleep-Disordered Breathing	50
10.2	Variability In Respiratory Event Parameters In OMC-SXB-20	59
10.3	Sponsor's Conclusions	85
10.4	Reviewer's Comments	86
11.	RISK MANAGEMENT PROGRAM ELEMENTS	. 87
11.1	Risk Management Program Proper	88
11.2	Xyrem® Physician Success Program Elements	89
11.3	Xyrem® Patient Success Program Elements	89
11.4	Post-Marketing Program Elements	91



12. PROPOSED LABELING......91

NDA .	21196 , Xyrem, Orphan Medical Inc.	6/13/02
12.1	Black Box Warning	92
12.2	Clinical Pharmacology	95
12.3	Clinical Trials	97
12.4	Contraindications	98
12.5	Warnings	99
12.6	Precautions	103
12.7	7 Adverse Reactions	104
12.8	B Drug Abuse And Dependence	104
13.	PROPOSED PATIENT MEDICATION GUIDE	106
13.1 avoi	What is the most important information I should know about Xyrem® / What id while taking Xyrem	
13.2	2 How should I store Xyrem®	107
13.3	Directions for using Xyrem®	107
14.	PROPOSED ADVERTISEMENT	107
15.	. DRUG STABILITY AND EXPIRATION DATING	107
16.	FOLLOW-UP OF PATIENTS AT STUDY SITE #8	107
16.1	Background	107
16.2 Clin	Extent To Which Site # 8 (Martha Hagaman, MD) Participated In Orphan-C nical Studies Included In NDA	
16.3	Additional Information Requested From Sponsor	108
16.4	Reviewer's Comments	112
17.	. AUDIT OF STUDY SITE #5	112
18.	. ADDITIONAL INFORMATION ABOUT A PATIENT AT SITE #41.	112
18.1	Background	112
18.2	Extent To Which Site #41 Enrolled Patients In Orphan-Sponsored Studies	113
18.3	Teleconference With Dr Mamelak: May 30, 2002	113



18.4	Conclusions114
19.	EXPOSURE DATA114
19.1	Overall Schematics For Clinical Trials In Narcoleptic Patients Included In NDA115
19.2	Tables116
19.3	Sponsor's Overall View Of Adequacy Of Exposure117
19.4	Additional Request For Information From Sponsor118
19.5	Reviewer's Comments119
20.	ADVISORY COMMITTEE MEETING120
20.1	Key Items Voted On120
20.2	Additional Recommendations121
20.3	Additional Comments122
21.	RISK-BENEFIT EQUATION AND OVERALL CONCLUSIONS 122
22.	RECOMMENDATIONS127



DOCKET

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.

