# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-196**

# CHEMISTRY REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
**REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS**

| **NDA 21-196** | **CHEM. REVIEW** #5 | **REVIEW DATE** 03-JUN-02 | |
|---|---|---|---|
| **SUBMISSION TYPE** | **DOCUMENT DATE** | **CDER DATE** | **ASSIGNED DATE** |
| AMENDMENT | 16-MAY-02 | 17-MAY-02 | 21-MAY-02 |

**NAME AND ADDRESS OF APPLICANT** Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305

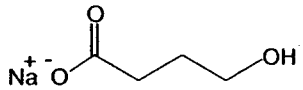
**DRUG PRODUCT NAME**

| | |
|---|---|
| Proprietary: | Xyrem® oral solution |
| Nonproprietary/USAN [1966]: | sodium oxybate |
| Code Name/Number: | |
| Chem. Type/Ther. Class: | 1P |

**PHARMACOLOGICAL CATEGORY/INDICATION** Reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy

| | | |
|---|---|---|
| **DOSAGE FORM** | Oral Solution | |
| **STRENGTHS** | 500 mg/mL | |
| **ROUTE OF ADMINISTRATION** | Oral | |
| **DISPENSED** | XXX RX | ___OTC |
| **SPECIAL PRODUCTS** | ___ Yes | XXX NO |

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA**
**Sodium 4-hydroxybutyrate**
4-Hydroxybutanoic acid monosodium salt
Sodium gamma hydroxybutyrate
$C_4H_7NaO_3$ Mol. Wt. 126.09
CAS Registry #: 502-85-2



**sodium oxybate**

**SUPPORTING DOCUMENTS**: IND —— IND —— (Treatment IND) and 12 packaging DMF's
**RELATED DOCUMENTS**: None
**CONSULTS**: None

**REMARKS/COMMENTS:** The sponsor has requested a 36-month expiry. The sponsor has submitted updated drug product stability from 6 drug product batches manufactured at —— and 4 drug product batches produced at ——. All batches were easily within specification. The impurity levels do not increase upon storage at 25°C/ ~ .

**CONCLUSIONS & RECOMMENDATIONS:** The requested tentative expiry of **36 months** is acceptable.

cc: Orig. NDA 21-196
HFD-120
HFD-120/TOliver
HFD-120/PM/AMHomonnay
HFD-120/MGuzewska
R/D Init by: MEG

Thomas F. Oliver, Ph.D., Chemist

Filename: n21196.05

**2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.**

---

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

---

/s/

---

Thomas Oliver
6/3/02 01:44:43 PM
CHEMIST

Maryla Guzewska
6/3/02 01:49:00 PM
CHEMIST

# NDA 21-196

## Xyrem® (sodium oxybate) oral solution

**Orphan Medical, Inc.**

**Chemistry Review**

**Thomas F. Oliver, Ph.D.**
**HFD-120**

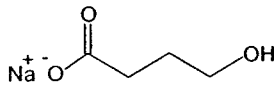
# Table of Contents

## CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-196 (Xyrem®, sodium oxybate)**
2. **CHEM. REVIEW #4**
3. **REVIEW DATE:** 21-MAR-2002
4. **REVIEWER:** Thomas F. Oliver, Ph.D

5. **PREVIOUS DOCUMENTS**

| Previous Documents | Document Date |
|---|---|
| Original | 30-SEP-2000 |
| Telecon (t01) | 05-DEC-2000 |
| Amendment | 07-DEC-2000 |
| **Review #1** | 09-FEB-2001 |
| Telecon (t02) | 08-JAN-2001 |
| Telecon (t03) | 10-JAN-2001 |
| Amendment | 12-JAN-2001 |
| Amendment | 19-JAN-2001 |
| Telecon (t04) | 25-JAN-2001 |
| Amendment | 26-JAN-2001 |
| Telecon (t05) | 01-FEB-2001 |
| Amendment | 06-FEB-2001 |
| Amendment | 08-FEB-2001 |
| Amendment | 15-FEB-2001 |
| Telecon (t06) | 02-MAR-2001 |
| **Review #2** | 19-MAR-2001 |
| Amendment | 16-MAR-2001 |
| Amendment | 12-APR-2001 |
| Amendment | 16-MAY-2001 |
| Telecon (t07) | 08-JUN-01/ 13-JUN-2001 |
| Amendment | 18-JUN-2001 |
| **Review #3** | 21-JUN-2001 |
| Telecon (t08) | 15-OCT-2001 |



**sodium oxybate**

6. **SUBMISSION BEING REVIEWED:**

| Submission Reviewed | Document Date |
|---|---|
| Amendment | 07-NOV-2001 |

7. **NAME AND ADDRESS OF APPLICANT**

Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305
Dr. Dayton Reardan
(952) 513-6969

8. **DRUG PRODUCT NAME**

| | |
|---|---|
| Proprietary: | Xyrem® oral solution |
| Nonproprietary/USAN [1966]: | sodium oxybate |
| Code Name/Number: | |
| Chem. Type/Ther. Class: | 1P |

9. **LEGAL BASIS FOR SUBMISSION** N/A

10. **PHARMACOLOGICAL CATEGORY/INDICATION** Reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy

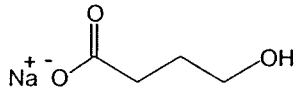
| | | | |
|---|---|---|---|
| 11. | **DOSAGE FORM** | Oral Solution | |
| 12 | **STRENGTHS** | 500 mg/mL | |
| 13. | **ROUTE OF ADMINISTRATION** | Oral | |
| 14. | **DISPENSED** | XXX RX | ___OTC |
| 15. | **SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) | ____ Yes | XXX NO |

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA**

**Sodium 4-hydroxybutyrate**

$C_4H_7NaO_3$ Mol. Wt. 126.09

CAS Registry #: 502-85-2



**sodium oxybate**

17. **RELATED/ SUPPORTING DOCUMENTS:**

**A. DMF's:**

| DMF # | Type | Holder | Item Referenced | Code[1] | Status[2] | Date Review Completed | Comments |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

[1]Action codes for DMF Table:

1--DMF Reviewed

Other codes indicate why the DMF was not reviewed, as follows:

2--Type 1 DMF

3--Reviewed previously and no revision since last review

4--Sufficient information in application

5--Authority to reference not granted

6--DMF not available

7--Other (explain under "Comments")

[2]Adequate, Inadequate

**B. Other Documents**

| Document | Application # | Description |
|---|---|---|
| IND | [redacted] | Commercial IND (Orphan Medical, Inc) |
| IND | [redacted] | Treatment IND (Orphan Medical, Inc) |

**18. STATUS**

| Consults/ CMC Related Reviews | Recommendation | Date | Reviewer |
|---|---|---|---|
| Biostatistics | Acceptable | 23-MAR-01 | Dr. Sharon Yan |
| EES | Acceptable | 06-NOV-01 | Ms. Janine D Ambrogio |
| Methods Validation | In Preparation | | |
| OPDRA | Acceptable | 27-JAN-00 | Peter Tam, RPh. |
| Microbiology | Acceptable | 23-MAY-01 | Dr. Neal Sweeney |
| Bioequivalence | Acceptable | 12-MAR-01 | Dr. Gerald Fetterly |
| EA | Acceptable<br>Categorical exemption:<br><1ppb in aquatic environment) | 09-FEB-01 | Dr. Thomas Oliver |
| Pharm/Tox | Acceptable | 02-FEB-01 | Dr. Barry Rosloff |

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

This page is blank

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
**REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS**

# SUMMARY REVIEW

**NDA 21-196** **CHEM. REVIEW** # 4 **REVIEW DATE** 22-MAR-02

| SUBMISSION TYPE | DOCUMENT DATE | CDER DATE | ASSIGNED DATE |
|---|---|---|---|
| AMENDMENT | 07-NOV-01 | 08-NOV-01 | 08-NOV-01 |

**NAME AND ADDRESS OF APPLICANT** Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305

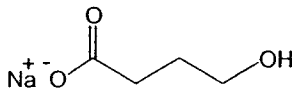
**DRUG PRODUCT NAME**

| | |
|---|---|
| Proprietary: | Xyrem® oral solution |
| Nonproprietary/USAN [1966]: | sodium oxybate |
| Code Name/Number: | |
| Chem. Type/Ther. Class: | 1P |

**PHARMACOLOGICAL CATEGORY/INDICATION** Reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with nacrolepsy

| | | |
|---|---|---|
| **DOSAGE FORM** | Oral Solution | |
| **STRENGTHS** | 500 mg/mL | |
| **ROUTE OF ADMINISTRATION** | Oral | |
| **DISPENSED** | XXX RX | ___OTC |
| **SPECIAL PRODUCTS** | ___ Yes | XXX NO |

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA**
**Sodium 4-hydroxybutyrate**
4-Hydroxybutanoic acid monosodium salt
Sodium gamma hydroxybutyrate
$C_4H_7NaO_3$
Mol. Wt. 126.09
CAS Registry #: 502-85-2



**sodium oxybate**

**SUPPORTING DOCUMENTS**: IND —— , IND —— (Treatment IND) and 12 packaging DMF's
**RELATED DOCUMENTS**: None

**CONSULTS**: The proposed trademark "Xyrem" was found acceptable by the Office of Post-Marketing Drug Risk Assessment (OPDRA) on 27-JAN-00. Compliance gave an overall recommendation of acceptable on 06-NOV-01. Microbiology found the NDA acceptable (see microbiology review #2, Dr. Neal Sweeney). The MV package is being prepared.

**REMARKS/COMMENTS:** The only CMC issue left unresolved from review #3 was the need for a successful re-inspection of the drug product manufacturing site, ——— site (only drug product manufacturer). Compliance found the site acceptable and gave an overall recommendation of acceptable on 06-NOV-01 (see attached EER report). The sponsor's requested 30 month expiry has been granted.

**CONCLUSIONS & RECOMMENDATIONS:** Recommend NDA 21-196 be approved.

cc: Orig. NDA 21-196
HFD-120
HFD-120/TOliver
HFD-120/PM/AMHomonnay
HFD-120/MGuzewska
R/D Init by: MEG

Thomas F. Oliver, Ph.D., Chemist

Filename: n21196.04.NDA.chemistrytemplate

6 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21196/000
Org Code : 120
Priority : 1P

Sponsor: ORPHAN MEDCL
13911 RIDGEWAY DR STE 250
MINNETONKA, MN 55305

Stamp Date : 02-OCT-2000
PDUFA Date : 09-APR-2002
Action Goal :
District Goal: 01-FEB-2001

Brand Name : XYREM (SODIUM OXYBATE)
500MG/ML ORAL SOL
Estab. Name:
Generic Name: SODIUM OXYBATE
Dosage Form: (SOLUTION)
Strength : 500 MG/ML

| FDA Contacts: | | | |
|---|---|---|---|
| A. HOMONNAY WEIKEL | Project Manager | (HFD-120) | 301-594-5535 |
| T. OLIVER | Review Chemist | (HFD-810) | 301-594-2570 |
| M. GUZEWSKA | Team Leader | (HFD-120) | 301-594-5571 |

---

Overall Recommendation: ACCEPTABLE on 06-NOV-2001by J. D AMBROGIO(HFD-324) 301-827-0062

WITHHOLD on 22-MAR-2001by P. LEFLER(HFD-324) 301-827-0062

---

Establishment : CFN : [redacted]

DMF No: [redacted]

Responsibilities: [redacted]

Profile : [redacted] OAI Status:
Last Milestone: OC RECOMMENDATION
Milestone Date: 13-OCT-00
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

---

Establishment : [redacted]

DMF No: AADA

Responsibilities: [redacted]

Profile : [redacted] OAI Status:
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-NOV-01
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile : [redacted] OAI Status:
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-NOV-01
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

---

Establishment : CFN : FEI :

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : [redacted] OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-MAR-01
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

---

Establishment : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : [redacted] OAI Status:
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-NOV-00
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

---

---

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

---

/s/

---

Thomas Oliver
3/29/02 10:48:52 AM
CHEMIST

Hasmukh Patel
3/29/02 10:54:37 AM
CHEMIST

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
**REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS**

**NDA 21-196** **CHEM. REVIEW** #3 **REVIEW DATE** 21-JUN-01

| SUBMISSION TYPE | DOCUMENT DATE | CDER DATE | ASSIGNED DATE |
|---|---|---|---|
| AMENDMENT | 16-MAR-01 | 20-MAR-01 | 20-MAR-01 |
| AMENDMENT | 12-APR-01 | 13-APR-01 | 13-APR-01 |
| AMENDMENT | 16-MAY-01 | 17-MAY-01 | 22-MAY-01 |
| AMENDMENT | 18-JUN-01 | 19-JUN-01 | 19-JUN-01 |

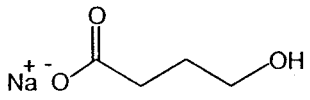
**NAME AND ADDRESS OF APPLICANT** Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305

**DRUG PRODUCT NAME**
Proprietary: Xyrem® oral solution
Nonproprietary/USAN [1966]: sodium oxybate
Code Name/Number:
Chem. Type/Ther. Class: 1P

**PHARMACOLOGICAL CATEGORY/INDICATION** Reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy

**DOSAGE FORM** Oral Solution
**STRENGTHS** 500 mg/mL
**ROUTE OF ADMINISTRATION** Oral
**DISPENSED** XXX RX ___OTC
**SPECIAL PRODUCTS** ___ Yes XXX NO

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA**
**Sodium 4-hydroxybutyrate**
4-Hydroxybutanoic acid monosodium salt
Sodium gamma hydroxybutyrate
$C_4H_7NaO_3$ Mol. Wt. 126.09
CAS Registry #: 502-85-2



**sodium oxybate**

**SUPPORTING DOCUMENTS**: IND ~~~ IND ~~~ (Treatment IND) and 12 packaging DMF's
**RELATED DOCUMENTS**: None
**CONSULTS**: The proposed trademark "Xyrem" was found acceptable by the Office of Post-Marketing Drug Risk Assessment (OPDRA) on 27-JAN-00. The EER was requested on 02-OCT-00 and the overall recommendation is withhold (copy attached). A microbiology consult was requested 19-JAN-01 and Dr. Neal Sweeney found microbiology acceptable (see review dated 23-MAY-01). The MV package is being prepared.

**REMARKS/COMMENTS:** ~~~~~~~~~~~~~~~~~~~~ (drug product manufacturer) received a **warning letter** 24-JAN-01, which detailed numerous cGMP deviations. ~~~~~ will remain unacceptable until a re-inspection can verify the firm's corrective actions. ~~~~ anticipates being ready for inspection in late July 2001.
The sponsor has provided only two batches with 9 months and one batch with 12 months of long term stability data for drug product produced at the ~~~~ site. The sponsor proposed a 36 month expiry but the data supports a tentative expiry of ~~~ months. Amendment dated 12-APR-01 provided responses to Microbiology's deficiencies and was found acceptable by Dr. Neal Sweeney (see microbiology review dated 23-MAY-01). As a result, microbial testing has been added to the drug product release protocol (see p. 2 of this review for final drug product specifications) and the stability protocol has been updated (see pp. 8-9 of this review). It should be noted the dosing cup does not have a line to fill to, which could be confusing to a patient. The issue has been brought to the attention of Dr. Ranjit Mani (clinical reviewer).

**CONCLUSIONS & RECOMMENDATIONS:** Not approvable based on the EER overall withhold recommendation.

cc: Orig. NDA 21-196
HFD-120
HFD-120/TOliver
HFD-120/PM/AMHomoki
HFD-120/MGuzewski
R/D Init by: MEG 8/21/01

/S/
Thomas F. Oliver, Ph.D., Chemist

Filename: n21196.03

9 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

# FDA CDER EES
# ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21196/000
Stamp: 02-OCT-2000 Regulatory Due: 02-JUL-2001
Applicant: ORPHAN MEDCL

Priority: 1P Org Code: 120
Action Goal: District Goal: 01-FEB-2001
Brand Name: XYREM (SODIUM OXYBATE) 500MG/ML ORAL SOL
Established Name:
Generic Name: SODIUM OXYBATE
Dosage Form: SOL (SOLUTION)
Strength: 500 MG/ML

FDA Contacts: A. HOMONNAY WEIKEL (HFD-120) 301-594-5535 , Project Manager
T. OLIVER (HFD-810) 301-594-2570 , Review Chemist
M. GUZEWSKA (HFD-120) 301-594-5571 , Team Leader

Overall Recommendation:

**WITHHOLD on 22-MAR-2001 by P. ALCOCK (HFD-324) 301-827-0062**

Establishment:
DMF No:
AADA No:

Profile:
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 13-OCT-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities:

Establishment:
DMF No:
AADA No:

Profile:
OAI Status: OAI ALERT
Last Milestone: OC RECOMMENDATION
Milestone Date: 13-OCT-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities:

Profile:
OAI Status: OAI ALERT
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-MAR-2001
Decision: WITHHOLD
Reason: DISTRICT RECOMMENDATION
WARNING LETTER ISSUED

Establishment:
DMF No:
AADA No:

# FDA CDER EES
# ESTABLISHMENT EVALUATION REQUEST
# SUMMARY REPORT

Profile: [redacted] OAI Status: **NONE** Responsibilities [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-MAR-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted] DMF No:
AADA No:

Profile: [redacted] OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **28-NOV-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
**REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS**

**NDA 21-196** **CHEM. REVIEW #2** **REVIEW DATE** 19-MAR-01

| SUBMISSION TYPE | DOCUMENT DATE | CDER DATE | ASSIGNED DATE |
|---|---|---|---|
| AMENDMENT | 12-JAN-01 | 16-JAN-01 | 16-JAN-01 |
| AMENDMENT | 19-JAN-01 | 22-JAN-01 | 22-JAN-01 |
| AMENDMENT | 26-JAN-01 | 29-JAN-01 | 29-JAN-01 |
| AMENDMENT | 06-FEB-01 | 07-FEB-01 | 07-FEB-01 |
| AMENDMENT | 08-FEB-01 | 09-FEB-01 | 12-FEB-01 |
| AMENDMENT | 15-FEB-01 | 20-FEB-01 | 21-FEB-01 |

**NAME AND ADDRESS OF APPLICANT** Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305

**DRUG PRODUCT NAME**

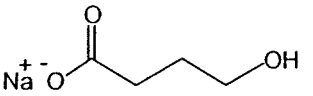
Proprietary: Xyrem® oral solution
Nonproprietary/USAN [1966]: sodium oxybate
Code Name/Number:
Chem. Type/Ther. Class: 1P

**PHARMACOLOGICAL CATEGORY/INDICATION** Reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy

**DOSAGE FORM** Oral Solution
**STRENGTHS** 500 mg/mL
**ROUTE OF ADMINISTRATION** Oral
**DISPENSED** XXX RX ___OTC
**SPECIAL PRODUCTS** ___ Yes XXX NO

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA**

Sodium 4-hydroxybutyrate
4-Hydroxybutanoic acid monosodium salt
Sodium gamma hydroxybutyrate
$C_4H_7NaO_3$ Mol. Wt. 126.09
CAS Registry #: 502-85-2



**sodium oxybate**

**SUPPORTING DOCUMENTS**: IND ——— IND ——— (Treatment IND) and 12 packaging DMF's
**RELATED DOCUMENTS**: None
**CONSULTS**: The proposed trademark "Xyrem" was found acceptable by the Office of Post-Marketing Drug Risk Assessment (OPDRA) on 27-JAN-00. The EER was requested on 02-OCT-00 (copy attached). A microbiology consult was requested 19-JAN-01 and Dr. Neal Sweeney found two deficiencies (see micro review dated 01-MAR-01). The MV package is being prepared.

**REMARKS/COMMENTS:** ——— was withdrawn as an alternate drug product manufacturer, which leaves ——— Impurity ——— has been identified to be ——— The impurity profiles for the toxicology and clinical batches appear similar, with the two most significant impurities being ——— — is known to be rapidly converted to GHB *in vivo*. The potential site specific degradant at ——— was not detected in any of the three ——— batches during the latest time point analysis, which lends credence to the sponsor's claim that the peak is an artifact of ——— Only 9 months (two batches) and 12 months (one batch) of long term stability data were provided from the ——— site (24 months of long term data was provided from ——— . The sponsor has requested a ——— expiry, but this is unacceptable at this time. The pH of the drug product increases after insertion of the PIBA (30 and 60 day stability study). The pH of the drug product also increases during storage in the bottle. The sponsor has not adequately addressed the possible additive effect of these events and how it would affect the impurity profile. A complete list of deficiencies and comments can be found on pp. 11-12 of this review.

**CONCLUSIONS & RECOMMENDATIONS:** Not approvable at this time.

cc: Orig. NDA 21-196
HFD-120
HFD-120/TOliver
HFD-120/PM/AMHomonnay
HFD-120/MGuzewska
R/D Init by: MEC /S/ 6/21/01

/S/
Thomas F. Oliver, Ph.D., Chemist

Filename: n21196.02

10 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

# FDA CDER EES
# ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 21196/000**
Stamp: **02-OCT-2000** Regulatory Due: **02-APR-2001**
Applicant: **ORPHAN MEDCL**

Priority: **1P** Org Code: **120**
Action Goal: District Goal: **01-FEB-2001**
Brand Name: **XYREM (SODIUM OXYBATE) 500MG/ML ORAL SOL**
Established Name:
Generic Name: **SODIUM OXYBATE**
Dosage Form: **SOL (SOLUTION)**
Strength: **500 MG/ML**

FDA Contacts: **A. HOMONNAY WEIKEL (HFD-120)** **301-594-5535 , Project Manager**
**T. OLIVER (HFD-810)** **301-594-2570 , Review Chemist**
**M. GUZEWSKA (HFD-120)** **301-594-5571 , Team Leader**

Overall Recommendation:

Establishment: [redacted]
DMF No:
AADA No:

Profile: [redacted] OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: [redacted] OAI Status: **OAI ALERT**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Profile: [redacted] OAI Status: **OAI ALERT**
Last Milestone: **DO RECOMMENDATION**
Milestone Date: **28-FEB-2001**
Decision: **WITHHOLD**
Reason: **PEND REG ACTION - WARNING LT**

Establishment: [redacted]
DMF No:
AADA No:

19-MAR-2001

# FDA CDER EES
# ESTABLISHMENT EVALUATION REQUEST
# SUMMARY REPORT



Profile: [redacted] OAI Status: NONE Responsibilities: [redacted]
Last Milestone: DO RECOMMENDATION
Milestone Date: 16-MAR-2001
Decision: ACCEPTABLE
Reason: INSPECTION

Establishment: [redacted] DMF No:
[redacted] AADA No:
[redacted]

Profile: [redacted] OAI Status: NONE Responsibilities:
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-NOV-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
**REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS**

**NDA 21-196** **CHEM. REVIEW # 1** **REVIEW DATE** 09-FEB-01

| SUBMISSION TYPE | DOCUMENT DATE | CDER DATE | ASSIGNED DATE |
|---|---|---|---|
| ORIGINAL | 30-SEP-00 | 02-OCT-00 | 05-OCT-00 |
| AMENDMENT | 07-DEC-00 | 08-DEC-00 | 13-DEC-00 |

**NAME AND ADDRESS OF APPLICANT** Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305

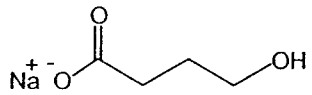
**DRUG PRODUCT NAME**

| | |
|---|---|
| Proprietary: | Xyrem® oral solution |
| Nonproprietary/USAN [1966]: | sodium oxybate |
| Code Name/Number: | |
| Chem. Type/Ther. Class: | 1P |

**PHARMACOLOGICAL CATEGORY/INDICATION** Reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy

| | | |
|---|---|---|
| **DOSAGE FORM** | Oral Solution | |
| **STRENGTHS** | 500 mg/mL | |
| **ROUTE OF ADMINISTRATION** | Oral | |
| **DISPENSED** | XXX RX | ___OTC |
| **SPECIAL PRODUCTS** | ___ Yes | XXX NO |

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA**
**Sodium 4-hydroxybutyrate**
4-Hydroxybutanoic acid monosodium salt
Sodium gamma hydroxybutyrate
$C_4H_7NaO_3$
Mol. Wt. 126.09
CAS Registry #: 502-85-2



**sodium oxybate**

**SUPPORTING DOCUMENTS**: IND —— , IND —— (Treatment IND) and 12 packaging DMF's
**RELATED DOCUMENTS**: None

**CONSULTS**: The proposed trademark "Xyrem" was found acceptable by the Office of Post-Marketing Drug Risk Assessment (OPDRA) on 27-JAN-00. The EER was requested on 02-OCT-00 (copy attached). A microbiology consult was requested 19-JAN-01. The MV package is being prepared.

**REMARKS/COMMENTS:** The drug substance will be manufactured by —— The drug product will be produced by —— Impurity —— has an inadequate specification of NMT —. Since impurity A has not be identified, the upper limit should be NMT — (see ICH Q3A "Impurities in New Drug Substances"; >2g per day). A degradant at —— appeared during stability testing of all three drug product batches manufactured at —— This degradant was not observed from stability testing of —— drug product. Only 9 months of long term stability data was provided from the —— site (24 months of long term data was provided from —— site). The sponsor has requested a 36-month expiration date, but this is unacceptable at this time. The pH of the drug product increases after insertion of the PIBA (30 and 60 day stability study). The pH of the drug product also increases during storage in the bottle. The sponsor provided no data evaluating the possible additive effect of these two events and how it would affect the impurity profile. —— were requested for all drug substance batches to evaluate the impurity profiles of the clinical and toxicology batches. A complete list of questions and comments, which were communicated to the sponsor, are found at the end of this review.

**CONCLUSIONS & RECOMMENDATIONS:** Not approvable at this time.

cc: Orig. NDA 21-196
HFD-120
HFD-120/TOliver
HFD-120/PM/AMHomonday
HFD-120/MGuzewska
R/D Init by: MFC /S/ 2/21/01

/S/
Thomas F. Oliver, Ph.D., Chemist

Filename: n21196.01

41 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

# FDA CDER EES
# ESTABLISHMENT EVALUATION REQUEST
# SUMMARY REPORT

Application: **NDA 21196/000**
Stamp: **02-OCT-2000** Regulatory Due: **02-APR-2001**
Applicant: **ORPHAN MEDCL**

Priority: **1P** Org Code: **120**
Action Goal: District Goal: **01-FEB-2001**
Brand Name: **XYREM (SODIUM OXYBATE) 500MG/ML ORAL SOL**
Established Name:
Generic Name: **SODIUM OXYBATE**
Dosage Form: **SOL (SOLUTION)**
Strength: **500 MG/ML**

FDA Contacts: **A. HOMONNAY WEIKEL (HFD-120)** **301-594-5535 , Project Manager**
**T. OLIVER (HFD-810)** **301-594-2570 , Review Chemist**
**M. GUZEWSKA (HFD-120)** **301-594-5571 , Team Leader**

Overall Recommendation:

Establishment: [redacted]
DMF No:
AADA N

Profile: [redacted] OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: [redacted] OAI Status: **OAI ALERT**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Profile: [redacted] OAI Status: **OAI ALERT**
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date: **16-OCT-2000**

Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

# FDA CDER EES
# ESTABLISHMENT EVALUATION REQUEST
# SUMMARY REPORT

Profile: [redacted] OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date: **16-OCT-2000**

---

Establishment: [redacted] DMF No:
AADA No:

Profile: [redacted] OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date: **22-JAN-2001**

---

Establishment: [redacted] DMF No:
AADA No:

Profile: [redacted] OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **28-NOV-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

# FDA CDER EES
# ESTABLISHMENT EVALUATION REQUEST
# SUMMARY REPORT

Application: **NDA 21196/000**
Stamp: **02-OCT-2000** Regulatory Due: **02-JUL-2001**
Applicant: **ORPHAN MEDCL**

Priority: **1P** Org Code: **120**
Action Goal: District Goal: **01-FEB-2001**
Brand Name: **XYREM (SODIUM OXYBATE) 500MG/ML ORAL SOL**
Established Name:
Generic Name: **SODIUM OXYBATE**
Dosage Form: **SOL (SOLUTION)**
Strength: **500 MG/ML**

FDA Contacts:
**A. HOMONNAY WEIKEL (HFD-120) 301-594-5535 , Project Manager**
**T. OLIVER (HFD-810) 301-594-2570 , Review Chemist**
**M. GUZEWSKA (HFD-120) 301-594-5571 , Team Leader**

Overall Recommendation:

**WITHHOLD on 22-MAR-2001 by P. ALCOCK (HFD-324) 301-827-0062**

Establishment: [redacted]
DMF No:
AADA No:

Profile: [redacted] OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: [redacted] OAI Status: **OAI ALERT**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Profile: [redacted] OAI Status: **OAI ALERT**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-MAR-2001**
Decision: **WITHHOLD**
Reason: **DISTRICT RECOMMENDATION**
**WARNING LETTER ISSUED**

Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

# ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

[redacted]

Profile: [redacted] OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-MAR-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

---

Establishment: [redacted] DMF No:
AADA No:

Profile: [redacted] OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **28-NOV-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

---