

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-411

CHEMISTRY REVIEW(S)

NDA 22-411

**OLEPTRO[™] (trazodone hydrochloride)
Extended-Release Tablets**

Labopharm

Sherita D. McLamore, Ph.D.

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| A. Labeling & Package Insert | n/a |
| B. Environmental Assessment Or Claim Of Categorical Exclusion | n/a |
| III. List Of Deficiencies To Be Communicated..... | n/a |

Chemistry Review Data Sheet

1. NDA 22-411
2. REVIEW: #2
3. REVIEW DATE: December 11, 2009
4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

| <u>Previous Documents</u> | <u>Document Date</u> |
|---------------------------|----------------------|
| Original Submission | September 18, 2008 |
| Amendment | February 9, 2009 |
| Amendment | May 6, 2009 |
| Amendment | May 26, 2009 |

6. SUBMISSION(S) BEING REVIEWED:

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|-------------------------------|----------------------|
| Amendment | September 9, 2009 |
| Amendment | November 11, 2009 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|-----------------|---------------------------|
| Name: | Labopharm Europe Limited |
| | The Seapoint Bldg |
| | 44 Clontarf Road |
| | Dunlin 3 |
| | Ireland |
| Address: | <u>US Agent</u> |
| | Canreg Inc. |
| | 450 North Lakeshore Drive |
| | Mundelein, IL 60060 |
| Representative: | Dr. Nicole Bruffato |

Chemistry Review Data Sheet

Telephone:

866-722-6734

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: OLEPTRO™ Extended-Release Tablets
- b) Non-Proprietary Name (USAN): trazodone hydrochloride
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Major Depressive Disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 150 mg and 300 mg

13. ROUTE OF ADMINISTRATION: oral

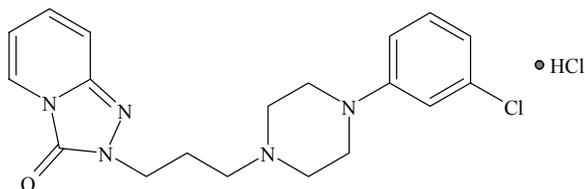
14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2-[3-[4-(*m*-chlorophenyl)-1-piperazinyl]-propyl]-*s*-triazolo[4,3-*a*] pyridin-3(2*H*)-one monohydrochlorideMolecular Formula: C₁₉H₂₂ClN₅O·HCl

Chemistry Review Data Sheet

Molecular Weight: 408.33



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|-------------------------|-----------------------|----------|
| (b) (4) | II | (b) (4) | Trazodone HCl | 3 | Inadequate ^a | | N/A |
| | III | (b) (4) | (b) (4) | 4 | n/a | | N/A |
| | III | (b) (4) | (b) (4) | 4 | n/a | | N/A |
| | III | (b) (4) | (b) (4) | 4 | n/a | | N/A |
| | III | (b) (4) | (b) (4) | 4 | n/a | | N/A |
| | III | (b) (4) | (b) (4) | 4 | n/a | | N/A |
| | III | (b) (4) | (b) (4) | 4 | n/a | | N/A |
| | III | (b) (4) | (b) (4) | 4 | n/a | | N/A |

^aDMF is inadequate because of inadequate tox studies but is being accepted to support the current NDA when considered with additional controls by NDA applicant.

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, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|--------------|
| NDA | 71-196 | Apotex, Inc |
| IND | 76,137 | Original IND |

Chemistry Review Data Sheet

18. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|--------------------------------------|-------------------------------------|-------------|-------------------------|
| Biometrics | N/A | N/A | N/A |
| EES | Acceptable | 10/07/09 | Office of Compliance |
| Pharm/Tox | N/A | N/A | Linda Fossom, Ph.D. |
| Biopharm | Acceptable | | Kofi Kumi Ph.D. |
| LNC | N/A | N/A | N/A |
| Methods Validation | N/A | N/A | Sherita McLamore, Ph.D. |
| DMEPA | N/A | N/A | N/A |
| EA | Categorical Exclusion Acceptable | 4/1/09 | Sherita McLamore, Ph.D. |
| Microbiology | N/A | N/A | N/A |

The Chemistry Review for NDA 22-411

The Executive Summary

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application can be approved in its present form. There are no additional CMC concerns.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

As a result of the Biopharm consult the following post-marketing commitments have been proposed:

- The in vitro alcohol test using the USP Apparatus III is not adequate. You should repeat the in vitro alcohol test once a final dissolution method and conditions are agreed upon with the Agency. It is recommended that you submit a protocol for review prior to conducting the test.
- We recommend the use of 50 -75 rpm in USP Type II apparatus. You are required to provide data using the appropriate condition at different speeds (rpms) to justify 150 rpm proposed dissolution methodology. We also recommend the following dissolution specification on an interim basis for one year; during this one year period, the sponsor is required to revise the dissolution method addressing the Agency's above mentioned comments and submit that to the Agency for review.

| Strength | Dissolution Limits at each timepoint (%) | | | |
|----------|--|-------|--------|--------|
| | 1 hr | 6 hrs | 12 hrs | 20 hrs |
| 150 mg | (b) (4) | | | |
| 300 mg | | | | |

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Trazodone hydrochloride is a Serotonin 2A Antagonist Reuptake Inhibitor that was marketed as Desyrel[®] (trazodone HCl) Tablets and approved for the treatment of depression under NDA 18-207 in 1981. Desyrel[®] was the first marketed immediate release formulation. Although Desyrel[®] has been discontinued since 2006, generic versions of Trazodone HCl are still marketed in the US.

The drug product, OLEPTRO[™] (Trazodone hydrochloride) Extended-Release Tablets is a once a day treatment for major depressive disorder (MDD). The drug product will be available as 150 and 300 mg extended release tablets with a maximum daily dose of 375 mg. Both the 150 and 300 mg drug products are scored for dosing

Executive Summary Section

flexibility (150 mg, 225 mg, 300 mg and 375 mg). Trazodone has been marketed in Europe for over 30 years and is marketed globally under a number of brand names. Trazodone HCl is currently available in immediate release formulations which include 50, 100, 150 and 300 mg tablets, 50 and 100 mg capsule and a 50 mg/5 mL oral liquid. The applicant indicates that unlike the immediate release formulations, the current extended release formulation is designed to maintain the benefits of improved sleep and have few sexual side-effects (commonly are associated with Trazodone) while eliminating the day-time somnolence which is associated with the immediate release formulations.

The drug product is manufactured via a (b) (4) process. The manufacturing process includes (b) (4)

The commercial batch sizes are (b) (4) tablets (150 mg) and (b) (4) tablets (300 mg). Both the 150 and 300 mg tablets will be packaged in the 60 cc (30 tablets), 150 cc (90 tablets), and 625 cc (500 tablets) white HDPE bottles (b) (4) and in blisters in packs of (b) (4) 30 tablets (b) (4)

(b) (4) The drug product will be manufactured and packaged by (b) (4)

The drug product will be available in two different strengths, 150 mg and 300 mg. Both strengths contain the same components (hypromellose, colloidal silicon dioxide, sodium stearyl fumarate and (b) (4) Black Ink); however, the compositions are not directly proportional. In addition, the 150 mg tablets contain (b) (4) (b) (4) and the 300 mg tablets contain (b) (4)

The applicant has requested a (b) (4) for the drug product. The applicant included 9 months of primary stability data in the original application and a 12 month update in September 2009. The applicant also provided 24 months of supportive stability data for pivotal scale batches manufactured at Labopharm. The data demonstrated that the drug product can be adequately stored (i.e. no trends observed, all data within proposed specifications) at 25° C/60%RH and at 40° C/75%RH in the HDPE bottles and in (b) (4) CR Alu paper film blisters.

In addition to the primary stability data, the applicant also included 18 months of supportive stability data for batches manufactured at the clinical site (Labopharm) and two months data for half tablets to support the label claim that the tablets may be broken along the score line to provide dosing flexibility. The data from Labopharm demonstrated that the drug product could be adequately stored for up to 18 months under long term conditions in HDPE bottles and in (b) (4) CR Alu paper film blisters.

All stability data were acceptable and within the prescribed acceptance criteria. The applicant has requested a (b) (4) for the drug product. While the applicant provided 18 months of data to support the 12 months of primary data included in this application, this data was only on two batches and did not adequately bracket all

Executive Summary Section

packaging configurations. Based on the primary and supportive stability data, the applicant has demonstrated that the drug product can be adequately stored (i.e. all data within specifications) at room temperature for 24 months in the proposed container closure system. As such, the applicant will be granted a **24-month expiry** for the drug product.

All sites were submitted to the Office of Compliance in October of 2008. The final recommendation from the Office of Compliance for this application is Acceptable (see appended EER).

The drug substance will be manufactured and packaged by (b) (4). The drug substance is described as a non-hygroscopic, white to almost white crystalline powder that melts with decomposition between 231°C-234°C. The drug substance has a molecular formula is $C_{19}H_{22}ClN_2O \cdot HCl$ and a molecular weight of 408.33. The drug substance shows no evidence of polymorphism and is highly stable. The applicant referenced DMF (b) (4) for all information pertaining to the drug substance. DMF (b) (4) contains up to 60 months of stability data for the drug substance. While DMF (b) (4) is considered inadequate, the data included in the DMF when reviewed in conjunction with the data submitted in this application provide adequate control of the manufacture of the drug substance.

B. Description of How the Drug Product is Intended to be Used

The drug product is being developed as an extended release formulation trazodone hydrochloride. The drug product has maximum daily dose of 375 mg and is being developed for the treatment of Major Depressive Disorder. The drug product will be packaged in 30, 90 and 500 count HDPE bottles (b) (4) foil seal and (b) (4) white rib CR cap or in blisters in packs of (b) (4) 30 c tablets (b) (4) CR Alu paper film).

C. Basis for Approvability or Not-Approval Recommendation

There are no additional concerns to be addressed from a CMC point of view. Accordingly, the recommendation from a CMC perspective is **APPROVAL**.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

SMcLamore/Date
RSood

Executive Summary Section

C. CC Block
Orig. NDA 22-411

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|----------------|---------------------------------------|
| NDA-22411 | ORIG-1 | LABOPHARM INC | TRAZODONE CONTRAMID OAD E-R CAPLET |

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

/s/

SHERITA D MCLAMORE
12/11/2009

RAMESH K SOOD
12/11/2009

Oleptro
(trazodone hydrochloride) extended-release tablets
NDA 22-411

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Labopharm Europe Limited
Dunlin 3, Ireland

Indication: Indicated for the treatment of major depressive disorder

Presentation: Oleptro (trazodone hydrochloride) extended-release tablets are available as colored film-coated, oblong tablets, score on both sides, printed as DDS 080 (150 mg tablets) and DDS 081 (300 mg tablets), packaged in 60 cc (30 count), 150 cc (90 count), 625 cc (500 count), HDPE bottles ^{(b) (4)} and in blister packs of ^{(b) (4)} 30 ^{(b) (4)} CR Alu paper film) tablets.

EER Status: Acceptable, 7-Oct-09

Consults: ONDQA Biopharmaceutics : recommends that the applicant should provide justification for the high paddle speed or develop a new dissolution method. This could be done as a PMC within 12-month of the approval. The new dissolution acceptance criteria are recommended. Methods Validation – Revalidation by Agency was not requested
EA – Categorical exclusion granted under 21 CFR §25.31(c)

Post-Approval Agreements: The Applicant should be asked to provide the following post marketing agreements.

1. The *in vitro* alcohol test using the USP Apparatus III is not adequate. You should repeat the *in vitro* alcohol test once a final dissolution method and conditions are agreed upon with the Agency. It is recommended that you submit a protocol for review prior to conducting the test.
2. We recommend the use of 50 -75 rpm in USP Type II apparatus. You are required to provide data using the appropriate condition at different speeds (rpms) to justify 150 rpm proposed dissolution methodology. We also recommend the following dissolution specification on an interim basis for one year; during this one year period, you are required to revise the dissolution method addressing the Agency's above mentioned comments and submit that to the Agency for review.

| Strength | Dissolution Limits at each timepoint (%) | | | |
|----------|--|-------|--------|--------|
| | 1 hr | 6 hrs | 12 hrs | 20 hrs |
| 150 mg | (b) (4) | | | |
| 300 mg | | | | |

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Please see my previous memorandum for details. The Office of Compliance had previously recommended an overall WITHHOLD due to the unacceptable inspection of the DS manufacturing site at the end of the previous review cycle. In the current cycle, the Office of Compliance has provided an overall “Acceptable” recommendation for all manufacturing sites.

Conclusion: Acceptable.

Drug product:

Please see my previous memorandum for drug product details. The applicant provided some additional stability data to support their proposed expiration period in this cycle. The applicant had requested a (b) (4) expiration dating period for this product. **An expiration dating period of 24 months is being granted to this product based on the submitted stability data and this information should be included in the action letter.**

Overall conclusion: The application is recommended for approval from CMC perspective. A 24-month drug product expiration period is being assigned to his product and this information should be included in the action letter.

Additional Items: No additional items

Ramesh Sood, Ph.D.
Branch Chief/DPA1/Branch 1/ONDQA

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|----------------------------|---------------------------|------------------------|--|
| ----- NDA-22411 | ----- ORIG-1 | ----- LABOPHARM INC | ----- TRAZODONE CONTRAMID OAD E-R CAPLET |

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

/s/

RAMESH K SOOD
12/11/2009

NDA 22-411

OLEPTRO™ (trazodone hydrochloride) Extended-Release Tablets

Labopharm

Sherita D. McLamore, Ph.D.

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| A. Labeling & Package Insert | 94 |
| B. Environmental Assessment Or Claim Of Categorical Exclusion | 97 |
| III. List Of Deficiencies To Be Communicated..... | Error! Bookmark not defined. |

Chemistry Review Data Sheet

1. NDA 22-411
2. REVIEW: #1
3. REVIEW DATE: July 13, 2009
4. REVIEWER: Sherita D. McLamore, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

n/a

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original Submission
Amendment
Amendment
Amendment

Document Date

September 18, 2008
February 9, 2009
May 6, 2009
May 26, 2009

7. NAME & ADDRESS OF APPLICANT:

Name:

Labopharm Europe Limited

The Seapoint Bldg
44 Clontarf Road
Dunlin 3
Ireland

Address:

US Agent
Canreg Inc.
450 North Lakeshore Drive
Mundelein, IL 60060

Representative:

Dr. Nicole Bruffato

Telephone:

866-722-6734

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: OLEPTRO™ Extended-Release Tablets
- b) Non-Proprietary Name (USAN): trazodone hydrochloride
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Major Depressive Disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 150 mg and 300 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

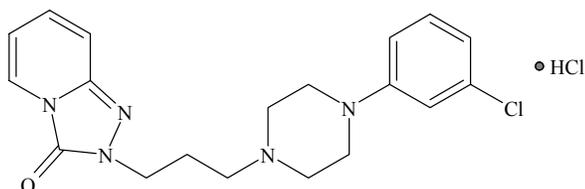
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]-propyl]-1,2,4-triazolo[4,3-a] pyridine-3(2H)-one hydrochloride

Molecular Formula: C₁₉H₂₂ClN₂O·HCl

Molecular Weight: 408.33

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|-------------------------|-----------------------|----------|
| (b) (4) | II | (b) (4) | Trazodone HCl | 3 | Inadequate ^a | | N/A |
| | III | | (b) (4) | 4 | n/a | | N/A |
| | III | | | 4 | n/a | | N/A |
| | III | | | 4 | n/a | | N/A |
| | III | | | 4 | n/a | | N/A |
| | III | | | 4 | n/a | | N/A |
| | III | | | 4 | n/a | | N/A |
| | III | | | 4 | n/a | | N/A |

^aDMF is inadequate because of inadequate tox studies but is being accepted to support the current NDA when considered with additional controls by NDA applicant.

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, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|--------------|
| NDA | 71-196 | Apotex, Inc |
| IND | 76,137 | Original IND |

18. STATUS:

Chemistry Review Data Sheet

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|--------------------------------------|-------------------------------------|-------------|-------------------------|
| Biometrics | N/A | N/A | N/A |
| EES | withhold | 8-Jul-09 | |
| Pharm/Tox | N/A | N/A | Linda Fossom, Ph.D. |
| Biopharm | Pending | Pending | Kofi Kumi Ph.D. |
| LNC | N/A | N/A | N/A |
| Methods Validation | N/A | N/A | Sherita McLamore, Ph.D. |
| DMEPA | N/A | N/A | N/A |
| EA | Categorical Exclusion Acceptable | 4/1/09 | Sherita McLamore, Ph.D. |
| Microbiology | N/A | N/A | N/A |

The Chemistry Review for NDA 22-411

The Executive Summary

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application cannot be approved in its present form. The CMC issues are included at the end of this review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

As a result of the Biopharm consult the following post-marketing commitments have been proposed:

- The in vitro alcohol test using the USP Apparatus III is not adequate. You should repeat the in vitro alcohol test once a final dissolution method and conditions are agreed upon with the Agency. It is recommended that you submit a protocol for review prior to conducting the test.
- We recommend the use of 50 -75 rpm in USP Type II apparatus. You are required to provide data using the appropriate condition at different speeds (rpms) to justify 150 rpm proposed dissolution methodology. We also recommend the following dissolution specification on an interim basis for one year; during this one year period, the sponsor is required to revise the dissolution method addressing the Agency's above mentioned comments and submit that to the Agency for review.

| Strength | Dissolution Limits at each timepoint (%) | | | |
|----------|--|-------|--------|--------|
| | 1 hr | 6 hrs | 12 hrs | 20 hrs |
| 150 mg | (b) (4) | | | |
| 300 mg | | | | |

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Trazodone hydrochloride is a Serotonin 2A Antagonist Reuptake Inhibitor that was marketed as Desyrel[®] (trazodone HCl) Tablets and approved for the treatment of depression under NDA 18-207 in 1981. Desyrel[®] was the first marketed immediate release formulation. Although Desyrel[®] has been discontinued since 2006, generic versions of Trazodone HCl are still marketed in the US.

The drug product, OLEPTRO[™] (Trazodone hydrochloride) Extended-Release Tablets is a once a day treatment for major depressive disorder (MDD). The drug product will be available as 150 and 300 mg extended release tablets with a maximum daily dose of 375 mg. Both the 150 and 300 mg drug products are scored for dosing

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flexibility (150 mg, 225 mg, 300 mg and 375 mg). Trazodone has been marketed in Europe for over 30 years and is marketed globally under a number of brand names. Trazodone HCl is currently available in immediate release formulations which include 50, 100, 150 and 300 mg tablets, 50 and 100 mg capsule and a 50 mg/5 mL oral liquid. The applicant indicates that unlike the immediate release formulations, the current extended release formulation is designed to maintain the benefits of improved sleep and have few sexual side-effects (commonly are associated with Trazodone) while eliminating the day-time somnolence which is associated with the immediate release formulations.

The drug product is manufactured via a (b) (4) process. The manufacturing process includes (b) (4)

(b) (4) tablets (150 mg) and (b) (4) tablets (300 mg). The commercial batch sizes are (b) (4) tablets (150 mg) and (b) (4) tablets (300 mg). Both the 150 and 300 mg tablets will be packaged in the 60 cc (30 tablets), 150 cc (90 tablets), and 625 cc (500 tablets) white HDPE bottles (b) (4) and in blisters in packs of (b) (4) 30 tablets (b) (4). The drug product will be manufactured and packaged by (b) (4).

The drug product will be available in two different strengths, 150 mg and 300 mg. Both strengths contain the same components (hypromellose, colloidal silicon dioxide, sodium stearyl fumarate and (b) (4) Black Ink), however, the compositions are not directly proportional. In addition, the 150 mg tablets contain (b) (4) and the 300 mg tablets contain (b) (4).

The drug substance will be manufactured and packaged by (b) (4). The drug substance is described as a non-hydroscopic, white to almost white crystalline powder that melts with decomposition between 231°C-234°C. The drug substance has a molecular formula for the drug substance is $C_{19}H_{22}ClN_2O \cdot HCl$ and a molecular weight of 408.33. The drug substance shows no evidence of polymorphism and is highly stable. The applicant referenced DMF (b) (4) for all information pertaining to the drug substance. DMF (b) (4) contains up to 60 months of stability data for the drug substance. While DMF (b) (4) was considered inadequate, the data provided in the DMF when reviewed in conjunction with the data provided in this application provide adequate control of the manufacture of the drug substance.

B. Description of How the Drug Product is Intended to be Used

The drug product is being developed as an extended release formulation trazodone hydrochloride. The drug product has maximum daily dose of 375 mg and is being developed for the treatment of Major Depressive Disorder. The drug product will be packaged in 30, 90 and 500 count HDPE bottles (b) (4) foil seal and (b) (4) white rib CR cap or in blisters in packs of (b) (4) 30 c tablets (b) (4) CR Alu paper film).

Executive Summary Section

The applicant has requested a (b) (4) for the drug product. The applicant included 9 months of primary stability data which demonstrated that the drug product can be adequately stored (i.e. no trends observed, all data within proposed specifications) at 25° C/60%RH and at 40° C/75%RH in the HDPE bottles and in (b) (4) CR Alu paper film blisters. In addition to the primary stability data, the applicant also included 18 months of supportive stability data for batches manufactured at the clinical site (Labopharm). This data demonstrated that the drug product could be adequately stored for up to 18 months under long term conditions in HDPE bottles and in (b) (4) CR Alu paper film blisters. The applicant argued that this data is comparable to the primary data (see page 70 of this review); however, biopharm reviewer Dr. Kofi Kumi concluded that there was a 21% difference in the C_{max} for the product manufactured at the commercial site (batch 112524BP1) and the product manufactured at the clinical site (batch 04A19602P7). After a thorough review of the data, it was concluded that this 21% difference is not clinically relevant. As such, the data from the clinical site will also be considered in the determination of the expiry.

In addition to the data on the whole tablets, the applicant has provided two months data for half caplets to support the label claim that the tablets may be broken along the score line to provide dosing flexibility.

All stability data were acceptable and within the prescribed acceptance criteria. The applicant has requested a (b) (4) for the drug product. While the applicant did provide 18 months of supportive stability data, this data was only on two batches and did not adequately bracket all packaging configurations. Based on the primary and supportive stability data, the applicant has demonstrated that the drug product can be adequately stored (i.e. all data within specifications) at room temperature for 18 months in the proposed container closure system. Accordingly, the proposed (b) (4) (b) (4) The applicant will receive an (b) (4) for the drug product.

All sites were submitted to the Office of Compliance in October of 2008. At this time (b) (4) (drug substance manufacturer) has a withhold recommendation. As such, the final recommendation from the Office of Compliance is WITHHOLD (see appended EER).

C. Basis for Approvability or Not-Approval Recommendation

Approvability of NDA 22-411 from a CMC perspective is contingent upon an acceptable recommendation from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

Executive Summary Section

B. Endorsement Block

SMcLamore/Date
RSood

C. CC Block

Orig. NDA 22-411

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/s/

Sherita McLamore
7/13/2009 04:30:10 PM
CHEMIST

Ramesh Sood
7/14/2009 07:32:10 AM
CHEMIST

Oleptro
(trazodone hydrochloride) extended-release tablets
NDA 22-411

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Labopharm Europe Limited
Dunlin 3, Ireland

Indication: Indicated for the treatment of major depressive disorder

Presentation: Oleptro (trazodone hydrochloride) extended-release tablets are available as colored film-coated, oblong tablets, score on both sides, printed as DDS 080 (150 mg tablets) and DDS 081 (300 mg tablets), packaged in 60 cc (30 count), 150 cc (90 count), 625 cc (500 count), HDPE bottles (b) (4) (b) (4) in blister packs of (b) (4) (b) (4) 30 (b) (4) CR Alu paper film) tablets.

EER Status: WITHHOLD, 8-Jul-09

Consults: ONDQA Biopharmaceutics : recommends that the applicant should provide justification for the high paddle speed or develop a new dissolution method. This could be done as a PMC within 12-month of the approval. The new dissolution acceptance criteria are recommended. Methods Validation – Revalidation by Agency was not requested
EA – Categorical exclusion granted under 21 CFR §25.31(c)

Post-Approval Agreements: The Applicant should be asked to provide the following post marketing agreements.

1. The *in vitro* alcohol test using the USP Apparatus III is not adequate. You should repeat the *in vitro* alcohol test once a final dissolution method and conditions are agreed upon with the Agency. It is recommended that you submit a protocol for review prior to conducting the test.
2. We recommend the use of 50 -75 rpm in USP Type II apparatus. You are required to provide data using the appropriate condition at different speeds (rpms) to justify 150 rpm proposed dissolution methodology. We also recommend the following dissolution specification on an interim basis for one year; during this one year period, the sponsor is required to revise the dissolution method addressing the Agency's above mentioned comments and submit that to the Agency for review.

| Strength | Dissolution Limits at each timepoint (%) | | | |
|----------|--|-------|--------|--------|
| | 1 hr | 6 hrs | 12 hrs | 20 hrs |
| 150 mg | (b) (4) | | | |
| 300 mg | | | | |

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Trazodone hydrochloride is a white to off-white crystalline powder. It contains no chiral centers and has no polymorphs. The CMC information for the manufacture and control of the drug substance was referenced to DMF (b) (4). A deficiency letter was sent to the DMF holder during the DMF review by the OGD reviewer. The DMF remains inadequate at the time of writing this memorandum. The applicant has addressed most of the deficiencies. The DMF still remains inadequate as a stand alone document. However, due to additional controls proposed by the NDA holder in the application, the drug substance quality as used by this applicant is acceptable. Labopharm will only use trazodone hydrochloride USP grade (b) (4) in the manufacture of Trazodone Contramid®. Trazodone hydrochloride will be manufactured by (b) (4). The drug substance will be packaged in (b) (4).

The Office of Compliance has recommended an overall WITHHOLD due to the unacceptable inspection of the DS manufacturing site.

Conclusion: Not acceptable.

Drug product:

The drug product is being developed as extended-release tablets. The composition of the two strengths is qualitatively similar but is not dose proportional. Hypermellose, colloidal silicon dioxide, sodium stearyl fumarate (b) (4) conform to USP/NF standards. The (b) (4) components also conform to the compendial standards. The formulation uses Contramid, a (b) (4) modified starch which meets NF specification and also complies with the requirements for both modified food starches and hydroxypropyl distarch phosphates as defined in the 21 CFR 172.892.

The drug product manufacturing includes (b) (4). The manufacturing includes appropriate in-process controls to ensure the product quality and consistency. The product quality is further ensured through final product specification that include tests and limits for appearance, identification (HPLC/UV), assay (HPLC), average weight, uniformity of dosage units by weight variation, hardness, (b) (4), HPLC purity (HPLC) and dissolution. All analytical methods used are appropriately validated.

The applicant has requested a (b) (4) expiration period for the product. An expiration period of (b) (4) is being assigned to this product based on the submitted stability data when stored in the commercial packaging system at room temperature.

Overall conclusion: Although all CMC related deficiencies have been resolved for this application, the application cannot be approved from CMC perspective because of the overall WITHHOLD recommendation from the office of Compliance.

Additional Items: No additional items

Ramesh Sood, Ph.D.
Branch Chief/DPA1/Branch 1/ONDQA

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/s/

Ramesh Sood
7/14/2009 07:43:25 AM
CHEMIST

Initial Quality Assessment Branch I

OND Division: Division of Psychiatry Products
NDA: 22-411 (paper)
Applicant: Labopharm Canada
Letter Date: 18-SEP-08
Stamp Date: 18-SEP-08
PDUFA Date: 18-JUL-09
Trademark: Trazodone Contramid® OAD (Oleptro)
Established Name: trazodone hydrochloride
Dosage Form: Extended release caplets (150 and 300 mg)
Route of Administration: Oral
Indication: Major Depressive Disorder
Assessed by: Thomas F. Oliver, Ph.D.

Summary

Trazodone hydrochloride, a Serotonin 2A Antagonist Reuptake Inhibitor, is indicated for the treatment of major depressive disorder. Desyrel® (trazodone hydrochloride, Bristol-Myers Squibb) was discontinued for sale in the United States since September 2006. As a result, Trazodone Hydrochloride Tablets, USP, manufactured by (b) (4) and commercialized by Apotex Corp. is the official reference listed drug in the Orange Book. The applicant has developed trazodone hydrochloride for major depressive disorder under IND 76,137. The applicant had an EOP-2 meeting (February 28, 2008) with the clinical division to discuss: information needed to support scoring of modified release tablets, dissolution testing. The applicant had a pre-NDA meeting (February 28, 2008) with the clinical division to discuss: drug product stability and stability data to support tablets. Minutes for both of these meetings can be found in DARTS and should be read by the reviewer.

Drug Substance

Trazodone hydrochloride is a white to off-white crystalline powder. It contains no chiral centers and has no polymorphs. The NDA applicant references DMF (b) (4) for information on trazodone hydrochloride (LoA dated 23-FEB-07). DMF (b) (4) was found inadequate (see review by Dr. Bingyuan Wu, OGD, April 28, 2008). A DMF deficiency letter dated April 28, 2008 was sent to the DMF sponsor. DARTS shows that a response has been received (September 5, 2008), but no review appears to have been completed at this time. (b) (4)

(b) (4)
Labopharm will only use trazodone hydrochloride USP grade (b) (4) in the manufacture of Trazodone Contramid®. Trazodone hydrochloride will be manufactured by (b) (4). The drug substance will be (b) (4)

Drug Product

Trazodone Contramid® OAD will be available as 150 mg and 300 mg extended release caplets for the treatment of Major Depressive Disorder. The recommended starting dose is 150 mg/day in adults. The usual dose is 300 mg/day. The maximum daily dose should not exceed 375 mg. The caplets are scored and may be bisected to provide flexibility in dosing. Trazodone Contramid OAD caplets are scored, film coated, extended release dosage forms manufactured (b) (4). Immediate release forms of the trazodone are associated with day-time somnolence attributable to the peaks in the plasma concentration that occur when taken three times daily. The applicant has designed this formulation to maintain the benefits of improved sleep and few sexual side-effects associated with trazodone, while eliminating the day-time somnolence attributed to immediate release forms. The caplet strengths (150 mg and 300 mg) are not directly proportional to each other. Both the 150 mg and 300 mg strengths contain the following excipients: Contramid®, hypromellose, colloidal silicon dioxide, sodium stearyl fumarate, (b) (4) (150 mg), (b) (4) (300 mg), and (b) (4) Black Ink. Hypromellose, colloidal silicon dioxide, and sodium stearyl fumarate are either USP or NF technical grade. (b) (4)

The commercial batch sizes are (b) (4) (150 mg) and (b) (4) (300 mg). The Trazodone Contramid® OAD caplets will be manufactured by (b) (4)

The caplets are packaged in the 60 cc (30 caplets), 150 cc (90 caplets), and 625 cc (500 caplets) white HDPE bottles (b) (4). In addition, caplets will be packaged in blisters in packs of (b) (4) 30 caplets (b) (4) CR Alu paper film).

Critical Issues for Review

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4
Labopharm will only use trazodone hydrochloride USP grade (b) (4) in the manufacture of Trazodone Contramid®. DMF (b) (4) will need to be evaluated and found acceptable, specifically for trazodone hydrochloride USP grade (b) (4)

• Impurities (b) (4) were previously discussed with the applicant (during IND development) as having structural alerts and potentially being genotoxic. It will need to be determined whether the applicant has satisfactorily addressed this issue. In addition, it will need to be determined whether there are any additional compounds that have structural alerts which are utilized or formed in the proposed commercial synthesis. The reviewer will need to discuss the outcome of this evaluation with the pharm/tox reviewer.

• The drug substance release specification for particle size of trazodone hydrochloride is NMT (b) (4). The acceptability of the particle size will need to be evaluated based upon what has been used clinically and the physical properties of the drug substance. It

will need to be determined whether agglomeration occurs as a function of time as there is no particle size test on stability.

- The applicant currently does not have a release specification (test method/ limits) for residual solvent testing as part of the trazodone hydrochloride release specification. The DMF holder currently tests for residual solvents but this is not part of the official release testing.

- The applicant has proposed a specification limit of NMT (b) (4) for “any single impurity”. It will need to be determined in conjunction with the pharm/tox reviewer whether the limit is acceptable.

- The applicant uses the term caplet which does not appear to be recognized by the Dosage Standards manual. It will need to be determined whether the term caplet is acceptable or whether the term capsule shaped tablet should be employed.

- Contramid® is a (b) (4) modified starch”. It is manufactured by (b) (4)
The reviewer will need to determine the acceptability of this excipient (including review of (b) (4) based on the information provided (including whether the amount ingested daily is acceptable).

- The compatibility of the excipients used in the drug product will need to be evaluated. In addition, the acceptability of the (b) (4) (150 mg), (b) (4) (300 mg), and (b) (4) Black Ink will need to be determined.

- The applicant has identified (b) (4) as critical steps in the manufacturing process. It will need to be known how working outside the established ranges affects the drug product and whether the applicant has adequate sampling and controls in place.

- The applicant has in-process controls during (b) (4) The reviewer will need to evaluate the adequacy of these controls.

- The applicant has in-process controls (b) (4) for the Trazodone Contramid caplets. The reviewer will need to evaluate the adequacy of these controls.

- The applicant states that the caplets are scored. The applicant will need to provide details of the scoring process. It will need to be determined how the manufacturer assures adequate scoring throughout the manufacturing process. The reviewer will need to evaluate whether the caplets can be adequately broken into two pieces.

- The sponsor will need to demonstrate that the half caplets correspond to 50% of the whole caplet. It will need to be determined whether the half caplet has an altered dissolution profile compared to the whole caplet. In addition, stability data for the half-caplets will need to be evaluated to support the clinical use of the product.
- The applicant refers to the 150 mg caplet as a “yellowish-beige film coated caplet scored on both sides” and to the 300 mg caplet as a “beige-orange film coated caplet scored on both sides”. The reviewer will need to secure samples and determine whether the description accurately captures the identity of the products.
- The applicant has proposed drug product impurity specification limits of NMT (b) (4) and NMT (b) (4). It will need to be determined in conjunction with the pharm/tox reviewer whether these limits are acceptable.
- The applicant has not set a specification limit for (b) (4) but has proposed to report their findings. The applicant will need to set a specification limit for (b) (4).
- The applicant has set a hardness specification limit of NLT (b) (4). It will need to be determined whether this limit is supported by [data from made batches, stability data and performance (e.g., ability to break at the score line and meet assay testing)].
- The sponsor has set a dissolution specification of: 1 hour: NMT (b) (4) 6 hours: (b) (4) (b) (4) 12 hours: (b) (4), and 24 hours: NLT (b) (4). It should be noted the 6 hour time point is (b) (4) for the 150 mg strength. The sponsor employs sinker baskets, a paddle speed of 150 rpm and a two phase dissolution system (pH 1.2 and pH 6.0). As a result, the adequacy of the dissolution method and specification limits will need to be determined. The dissolution data will need to be closely scrutinized across the pivotal clinical batches, the stability batches, and the commercial batches for any inconsistencies. The ONDQA dissolution group should be consulted (see comment at end).
- The role of particle size on product performance will need to be evaluated, and if needed, adequate controls need to be in place to ensure consistent product performance. The sponsor will need to demonstrate that particle size has no clinical ramifications or that particle size (e.g., shape under the curve) as measured in clinical, stability, and commercial batches is rationally controlled to ensure product performance (as outlined in labeling).
- It appears the dose strengths (150 mg and 300 mg of trazodone hydrochloride) are correctly expressed as 150 mg and 300 mg trazodone hydrochloride in the label. However, the reviewer will need to verify that the 150 mg and 300 mg listed in the components/composition section actually refers to the amount of the hydrochloride (and not free base).

•The sponsor has proposed an expiry of (b) (4) for Trazodone Contramid OAD caplets. Any stability differences between strengths (150 mg vs 300 mg) and packaging configurations (HDPE bottles vs blisters) will need to be evaluated and factored in when assigning the expiry. In addition, it will need to be determined when all packaging counts are represented with stability data (i.e., matrixed/ bracketed).

Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. Since Dr. Sherita McLamore was involved in the pre-NDA meeting, she would be a prudent choice as the CMC reviewer. My recommendation would be for a single reviewer to be assigned to the NDA. Four sites were submitted into EES (31-OCT-08), however, the applicant will be asked for clarification on the drug substance sites and one drug product site (email was sent to clinical PM: asking for CFN#s and more specific description of function at each of these sites). In accordance with 21 CFR §25.31, Labopharm claims a categorical exclusion [25.31(a)] from the requirement for an Environmental Assessment or Environmental Impact Statement as approval of the drug product will not increase the use of the active moiety. The dissolution should be consulted to the ONDQA dissolution group.

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/s/

Thomas Oliver
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