CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-745

CHEMISTRY REVIEW(S)

MEMORANDUM

From:	Danae D. Christodoulou, Ph.D., ONDQA Branch II
Through:	Ali Al Hakim, Ph. D., Branch Chief, ONDQA Branch II;
To:	NDA 21-745
Subject:	Review of final draft carton and container labels
Date:	12/18/08

Revised carton and container labels were submitted to NDA 21-745 on 12/8/08 and 12/15/08.

The current carton and container labels addressed labeling comments from Chemistry Review #2, by Sue Ching Lin, dated 5/11/07 and additional clarifications requested on 12/12/08 through the Project Manager K. Davies. The sponsor was asked to confirm the presentations which are intended for marketing at present, and to increase the fontsize of the established name on the blisters.

Submitted:

1. PI, dated 12/2/08.
2. Container labels for the 100 mg, 200 mg, 300 mg 30-tablet and 90-tablet packaging configurations.
3. Carton labels for the 100 mg 11 x 1 blister (unit dose) and the 200 mg 5 X 1 blister (unit dose) physician samples.
4. Blister card back and front for the examples in 3.
5. Blister card back and front for the examples in 3 were revised and resubmitted on 12/12/08, with the explanation that these were the only blister presentations intended for physician samples at this time.

Comments:

The applicant revised the presentation of the established name to (tramadol hydrochloride extended release tablets). This is a change from the previous submitted labeling on 4/30/07, where the applicant had selected (tramadol hydrochloride) extended-release tablets as the established name. The proprietary name Ryzolt® is now connected to the dosage form. This change, i.e., Ryzolt® (tramadol hydrochloride extended release tablets) was implemented on the current Package Insert (PI), and this revision was made consistent throughout the PI.

The carton and container labels submitted, including the revised physician samples (blisters), are acceptable. The prominence of font of the established name was increased and it is sufficient.

b(4)

In addition, the applicant clarified that the submitted 100 mg 11 x 1 blister (unit dose) and the 200 mg 5 X 1 blister (unit dose) are physician samples.

Conclusion:
No outstanding CMC issues remain for NDA 21-745 and the NDA is recommended for approval.

Danae D. Christodoulou, Ph.D.
Pharmaceutical Assessment Lead, ONDQA

Ali Al-Hakim, Ph.D.
Branch II Chief, ONDQA

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/s/

Danae Christodoulou
12/18/2008 04:43:38 PM
CHEMIST

Ali Al-Hakim
12/18/2008 04:49:03 PM
CHEMIST

NDA 21-745

Ryzolt (tramadol hydrochloride) Extended-release Tablets

Labopharm Canada Inc.

Sue-Ching Lin

Review Chemist

Office of New Drug Quality Assessment
Division of Pre-marketing Assessment and Manufacturing Science
Branch V

CMC REVIEW OF NDA 21-745
For the Division of Anesthesia, Analgesia, and
Rheumatology Products (HFD-170)
Rheumatology Products

Table of Contents

CMC Review Data Sheet

1. NDA 21-745

2. REVIEW #: 2

3. REVIEW DATE: 07-May-2007

4. REVIEWERS: Sue-Ching Lin

5. PREVIOUS DOCUMENTS:

Chemistry Review #1 Cycle	Document Date
Original NDA Submission	25-Nov-2005
Amendment (BZ) (Contramid® information)	01-Mar-2006
Amendment (BZ) (DP stability)	28-Mar-2006
Amendment (BZ) (DP stability analysis)	07-Apr-2006
Amendment (BZ) (providing samples)	02-May-2006
Amendment (BZ) (proposing new trade names & color labels)	31-May-2006
Amendment (BL) (revised package insert)	12-Jun-2006
Amendment (BC) (response to CMC requests)	20-Jun-2006
Amendment (BC) (response to CMC requests)	25-Jul-2006
Amendment (BC) (response to CMC requests)	18-Aug-2006

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed in this Cycle	Document Date
Resubmission (AZ)	18-Dec-2006
Amendment (BZ) (updated stability data and revised package insert and container labels)	28-Feb-2007
Amendment (BC) (updated stability data in electronic format)	01-Mar-2007
Amendment (BL) (updated container labels)	30-Apr-2007

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Labopharm Canada Inc.
Address:	480 Armand-Frappier Blvd. Laval, Quebec Canada H7V 4B4
Representative:	Becky Prokipcak, Ph.D., Senior Director, Regulatory Affairs CanReg Inc. 450 North Lakeshore Drive Mundelein, IL 60060
Telephone:	(866) 722-6734

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ryzolt (DMETS has no objections to the use of Ryzolt as the proprietary name. Refer to the DMETS 9/22/06 and 4/13/07 reviews in DFS)
b) Non-Proprietary Name: tramadol hydrochloride extended-release tablets
c) Code Name/# (ONDQA only): 3TRMDN0 (DMF holder ——— company code) b(4)
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5 (new formulation, per the new MAPP 7500.3)
- Submission Priority: S

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

Referenced Listed Drug: NDA 20-281, Ultram (tramadol hydrochloride tablets) 50 mg, Ortho-McNeil Pharmaceutical, Inc.

10. PHARMACOL. CATEGORY: analgesic

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 100 mg, 200 mg, and 300 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: √ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
____SPOTS product – Form Completed

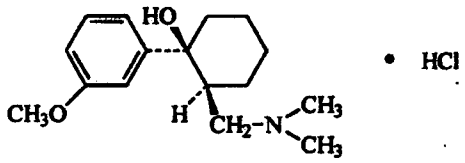
√ Not a SPOTS product

CMC Review Data Sheet

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

(±)-*cis*-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride

RR,SS-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride b(4)



$C_{16}H_{25}NO_2$. HCl MW 299.84

tramadol hydrochloride

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					adequate	4/4/07	Reviewed by Danae Christodoulou
					N/A		
					N/A		

b(4)

[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)

CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	64,317	Tramadol hydrochloride Contramid
NDA	21-692	Ralivia ER Tablets
NDA	20-281	Ultram

b(4)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	5/7/07	S. Ferguson
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS	The proposed proprietary names Ryzolt® is acceptable.	4/13/07	Judy Park
EA	Categorical exclusion (see review)		Sue-Ching Lin
Microbiology	N/A		

CMC Review for NDA 21-745

The Executive Summary

I. RECOMMENDATIONS

A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA is recommended for approval.

The labeling comments for the package insert (pages 14 to 16 of this review) will not be conveyed to the applicant at this time. The DAARP has decided not to approve this NDA due to clinical deficiencies; hence, all aspects of labeling would be handled in the next cycle. Refer to page 14 of this review for details.

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

None

II. SUMMARY OF CMC ASSESSMENTS

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

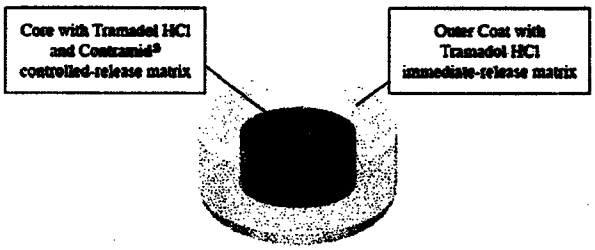
(1) Drug Substance

The active ingredient is tramadol hydrochloride. It is manufactured by ——— ——— Detailed information on the drug substance is referenced to DMF ———, which was reviewed on April 4, 2007 and found to be adequate. b(4)

Tramadol hydrochloride is included in the current European Pharmacopoeia. Although there is no current USP monograph for tramadol hydrochloride, a proposed monograph for tramadol hydrochloride was published in the March/April 2005 Pharmacopoeial Forum (Volume 31 Number 2). The drug substance specification proposed in this NDA includes all the requirements in the proposed USP monograph for tramadol hydrochloride with tighter acceptance criteria for total impurities and additional tests on melting point and particle size distribution.

(2) Drug Product

The drug product is an extended-release tablet dosage form, comprising an immediate-release compression coat over an extended-release core.



With the exception of the following three excipients: Contramid® _____ b(4)
_____, all the inactive ingredients are USP/NF materials. Contramid®, which has the chemical structure of hydroxypropyl distarch phosphate, meets the NF requirements for Pregelatinized Modified Starch. On contact with water, Contramid® swells to form a matrix that controls the release rate of tramadol hydrochloride in the tablet core. The tablet coat does not contain Contramid®. It is designed to disintegrate immediately after administration and provide a fast onset of action.

The tablets are manufactured using _____ b(4)
_____

The tablets are formulated in three different strengths: 100 mg, 200 mg, and 300 mg. The tablets are described as white to off-white, beveled edge, round biconvex tablets, plain on one side and printed black " _____ b(4)
respectively for each strength on the other side. They are packaged in HDPE bottles and blisters.

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

The drug product is indicated for the management of moderate to moderately severe pain. It is intended to be administered once daily and will be dispensed by prescription only. The tablets should be swallowed whole with liquid and not split, chewed, dissolved, or crushed.

The primary stability batches were manufactured at the proposed commercial manufacturing facility (Confab). Primary stability data were submitted for all three strengths and include stability results at 25°C/60%RH storage conditions (36 months for 1 batch and 24 months for 2 batches), 30°C/65%RH (12 months for 3 batches), and 40°C/75%RH (6 months for 3 batches). Thirty-six months of supportive stability data were submitted for the drug product manufactured —— (for clinical batches) for all three strengths packaged in blisters and one of the proposed bottle sizes (100-count). The submitted stability data support the proposed expiration period of — months. b(4) b(4)

C. Basis for Approvability or Not-Approval Recommendation

The CMC information of the drug substance was referenced to DMF ——, which was recently reviewed on April 4, 2007 and found to be adequate.

A detailed pharmaceutical development report was submitted to the NDA. The drug product was developed to provide the early onset of analgesia associated with immediate-release forms, such as Ultram, and also maintain effective analgesia for 24 hours following once daily administration. Using non-compartmental pharmacokinetic modeling, the applicant generated target plasma profiles, which was then deconvoluted to generate target in-vitro dissolution profiles. The formulations of the 100-mg, 200-mg, and 300-mg tablets were designed and modified to match the target dissolution profiles and plasma profiles. Critical parameters and critical quality attributes were identified.

The manufacture process, the control of excipients, and the specification are adequate to ensure consistency in the quality of the drug product. The packaging materials were found to be adequate.

The Division of Medication Errors and Technical Support (DMETS) has no objections to the use of the proposed proprietary name "Ryzolt®."

A re-evaluation of all the facilities for the manufacture and control of the drug substance and drug product was submitted by this reviewer to the Office of Compliance. An overall acceptable recommendation was issued by the Office of Compliance on May 7, 2007.

During the 4/19/07 team meeting for this NDA, Dr. Bob Rappaport, DAARP Division Director, requested that, since the clinical division has decided not to approve this NDA, no labeling discussions will be held for the package insert. He said that it is fine to send comments for container labeling. But he asked to hold the comments for package insert. Consequently, the comments regarding package insert will need to be conveyed to the applicant in the future, along with comments from other disciplines, if there is a labeling meeting for the package insert for a future resubmission.

III. ADMINISTRATIVE

A. Reviewer's Signature

(See appended electronic signature page)

Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Ravi Harapanhalli, Ph.D., Branch Chief, Branch V, ONDQA

C. CC Block:

Entered electronically in DFS

10 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Sue Ching Lin
5/11/2007 03:00:01 PM
CHEMIST

Ravi Harapanhalli
5/11/2007 03:12:24 PM
CHEMIST

NDA 21-745

Tramadol Hydrochloride Extended-Release Tablets

Labopharm Canada Inc.

Sue-Ching Lin (Overall)
Ted Chang, Ph.D. (Manufacturing Science)

Chemistry, Manufacturing, and Controls (CMC)
Team Review of Original NDA

Office of New Drug Quality Assessment
Pre-Marketing Division III
for
Division of Anesthesia, Analgesia, and
Rheumatology Products

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CMC Review Data Sheet

1. NDA 21-745

2. REVIEW #: 1

3. REVIEW DATE: 07-Aug-2006

4. REVIEWERS:
   Ted Chang (manufacturing science aspect)
   Sue-Ching Lin (overall)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 64,317 CMC Pre-NDA meeting	02-Oct-2003
IND 64,317 sponsor meeting (about exclusivity and NDA submission)	25-Oct-2005
[redacted]	24-May-2002 b(4)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Submission	25-Nov-2005
Amendment (BZ) (Contramid® information)	01-Mar-2006
Amendment (BZ) (DP stability)	28-Mar-2006
Amendment (BZ) (DP stability analysis)	07-Apr-2006
Amendment (BZ) (providing samples)	02-May-2006
Amendment (BZ) (proposing new trade names & color labels)	31-May-2006
Amendment (BL) (revised package insert)	12-Jun-2006
Amendment (BC) (response to CMC requests)	20-Jun-2006
Amendment (BC) (response to CMC requests)	25-Jul-2006
Amendment (BC) (response to CMC requests)	18-Aug-2006

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Labopharm Canada Inc.
Address:	480 Armand-Frappier Blvd. Laval, Quebec Canada H7V 4B4
Representative:	Becky Prokipcak, Ph.D., Senior Director, Regulatory Affairs CanReg Inc. 450 North Lakeshore Drive Mundelein, IL 60060
Telephone:	(866) 722-6734

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Deflexit or Ryzolt (proposed by the applicant, but not agreed by DDMAC nor by the clinical division, refer to the DMETS 7/14/06 memo in DFS)
b) Non-Proprietary Name: tramadol hydrochloride extended-release tablets
c) Code Name/# (ONDQA only): 3TRMDN0 (DMF holder ——— company code) b(4)
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5 (new formulation, per the new MAPP 7500.3)
- Submission Priority: S

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

Referenced Listed Drug: NDA 20-281, Ultram (tramadol hydrochloride tablets) 50 mg, Ortho-McNeil Pharmaceutical, Inc.

10. PHARMACOL. CATEGORY: analgesic

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 100 mg, 200 mg, and 300 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: √ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

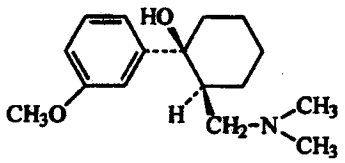
√ Not a SPOTS product

CMC Review Data Sheet

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

(±)-*cis*-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride

RR,SS-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride – b(4)



• HCl

$C_{16}H_{25}NO_2$. HCl MW 299.84

tramadol hydrochloride

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					adequate	5/2/06	
					N/A		
					N/A		

b(4)

[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
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

b(4)

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

CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	64,317	Tramadol hydrochloride Contramid
NDA	21-692	Ralivia ER Tablets
NDA	20-281	Ultram

b(4)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	8/1/06	S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
Office of Drug Safety	The proposed proprietary names ——— and Ryzolt) are not acceptable	7/14/06 (DMETS)	Linda Wisniewski
EA	Categorical exclusion (see review)		
Microbiology	N/A		

b(4)

CMC Review for NDA 21-745

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA is recommended for approval.

Some of the labeling comments will need to be conveyed to the applicant, if there is a resubmission to this NDA (see page 10 of this review under Basis of Approvability).

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

None

II. Summary of CMC Assessments

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

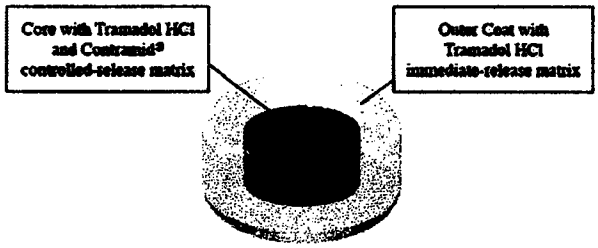
(1) Drug Substance

The active ingredient is tramadol hydrochloride. It is manufactured by [redacted] Detailed information on the drug substance is referenced to DMF [redacted], which was reviewed on May 2, 2006 and found to be adequate. Note that [redacted] b(4)

Tramadol hydrochloride is included in the current European Pharmacopoeia. Although there is no current USP monograph for tramadol hydrochloride, a proposed monograph for tramadol hydrochloride was published in the March/April 2005 Pharmacopoeial Forum (Volume 31 Number 2). The drug substance specification proposed in this NDA includes all the requirements in the proposed USP monograph for tramadol hydrochloride with tighter acceptance criteria for total impurities and additional tests on melting point and particle size distribution.

(2) Drug Product

The drug product is an extended-release tablet dosage form, comprising an immediate-release compression coat over an extended-release core.



With the exception of the following three excipients: Contramid®, [redacted] Black Ink, all the inactive ingredients are USP/NF materials. Contramid®, which has the chemical structure of hydroxypropyl distarch phosphate, meets the NF requirements for Pregelatinized Modified Starch. On contact with water, Contramid® swells to form a matrix that controls the release rate of tramadol hydrochloride in the tablet core. The tablet coat does not contain Contramid®. It is designed to disintegrate immediately after administration and provide a fast onset of action.

The tablets are manufactured using [redacted] b(4

The tablets are formulated in three different strengths: 100 mg, 200 mg, and 300 mg. The tablets are described as white to off-white, beveled edge, round biconvex tablets, plain on one side and printed black [redacted] b(4) respectively for each strength on the other side. They are packaged in HDPE bottles and blisters.

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

The drug product is indicated for the management of moderate to moderately severe pain. It is intended to be administered once daily and will be dispensed by prescription only. The tablets should be swallowed whole with liquid and not split, chewed, dissolved, or crushed.

The primary stability batches were manufactured at the proposed commercial manufacturing facility (Confab). Primary stability data were submitted for all three strengths and include stability results at 25°C/60%RH storage conditions (24 months for 1 batch and 12 months for 2 batches), 30°C/65%RH (12 months for 3 batches), and 40°C/75%RH (6 months for 3 batches). Supportive stability data were submitted for all three strengths packaged in blisters and one of the proposed bottle sizes (100-count only). Statistical analysis was performed on the stability data from the batches manufactured at the commercial site (Confab). Based on the results provided in the statistical analysis, an expiration period of 24 months is granted, instead of the proposed ——months. b(4)

b(4)

C. Basis for Approvability or Not-Approval Recommendation

The CMC information of the drug substance was referenced to DMF——, which was reviewed on May 2, 2006 and found to be adequate. b(4)

A detailed pharmaceutical development report was submitted to the NDA. The drug product was developed to provide the early onset of analgesia associated with immediate-release forms, such as Ultram, and also maintain effective analgesia for 24 hours following once daily administration. Using non-compartmental pharmacokinetic modeling, the applicant generated target plasma profiles, which was then deconvoluted to generate target in-vitro dissolution profiles. The formulations of the 100-mg, 200-mg, and 300-mg tablets were designed and modified to match the target dissolution profiles and plasma profiles. Critical parameters and critical quality attributes were identified.

All the inactive ingredients are USP/NF materials except Contramid® ——— and ——— Black Ink. The specifications of the non-compendial excipients, as revised, are adequate. b(4)

b(4)

The same system also checked [redacted] step.

b(4)

The Office of Drug Safety and the clinical division have objections to the use of the proposed proprietary names [redacted] and "Ryzolt"). However, a proprietary name is not a requirement for the approval of the NDA.

The reviewers gave a presentation regarding CMC review of this NDA at the 7/13/06 ONDQA Peer Review Forum. There was great interest during the forum and some interesting questions were raised in the area of manufacturing and controls. These issues have been addressed by the applicant. Through the communications with the investigator who performed the pre-approval inspection at the drug product manufacturing site, these issues were further clarified. For the issues and responses, please refer to page 101 of this review for details.

The Office of Compliance has issued an "acceptable" recommendation for each facility used for manufacturing and control of the drug substance and drug product.

During the 7/18/06 meeting, the clinical division decided that this NDA will not be approved due to clinical deficiencies and thus there will be no labeling negotiations with the applicant. However, the labeling comments, as they appear on pages 100 of this review, will need to be communicated to the applicant if there is a resubmission to this NDA.

III. Administrative

A. Reviewer's Signature

(See appended electronic signature page)

Sue-Ching Lin, Reviewer, ONDQA
Ted Chang, Pharmaceutical Scientist, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Ravi Harapanhalli, Branch Chief, Branch V, ONDQA

C. CC Block:

Entered electronically in DFS

93 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Sue Ching Lin
9/18/2006 03:32:32 PM
CHEMIST

Ted Chang
9/18/2006 03:40:26 PM
CHEMIST

Ravi Harapanhalli
9/20/2006 09:11:16 AM
CHEMIST

Initial Quality Assessment
Branch V
Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

OND Division:	Anesthesia, Analgesia and Rheumatology
NDA:	21-745
Applicant:	Labopharm
Stamp date:	November 29, 2005
PDUFA Date:	September 28, 2006
Trademark:	Tramadol Contramid® OAD tablets
Established Name:	Tramadol Hydrochloride
Dosage Form:	Tablet (controlled Release)
Route of Administration:	Oral
Indication:	Management of moderate to moderately severe pain
Pharmaceutical Assessment Lead:	Ali Al-Hakim, Ph.D.

	YES	NO
ONDQA Fileability:	√	___
Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summary

The drug product Tramadol Contramid® OAD tablets, is formulated to deliver two types of release characteristics (immediate and controlled). Therefore, tramadol hydrochloride tablets consists of a dual-matrix delivery system with an outer compression coat (containing tramadol hydrochloride) providing immediate release characteristics and inner core containing tramadol hydrochloride and Contramid®, which provides the controlled-release (continuous release over 24 hours). Contramid® (hydroxypropyl distarch phosphate) is a modified starch obtained by cross-linking of high amylose starch to produce a 3-dimensional structure that is combined with tramadol. Tramadol Contramid® OAD tablets are available as 100 mg, 200 mg and 300 mg controlled release tablets for once daily administration packaged in blister strip (100mg, 200 and 300mg) and HDPE bottle (30, 90 ——— tablets) for b(4)

B. Review, Comments and Recommendations

Drug Substance[1]

b(4)

[1] The applicant reported that the drug substance complies with the European Pharmacopeia. However, once the material adopted by USP monograph, Labopharm commits to comply with USP monograph.

12 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Ali Al-Hakim
1/20/2006 06:24:10 PM
CHEMIST

Ravi Harapanhalli
1/20/2006 06:41:58 PM
CHEMIST