CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-217s000

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: 10-Nov-2009

From: Yong Hu, Ph.D., CMC Reviewer, Branch II/DPA I/ONDQA

To: NDA 21-217, Exalgo (Hydromorphone Hydrochloride) Extended-Release Tablets

Through: Prasad Peri, Ph.D., Branch Chief (Acting), Branch II/DPA I/ONDQA

Subject: Approval recommendation

In the CMC review #2, dated 22-Oct-2009, the NDA is recommended for approval pending on the following:

1. Agreement on post-approval annual microbial limits testing of the drug product for the first three post-approval batches (lowest and highest strengths).
2. Acceptable cGMP recommendation on manufacturing facilities by the Office of Compliance.

These outstanding items have been addressed since then, thus NDA 21-217 is now recommended for approval from CMC perspective. See details below.

Agreement on post-approval annual microbial limits testing of the drug product:

In the correspondence dated 27-Oct-2009, the applicant states: "Neuromed agrees to annual microbial limits testing annually on stability for the first three post- approval batches for the lowest and highest strengths."

Acceptable cGMP recommendation on manufacturing facilities by the Office of Compliance:

The overall recommendation made in EES on 02-Nov-2009 is "Acceptable." See the attached EES Summary Report.

In conclusion, NDA 21-217 is recommended for approval from CMC perspective.

ATTACHMENT

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 21217/000	**Sponsor:**	NEUROMED PHARMS
Org. Code:	170		755 BUSINESS CENTER DR
Priority:	3S		HORSHAM, PA 19044
Stamp Date:	29-DEC-1999	**Brand Name:**	DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6
PDUFA Date:	22-NOV-2009	**Estab. Name:**	
Action Goal:		**Generic Name:**	HYDROMORPHONE HCL
District Goal:	23-SEP-2009	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; TABLET, CONTROLLED RELEASE; HYDROMORPHONE HYDROCHLORIDE; 8MG 002; TABLET, CONTROLLED RELEASE; HYDROMORPHONE HYDROCHLORIDE; 16MG 003; TABLET, CONTROLLED RELEASE; HYDROMORPHONE HYDROCHLORIDE; 32MG 004; TABLET, CONTROLLED RELEASE; HYDROMORPHONE HYDROCHLORIDE; 64MG		

FDA Contacts:	D. WALKER	Project Manager	(HFD-170)	301-796-4029
	Y. HU	Review Chemist		301-796-5031
	D. CHRISTODOULOU	Team Leader		301-796-1342

Overall Recommendation:	ACCEPTABLE	on 02-NOV-2009	by S. FERGUSON	(HFD-322)	301-796-3247
	WITHHOLD	on 14-SEP-2000	by DAMBROGIOJ		

Establishment:	**CFN:** 2938701 **FEI:** 2938701		
	ALZA CORP 700 EUBANKS DR VACAVILLE, CA 956889470		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE RELEASE TESTER		
Profile:	TABLETS, EXTENDED RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	02-NOV-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 2950681 **FEI:** 1000123587

ALZA CORP
1015 JOAQUIN ST

MOUNTAIN VIEW, CA 94043

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

Profile: TABLETS, EXTENDED RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-SEP-2000

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TABLETS, EXTENDED RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-JUL-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-JUL-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	09-JUL-2009		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21217	ORIG-1	NEUROMED PHARMACEUTICALS LTD	DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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/s/

YONG HU
11/10/2009
This NDA is recommended for Approval from CMC perspective.

PRASAD PERI
11/10/2009

Exalgo® (Hydromorphone HCl) Extended-release Tablets

NDA 21-217

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Neuromed Pharmaceuticals
301-2389 Health Sciences Mall
Vancouver, British Columbia
V6T 1Z3 Canada

Representative: Susan Franks,
Premier Research Group
755 Business Center Drive
Horsham, PA 19044

Indication: Exalgo® extended-release tablets are indicated for the management of moderate to severe pain in opioid tolerant patients requiring continuous, around the clock opioid analgesia for an extended period of time. Each tablet is to be administered for a 24 hour period.

Presentation: Exalgo® tablets are formulated in 8, 12, 16, 32, and 64 mg strengths, and packaged into white high-density polyethylene (HDPE) 75 cc bottles with induction seal and a (b) (4) child-resistant (CR) closure. Each bottle contains 100 tablets and one (b) (4) desiccant pouch (b) (4)

EER Status: Recommendation Pending

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Revalidation by Agency was not requested
Pharm/toxicology – Acceptable

Original Submission: 29-Dec-1999
Resubmission: 22-May-2009

Post-Approval CMC Commitments:

The sponsor is requested to perform microbial testing for drug product on stability (12, 24 and 36 months) for the low (8 mg) and high strength (64 mg) products for the first three commercial batches. This data was not provided for the commercial scale batches as the drug substance itself is considered to inhibit microbial growth. But the drug product has a proposed moisture content acceptance criteria of NMT (b) (4)

Drug Substance:

The drug substance, hydromorphone hydrochloride, is a semi synthetic drug substance derived from oripavine which is obtained from plants. The USAN modified name is hydromorphone hydrochloride and the IUPAC nomenclature is Morphinan-6-one, 4,5-alpha-epoxy-3-hydroxy-17-methyl-, hydrochloride, (5'-alpha). Previous source was (b) (4) and in this resubmission has been replaced by a new supplier: (b) (4). The (b) (4) drug substance is a white to almost white powder. It is freely soluble in water; slightly soluble in methanol and ethanol; (b) (4) insoluble in acetone. The drug substance is (b) (4) (b) (4) (b) (4)

The chemistry, manufacture, and controls of hydromorphone hydrochloride are described in (b) (4) DMF (b) (4). The drug substance is manufactured in (b) (4) The structure of hydromorphone hydrochloride is characterized by comparing to a reference standard in addition to other spectrometric and chromatographic techniques. (b) (4)

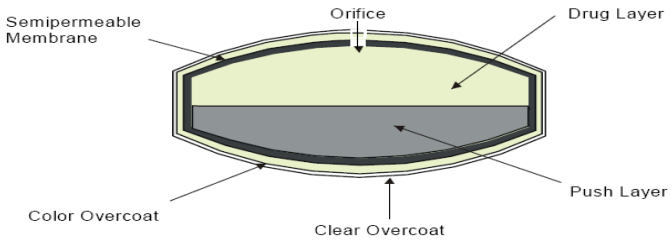
The proposed release specifications for hydromorphone hydrochloride include in addition to the USP monograph specifications, limits on: Description, Melting Point, Related Substances, (b) (4) and Particle Size Distribution.

The drug substance is stored in (b) (4) bags contained in a (b) (4) drums. Stability and retest period information are all referenced to the Drug Master File.

Conclusion: The drug substance is satisfactory

Drug Product:

The drug product is a Oros® Push Pull Technology based extended-release tablet with a laser drilled orifice on one side. The side of the tablet where the orifice is located, is distinguished from the other side by the color of the tablet. The orifice (b) (4) is where the drug comes out of the tablet inside the body. The tablet is to be administered as a whole without crushing or splitting. The drug product is manufactured at Alza® Corporation, CA.



There are five strengths: 8 mg (red), 12 mg (dark yellow), 16 mg (yellow), 32 mg (b) (4), and 64 mg (b) (4) of hydromorphone hydrochloride with different amounts of overages that are used for the 8, 12 and 16 mg strengths. (b) (4) The tablets are distinguished by their size, markings on the tablet and their color.

The drug product is manufactured (b) (4) (b) (4)

Specification of the drug product include: Appearance, Identification by IR and HPLC, Assay, Content uniformity (USP <905>), Dissolution, Moisture content, (b) (4) and Microbial Limits on stability. It was demonstrated that hydromorphone hydrochloride exhibited very low water activity (b) (4) along with some reports of antimicrobial activity and hence the potential of microbial growth is very low. The applicant demonstrated that the drug product is compliant with microbial limits at release. A commitment to monitor the microbial content of the first three commercial batches of the 8 mg and 64 mg strength products is being sought.

Adequate stability data for the drug product has been provided to issue a 30 month shelf life for the 8 mg strength and 36 months for all other strengths (12 mg, 16 mg, 32 mg, and 64 mg per tablet).

Conclusion: The drug product is satisfactory.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested.

Overall Conclusion:

From a CMC perspective, the application is approvable pending acceptable cGMP recommendation from the Office of Compliance.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21217	ORIG-1	NEUROMED PHARMACEUTICALS LTD	DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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/s/

PRASAD PERI
10/23/2009

NDA 21-217

Exalgo (Hydromorphone Hydrochloride) Extended-Release Tablets

Neuromed Pharmaceuticals Ltd.

Yong Hu, Ph.D.

ONDQA/Division of Pre-Marketing Assessment I/Branch II

For The

Division of Anesthesia, Analgesia and Rheumatology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-217

2. REVIEW #: 2

3. REVIEW DATE: 22-Oct-2009

4. REVIEWER: Yong Hu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	29-Dec-1999
CMC review #1	20-Aug-2000
FDA Approvable Letter	27-Oct-2000
FDA-Knoll (Applicant) Meeting Minutes	07-Dec-2000
FDA (b) (4) (Manufacturer) Meeting Minutes	24-Jan-2003
FDA-ALZA (Sponsor) Meeting Minutes	03-Feb-2005
FDA-Neuromed (Applicant) Pre-NDA Meeting Minutes	08-Aug-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA Resubmission (Complete Response)	22-May-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Neuromed Pharmaceuticals Ltd.
Address:	301-2389 Health Sciences Mall Vancouver, British Columbia V6T 1Z3 Canada
Representative:	Susan Franks, Premier Research Group 755 Business Center Drive Horsham, PA 19044
Telephone:	215-907-1330 ext 1025

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Exalgo

b) Non-Proprietary Name (USAN): Hydromorphone HCl

c) Code Name/# (ONDC only): OROS Hydromorphone HCl

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505 b(1), Complete Response to Approvable Letter

10. PHARMACOL. CATEGORY:

Analgesic (Narcotic)

11. DOSAGE FORM:

Extended-release tablet

12. STRENGTH/POTENCY:

8, 12, 16, and 32 mg (as per Form 356h). The 64 mg is also included in the body of the NDA.

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: __x_Rx ___OTC

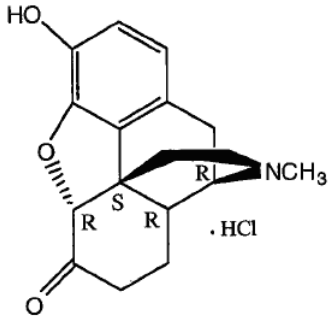
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x___Not a SPOTS product

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

USAN:	Hydromorphone hydrochloride
Chemical names:	Morphinan-6-one,4,5-epoxy-3-hydroxy-17-methyl-, hydrochloride, (5a)- 4,5a-Epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride
CAS number, if available:	71-68-1
Molecular Formula:	$C_{17}H_{19}NO_3$. HCl
Molecular Weight:	321.80
Chemical Structure:	



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	22-Aug-2009	The holder has provided adequate response to the deficiencies.
	III			4	N/A	N/A	Enough information in application
	III			4	N/A	N/A	Enough information in application
	III			4	N/A	N/A	Enough information in application
	IV			4	N/A	N/A	Enough information in application

(b) (4)	III	(b) (4)	4	N/A	N/A	Enough information in application
	III		4	N/A	N/A	Enough information in application
	III		4	N/A	N/A	Enough information in application
	III		4	N/A	N/A	Enough information in application
	III		4	N/A	N/A	Enough information in application

[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
IND	(b) (4)	Sponsor: Johnson and Johnson; Product: Dilaudid (Hydromorphone HCl) SR Tablets;
IND	78,223	Sponsor: Neuromed Pharma Inc Product: OROS Hydromorphone HCl tablet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	Adequate safety qualification to support the specification limit NMT (b) (4) of the drug product degradant hydromorphone N-oxide	16-Oct-2009	Belinda Hayes, Ph.D.
Biopharm	Biowaiver is recommended for the 12 mg strength. New dissolution specifications are recommended. (b) (4)	30-Sep-2009	John Duan, Ph.D.
LNC	NA		
Methods Validation	NA		
OPDRA	NA		
EA	The applicant has requested a claim for categorical exclusion from the requirements of an environmental analysis. Deemed adequate in Review #1.		
Microbiology	NA. This is a solid oral dosage form. Development data shows low potential of microbial contamination and growth in tablets. Microbial testings were conducted at batch release but not on stability. The applicant will be requested to conduct post-approval annual microbial limits testing of the drug product for the first three post-approval batches (lowest and highest strengths).		

The Chemistry Review for NDA 21-217

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is a resubmission to address the deficiencies identified in the Agency's approvable letter, dated 27-Oct-2000, and to propose a new dosage strength (12 mg). In addition, the resubmission proposes a new drug substance supplier, (b) (4)

This application is approvable pending on the following:

1. Agreement on post-approval annual microbial limits testing of the drug product for the first three post-approval batches (lowest and highest strengths).
2. Acceptable cGMP recommendation on manufacturing facilities by the Office of Compliance.

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

None at this time.

II. Summary of Chemistry Assessments

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

The drug product is Exalgo® (hydromorphone hydrochloride) extended-release tablets, 8, 12, 16, 32, and 64 mg. The 12 mg is the new strength proposed in this resubmission. The products is also referred to as "OROS® Hydromorphone HCl" by the applicant, as the formulation employs the OROS® technology to achieve extended release. The product is indicated for the management of moderate to severe pain in opioid tolerant patients requiring continuous, around the clock opioid analgesia for an extended period of time. The product is packaged into white high-density polyethylene (HDPE) 75 cc bottles with induction seal and a (b) (4) child-resistant (CR) closure. Each bottle contains 100 tablets and one (b) (4) desiccant pouch (b) (4).

As discussed above, ALZA's OROS® Push-Pull™ technology is used to deliver the hydromorphone HCl drug substance in a controlled manner over 24 hours. The core of the tablets consists of a drug layer and a push layer. A semi-permeable membrane, also referred to as the rate-controlling membrane, surrounds the core. This membrane provides a rate control of the water influx resulting in drug release. An orifice is drilled on the drug layer dome of the tablet to provide an exit port for the dissolved drug. The push layer contains a polymer that, when hydrated, expands to push the dissolved drug (solution) out of the tablet. The color overcoat applied to the tablet provides product and dose differentiation. Since the rate-controlling membrane shell is insoluble in body fluids, the tablet shell expelled from the patient may contain residual amount of drug that is not released into the body. (b) (4) The manufacturing process for the 12 mg tablet is the same as that for the other strengths.

The in-vitro drug release of the 12 mg tablet is dose proportional to the 16 mg, 32 mg, and 64 mg and very close to 8 mg as determined by the Biopharmaceutics reviewer. The 8 mg, 12 mg, and 16 mg dosage strengths have the same compositions for the drug and push layers, with the exception of the color overcoat composition.

The drug substance supplier has been changed from (b) (4), proposed in the original submission, to (b) (4). The drug substance information is provided in DMF (b) (4). The applicant showed that drug substance particle size does not impact tablet dissolution. However, the applicant proposed a particle size specification for the drug substance to minimize the drug loss (b) (4) to ensure the tablet content uniformity.

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

The EXALGO tablets are to be swallowed whole and are not to be broken, chewed, dissolved, crushed or injected. The tablets are intended for once daily administration. The dose range of EXALGO is 12 mg to 64 mg. The tablet strengths supplied are 8, 12, 16, and 32 mg.

The product is to be stored at 25ºC (77ºF); excursions permitted to 15-30°C (59-86°F).

The following expiration dating periods are granted for the commercial bottle packaging configuration.

8 mg – 30 months
12, 16, 32, and 64 mg – 36 months

C. Basis for Approvability or Not-Approval Recommendation

The applicant has addressed the CMC deficiencies in the approvable letter of 27-Oct-2000 sufficiently. The CMC information for the new strength, 12 mg, is adequate. Biowaiver for the 12 mg is recommended by the Biopharmaceutics Review Team. The applicant has also provided adequate comparability data to qualify the new drug substance supplier, (b) (4)

III. Administrative

A. Reviewer's Signature
See electronic signatures.

B. Endorsement Block
See electronic signatures.

C. CC Block
DARRP/Diana Walker
ONDQA/Prasad Peri
ONDQA/Danae Christodoulou
ONDQA/John Duan
DARRP/Belinda Hayes
DARRP/ Elizabeth Kilgore

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21217	ORIG-1	NEUROMED PHARMACEUTICALS LTD	DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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/s/

YONG HU

10/22/2009

This application is approvable pending on the following:
1. Agreement on post-approval annual microbial limits testing of the drug product for the first three post-approval batches (lowest and highest strengths).
2. Acceptable cGMP recommendation on manufacturing facilities by the Office of Compliance.

PRASAD PERI

10/23/2009

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

)lication:	NDA 21217/000	**Sponsor:**	NEUROMED PHARMS
Org. Code:	170		755 BUSINESS CENTER DR
Priority:	3S		HORSHAM, PA 19044
Stamp Date:	29-DEC-1999	**Brand Name:**	Exalgo (hydromorphone HCl) 8/12/16/32
PDUFA Date:	22-FEB-2010	**Estab. Name:**	
Action Goal:		**Generic Name:**	HYDROMORPHONE HCL
District Goal:	23-SEP-2009	**Product Number; Dosage Form; Ingredient; Strengths**	001; TABLET, CONTROLLED RELEASE; HYDROMORPHONE HYDROCHLORIDE; 8MG 002; TABLET, CONTROLLED RELEASE; HYDROMORPHONE HYDROCHLORIDE; 16MG 003; TABLET, CONTROLLED RELEASE; HYDROMORPHONE HYDROCHLORIDE; 32MG 004; TABLET, CONTROLLED RELEASE; HYDROMORPHONE HYDROCHLORIDE; 64MG

FDA Contacts:	D. WALKER	Project Manager	(HFD-170)	301-796-4029
	Y. HU	Review Chemist		301-796-5031
	D. CHRISTODOULOU	Team Leader		301-796-1342

Overall Recommendation:	ACCEPTABLE	on 02-NOV-2009	by S. FERGUSON	(HFD-322)	301-796-3247
	WITHHOLD	on 14-SEP-2000	by DAMBROGIOJ		

Establishment: **CFN:** 2938701 **FEI:** 2938701

ALZA CORP
700 EUBANKS DR

VACAVILLE, CA 956889470

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

Profile: TABLETS, EXTENDED RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-NOV-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

ablishment: **CFN:** 2950681 **FEI:** 1000123587

ALZA CORP
1015 JOAQUIN ST

MOUNTAIN VIEW, CA 94043

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

Profile: TABLETS, EXTENDED RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-SEP-2000

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TABLETS, EXTENDED RELEASE **OAI Status:** NONE

t Milestone: OC RECOMMENDATION

Milestone Date: 10-JUL-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-JUL-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

ablishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	09-JUL-2009		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

lication:	NDA 21217/000	**Action Goal:**	
Stamp Date:	29-DEC-1999	**District Goal:**	23-SEP-2009
Regulatory:	22-FEB-2010		
Applicant:	NEUROMED PHARMS	**Brand Name:**	Exalgo (hydromorphone HCl) 8/12/16/32
	755 BUSINESS CENTER DR	**Estab. Name:**	
	HORSHAM, PA 19044	**Generic Name:**	HYDROMORPHONE HCL
Priority:	3S	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	170	001; TABLET, CONTROLLED RELEASE; HYDROMORPHONE HYDROCHLORIDE; 8MG 002; TABLET, CONTROLLED RELEASE; HYDROMORPHONE HYDROCHLORIDE; 16MG 003; TABLET, CONTROLLED RELEASE; HYDROMORPHONE HYDROCHLORIDE; 32MG 004; TABLET, CONTROLLED RELEASE; HYDROMORPHONE HYDROCHLORIDE; 64MG	

Application Comment: THE NDA IS FOR DILAUDID (HYDROMORPHONE HYDROCHLORIDE) CONTROLLED-RELEASE TABLETS (on 23-MAR-2000 by HARAPANHALLI)

FDA Contacts:				
	D. WALKER	Project Manager	(HFD-170)	301-796-4029
	Y. HU	Review Chemist		301-796-5031
	D. CHRISTODOULOU	Team Leader		301-796-1342

Overall Recommendation:	ACCEPTABLE	on 02-NOV-2009	by S. FERGUSON	(HFD-322)	301-796-3247
	WITHHOLD	on 14-SEP-2000	by DAMBROGIOJ		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ıblishment: **CFN:** 2938701 **FEI:** 2938701

ALZA CORP

700 EUBANKS DR
VACAVILLE, CA 956889470

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

Estab. Comment: CURRENT MANUFACTURER AND RELEASE TESTER OF THE DRUG PRODUCT IN THE 2009 RESUBMISSION. (on 30-JUN-2009 by D. CHRISTODOULOU () 301-796-1342)

Profile: TABLETS, EXTENDED RELEASE **OAI Status:** NONE

Milestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
SUBMITTED TO OC	23-MAR-2000				HARAPANHALLI
SUBMITTED TO DO	24-MAR-2000	10-Day Letter			FERGUSONS
DO RECOMMENDATION	12-SEP-2000			ACCEPTABLE BASED ON FILE REVIEW	MEDWARDS
OC RECOMMENDATION	14-SEP-2000			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ
SUBMITTED TO OC	06-JUL-2009				CHRISTODOULO
ƷMITTED TO DO	06-JUL-2009	10-Day Letter			STOCKM
ASSIGNED INSPECTION TO IB	09-OCT-2009	Product Specific			RYOUNG
INSPECTION SCHEDULED	09-OCT-2009		23-OCT-2009		RYOUNG
INSPECTION PERFORMED	30-OCT-2009		30-OCT-2009		RYOUNG
DO RECOMMENDATION	02-NOV-2009			ACCEPTABLE INSPECTION	RYOUNG
OC RECOMMENDATION	02-NOV-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ıblishment: **CFN:** 2950681 **FEI:** 1000123587

ALZA CORP

1015 JOAQUIN ST
MOUNTAIN VIEW, CA 94043

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

Estab. Comment: CURRENT PACKAGER OF THE DRUG PRODUCT IN THE 2009 RESUBMISSION. (on 30-JUN-2009 by D. CHRISTODOULOU () 301-796-1342)

Profile: TABLETS, EXTENDED RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	23-MAR-2000				HARAPANHALLI
SUBMITTED TO DO	24-MAR-2000	10-Day Letter			FERGUSONS
DO RECOMMENDATION	12-SEP-2000			ACCEPTABLE	MEDWARDS
				BASED ON FILE REVIEW	
OC RECOMMENDATION	14-SEP-2000			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ıblishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Estab. Comment: CURRENT PACKAGER FOR THE DRUG PRODUCT IN THE 2009 RESUBMISSION. (on 30-JUN-2009 by D. CHRISTODOULOU () 301-796-1342)

Profile: TABLETS, EXTENDED RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	06-JUL-2009				CHRISTODOULO
SUBMITTED TO DO	07-JUL-2009	GMP Inspection			STOCKM
DO RECOMMENDATION	10-JUL-2009			ACCEPTABLE	RHERNAND
ACCEPTABLE RECOMMENDATIONS FOR PACKAGER OPERATIONS ONLY ,BASED ON FIRM PREVIOUS INSPECTION CLASSIFICATION (NAI)DATED JUNE 8, 2009.				BASED ON FILE REVIEW	
OC RECOMMENDATION	10-JUL-2009			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ıblishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Estab. Comment: CURRENT DRUG SUBSTANCE MANUFACTURER IN THE 2009 RESUBMISSION. (on 06-JUL-2009 by D. CHRISTODOULOU () 301-796-1342)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	06-JUL-2009				CHRISTODOULO
SUBMITTED TO DO	06-JUL-2009	10-Day Letter			STOCKM
DO RECOMMENDATION	07-JUL-2009			ACCEPTABLE	MWOLESKE
A GMP INSPECTION WAS CONDUCTED 3/20-27/2009 AND WAS CLASSIFIED NO ACTION INDICATED. PROFILE CLASS CSN WAS ACCEPTABLE. THE DISTRICT'S RECOMMENDATION IS ACCEPTABLE.				BASED ON FILE REVIEW	
OC RECOMMENDATION	07-JUL-2009			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ıblishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Estab. Comment: CURRENT STABILITY TESTER FOR THE DRUG PRODUCT IN THE 2009 RESUBMISSION. (on 30-JUN-2009 by D. CHRISTODOULOU () 301-796-1342)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	06-JUL-2009				CHRISTODOULO
OC RECOMMENDATION	09-JUL-2009			ACCEPTABLE BASED ON PROFILE	KIEL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21217/000**
Priority: **3S**
Org Code: **170**
Stamp: **29-DEC-1999** Regulatory Due: **29-OCT-2000**
Action Goal:
District Goal: **30-AUG-2000**
Applicant: **KNOLL PHARM**
Brand Name: **DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6**
Established Name:
Generic Name: **HYDROMORPHONE HCL**
Dosage Form: **SRT (SUSTAINED RELEASE TABLET**
Strength: **8, 16, 32, 64 MG**

FDA Contacts:
J. MILSTEIN (HFD-170) 301-827-7410 , Project Manager
R. HARAPANHALLI (HFD-160) 301-827-7510 , Review Chemist
E. LEUTZINGER (HFD-160) 301-827-7510 , Team Leader

Overall Recommendation:

WITHHOLD on 14-SEP-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **2938701**
ALZA CORP
700 EUBANKS DR
VACAVILLE, CA 95688
DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **14-SEP-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE LABELER**
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Establishment: **2950681**
ALZA CORP
1015 JOAQUIN ST
MOUNTAIN VIEW, CA 94043
DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **14-SEP-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE LABELER**
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Establishment: (b) (4)
(b) (4)
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-MAR-2000**
Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: (b) (4)

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **27-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**

Establishment: **2249197**
KNOLL PHARMACEUTICAL CO
140 HANOVER AVENUE
CEDAR KNOLLS, NJ 07927

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**
FINISHED DOSAGE STABILITY TESTER

Establishment: **2211084**
KNOLL PHARMACEUTICALS
30 NORTH JEFFERSON RD
WHIPPANY, NJ 07981

DMF No:
AADA No:

Profile: **TTR** OAI Status: **POTENTIAL OAI**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
FINISHED DOSAGE PACKAGER

Nilstein

OCT 2 7 2000

DIVISION OF ANESTHETICS, CRITICAL CARE AND ADDICTION DRUG PRODUCTS (DACCAD, HFD-170)

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-217 **REVIEWED DATE:** 20-AUG-2000 (Revised 10/24/00)

CHEM.REVIEW #: 1 **REVIEWER:** Ravi S. Harapanhalli, Ph.D.

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	28-DEC-99	29-DEC-99	05-JAN-00

NAME & ADDRESS OF APPLICANT: KNOLL PHARMACEUTICAL COMPANY
3000 Continental Drive- North
Mt. Olive, NJ, 07828-1234
Contact name: Robert W. Ashworth, Ph.D.
Phone #: (973) 426-6012

DRUG PRODUCT NAME

Proprietary: DILAUDID CR™
Nonproprietary/USAN: HYDROMORPHONE HYDROCHLORIDE
Code Names/#'s: MP-123456B
Chemical Type/Therapeutic Class: **3**

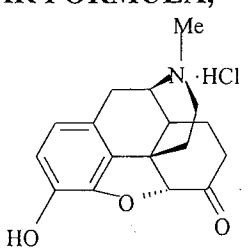
ANDA Suitability Petition/DESI/Patent Status: N/A
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Management of moderate to severe pain when an opioid analgesic is appropriate for a few days.

DOSAGE FORM: Tablets
STRENGTHS: 8 mg, 16 mg, 32 mg, and 64 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: _X_ **Rx** __ **OTC**
SPECIAL PRODUCTS: Yes __ **No** X
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Molecular formula: $C_{17}H_{19}NO_3 \cdot HCl$; Molecular weight: 321.80



SUPPORTING DOCUMENTS:

Type/ Number	Subject	Holder/LOA	Status	Reviewer/ Date	Letter Date
Type IV/V DMF 9183 Excipients and Pharm/Tox Data Only available	OROS /GITS (Gastrointestinal Therapeutic System) Technology	ALZA Corporation	Active (DMF was not reviewed)	Many approved NDAs based on OROS/GITS	N/a
Type III DMF (b) (4)	(b) (4)		Adequate	R. Harapanhalli 09/26/00	N/a
Type III DMF (b) (4)			Adequate	Karen Bernard 12/12/94	N/a
Type III DMF (b) (4)			Adequate	Michael Smela (08/31/95) and Xavier Ysern (12/01/98	N/a
Type III DMF (b) (4)			Inadequate	R. Frankewich (07/28/00)	07/28/00
Type III DMF (b) (4)			Inadequate	R. M. Patel/ 05/24/00	05/25/00
Type III DMF (b) (4)			Adequate	Prasad Peri 06/14/00	N/a
Type III DMF (b) (4)			Adequate	Moo-Jhong Rhee (08/08/95)	N/a

Type IV DMF (b) (4)	(b) (4) (b) (4)	(b) (4)	Adequate	R.S. Harapanhalli (09/22/00)	N/a
Type IV DMF (b) (4)	(b) (4)		Adequate	R. S. Harapanhalli (10/06/00)	N/a
Type IV DMF (b) (4)			Not reviewed. Adequate info in the NDA.	R. S. Harapanhalli	N/a

RELATED DOCUMENTS (if applicable):

Type/ Number	Subject	Holder/LOA	Status	Reviewer/ Date	Letter Date
(b) (4)			Active		N/a
			Active		N/a
NDA 19-034	Dilaudid® HP (hydromorphone HCl) Injection	Knoll Pharmaceutical Company	Approved		N/a

CONSULTS:
EER Consult: All facilities "acceptable", however OAI letter sent by OC to Knoll, which affects all drug products. Current OC status is "Withhold."
OPDRA/LNC-Medication Error Consult: Approved

REMARKS/COMMENTS:
Several issues pertaining to the acceptance testing of (b) (4), the starting material, and other reagents and solvents were identified. The drug substance specifications should include limits on (b) (4) content, (b) (4), and particle size. Additional data on the characterization of reference materials are needed. The drug product specifications should be revised to ensure that no toxicological qualifications are warranted. The dissolution specifications should be revised to include lower limit at 0-4 h, (b) (4), release at 0-10 h, and NLT (b) (4) at 24 h, as recommended by this reviewer and Biophar.

CONCLUSIONS & RECOMMENDATIONS:
While the CMC section of this NDA contains essential elements of drug product quality, the sponsor should address the listed deficiencies satisfactorily before approval. This will

ensure better control over the drug product quality as it relates to the safety and efficacy. DMFs (b) (4) were found to be inadequate to support the container closure systems. The OPDRA consult recommended the trademark "Dilaudid CR™. However, the Office of Compliance recommended "Withhold" status for this drug product in its cGMP inspections dated September 14, 2000. From CMC perspective, the NDA is "not approvable." Before approval the sponsor should satisfactorily resolve the listed deficiencies to the NDA; the DMFs (b) (4) should be adequately amended, and acceptable cGMP recommendation should be obtained from the Office of Compliance.

Rharapanhalli 10/27/00

Ravi S. Harapanhalli, Ph.D.
Review Chemist

cc: Orig. NDA 21-217
HFD-170/NDA Division File
HFD-160/harapanhalli/
HFD-170/MO/
HFD-170/Pharmacologist/Heberny
HFD-160/Micro/PCooney
HFD-170/CSO/Jmilstein
HFD-820/Gibbs
R/D Init by: Dale Koble 10/27/00
filename: c:/mydocs/ndas/21217a