CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022370Orig1s000

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 22-370
Subject: Addendum to CMC Review
Date: 2/2/09

EER: The applicant withdrew the original packager, (b) (4), in a communication submitted to NDA 22-370 on January 6, 2009. The EER was updated to reflect the change, and the Office of Compliance gave an overall "Acceptable" cGMP recommendation for this application on 2/2/09.

There are no CMC outstanding issues remaining, and NDA 22-370 is recommended for approval.

Danae D. Christodoulou, Ph.D. 2/2/09
Pharmaceutical Assessment Lead, ONDQA

Ali Al-Hakim, Ph.D. 2/2/09
Branch II Chief, ONDQA

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

/s/

Danae Christodoulou
2/2/2009 02:20:16 PM
CHEMIST
Addendum to CMC review

Ali Al-Hakim
2/2/2009 02:37:31 PM
CHEMIST

NDA 22-370

CIP-TRAMADOL ER CAPSULES

Cipher Pharmaceuticals LTD

Danae D. Christodoulou
Office of New Drug Quality Assessment
Division of Premarketing Assessment I, Branch II

CMC Review of NDA 22-370
For the Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)

Table of Contents

Chemistry Review Data Sheet

1. NDA or ANDA: 22-370

2. REVIEW #: 1

3. REVIEW DATE: 11/18/08

4. REVIEWER: Danae D. Christodoulou

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
NDA (b) (4)	
ORIGINAL SUBMISSION N-000 AND AMENDMENTS	26-JUN-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 22-370	
ORIGINAL SUBMISSION N-000	14-APR-2008
AMENDMENT BZ	20-OCT-2008
AMENDMENT BZ	08-SEP-2008
AMENDMENT BZ	27-JUN-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Cipher Pharmaceuticals Inc.
Address:	5650 Tomken Road, Unit 16, Ontario L4W 4P1, Canada

Chemistry Review Data Sheet

Representative: Conrad M. Shumadine, Esq., Wilcox & Savage PC, One Commercial Place, Suite 1800, Norfolk, VA 23510

Telephone: 757-628-5525

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: CIP-TRAMADOL ER CAPSULES
b) Non-Proprietary Name (USAN): Tramadol HCl
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2). RLD: ULTRAM® (tramadol HCl) tablets and ULTRAM® ER (tramadol HCl) ER tablets by Ortho-McNeil Pharmaceuticals Inc.

10. PHARMACOL. CATEGORY: Analgesic

11. DOSAGE FORM: Extended-release capsules

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

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

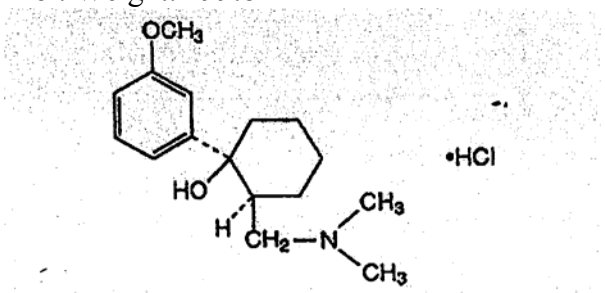
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

RR,SS-2-(dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexan-1-ol hydrochloride

Mol. Formula: $C_{16}H_{25}NO_2.HCl$

Mol. Weight: 299.84



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1, 4	Adequate	4/4/07	Review #6, D. Christodoulou DMF deemed adequate in previous reviews.
	IV			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	IV			4	N/A		

(b) (4)	III	(b) (4)	(b) (4)	4	N/A		
	III	(b) (4)		4	N/A		
	III	(b) (4)		4	N/A		

[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)	(b) (4)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted: Sufficient long term real time stability data to assess expiration dating provided.		
EES	Pending		
Pharm/Tox	Not consulted: Impurities are qualified/meet ICH Q3A Guidelines.		
Biopharm	AP. Provided feedback on in vitro drug release specifications.	3/26/2007	Lei Zhang
LNC	Not consulted: Conventional dosage form.		
Methods Validation	Not recommended for validation; methods do not meet ONDQA Criteria for MV.		
DMETS	Revisions proposed	2/22/07	M. Safarik
EA	N/A Categorical exclusion claimed; deficient: EIC based on the 5th year projected sales calculation not provided.		
Microbiology	N/A Solid oral dosage form which does not promote microbial growth.		

The Chemistry Review for NDA 22-370

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable pending acceptable cGMP recommendation from the Office of Compliance.

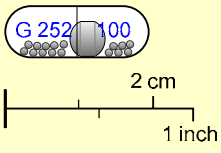
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Applicant affirmed to provide validation studies reports upon completion.

II. Summary of Chemistry Assessments

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

CIP-TRAMADOL ER (tramadol hydrochloride) extended-release) capsules are a new formulation of tramadol HCl for analgesia. The drug product consists of extended release film coated white beads and an immediate release tablet encapsulated in white opaque, size 1, 0 and 00, hard gelatin capsules. Strengths are 100 mg, containing a 25 mg immediate release tablet, and 200 mg and 300 mg containing a 50 mg tablet and the appropriate amount of film coated beads (b) (4). The drug product is an extended release oral dosage form with (b) (4) in-vitro drug release within 1h, (b) (4) within 7-8h and (b) (4) after 24h. The capsules are packaged in white HDPE round bottles with CR closures.



CIP-Tramadol ER Capsule

Tramadol ER Capsule Configuration

Capsule Strength	IR-Tablet Strength	ER-Beads Strength
100 mg	25 mg	75 mg
200 mg	50 mg	150 mg
300 mg	50 mg	250 mg

Tramadol is a CNS acting analgesic with a combined effect on opioid receptors, noradrenergic and serotonergic neurotransmission and inhibition of monoamine uptake. Tramadol HCl is isolated as a single polymorph from isopropanol and it is a chiral molecule with 2 asymmetric centers. The drug substance is used as the racemate, since both optical isomers exhibit pharmacological activity. The (+) enantiomer binds to the μ-opioid receptor and preferentially inhibits serotonin reuptake, whereas the (-) enantiomer inhibits norepinephrine reuptake. The effects of both enantiomers are complementary and synergistic and result in the analgesic effect of tramadol. O-desmethyl tramadol, the major active metabolite, also has two enantiomers, shows higher affinity for the μ -opioid receptor and has at least twice the analgesic potency of the parent drug.

Tramadol HCl is a white to off-white crystalline solid, highly soluble in water (b) (4) and MeOH (b) (4) with a pH of about 5 in (b) (4) aqueous solution. The high water solubility of tramadol impacted development of this extended release formulation; drug release is effected via diffusion through a polymeric membrane.

The drug substance is stable to light and moisture. The observed identified impurities are the (b) (4) (b) (4) Identified impurities are not detectable in the drug product and unidentified impurities remain below ICH Q3A acceptable limits through the product's shelf-life. Retest date for the drug substance is (b) (4).

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

CIP-TRAMADOL ER (tramadol hydrochloride) extended-release 100, 200 and 300 mg capsules are administered once daily. The drug product is supplied in three count-size configurations: 7 capsules in 30-ml and 75-ml bottles; 30 capsules in 40-ml and 75-ml bottles; 90 capsules in 75-ml and 200-ml bottles with desiccant. Expiration dating period of 36 months may be granted based on the evaluation of the primary stability data. The recommended storage conditions are: "Store at 25°C [77°F]; excursions permitted to 15°C to 30°C [59°F – 86°F]".

C. Basis for Approvability or Not-Approval Recommendation

Tramadol is a CNS acting analgesic with a combined effect on opioid receptors, noradrenergic and serotonergic neurotransmission and inhibition of monoamine uptake. The development of the extended release CIP-TRAMADOL ER capsules aims at obtaining (b) (4) .

To allow for rapid onset and prolonged drug release, the extended-release capsules contain an immediate release (IR) tablet and extended release (ER) beads. The 100 mg capsule contains a 25 mg IR tablet and coated ER beads and the 200 mg and 300 mg capsules a 50 mg IR tablet (corresponding to the currently marketed 50 mg ULTRAM) and coated ER beads. The formulations are compositionally proportional with immediate release to extended release (IR:ER) component ratio of 1:3 (100 and 200 mg strengths) and 1:5 (300 mg strength).

The drug substance, Tramadol HCl, is manufactured by (b) (4) and referenced to DMF (b) (4). The DMF was reviewed and deemed adequate. The analytical methods and control of structurally related impurities are based on the Ph. Eur. Monograph for Tramadol HCl. The release of tramadol from the coated beads is based on the diffusion of a soluble substance through an insoluble permeable membrane, Eudragit NE30D, and obeys Fick's Law of Diffusion.

The drug product is controlled as finished capsules and during manufcaturing of drug product intermediates, (b) (4) (b) (4) pivotal (clinical and primary stability) batches of bulk capsules were manufactured at pilot scale and packaged in the proposed commercial 30 and 90-count configurations in HDPE bottles with CR closures and desiccant. Production scale batches (b) (4) are not available but planned for manufacture after approval of the NDA.

The drug product is supported by sufficient stability data on the primary batches: longest up to 36-month under normal storage, 24-month under intermediate and 6-month under accelerated storage conditions. No significant degradation is observed (no individual impurities detected

and total impurities remain (b) (4)). (b) (4) The applicant agreed to revise the drug release acceptance criteria for the dissolution method. This was based on the Agency recommendation. See "Approvable" letter dated May 2, 2007 for NDA (b) (4). In addition, the applicant agreed to implement higher level testing S1 and S2, as needed, as per USP <711>.

The dissolution specification was based on in-vitro dissolution profiles of the (b) (4) primary pilot scale stability and clinical batches. In the current submission, the applicant proposed to revise the drug release acceptance criteria after production and evaluation of (b) (4) commercial (production scale) batches. This proposal is acceptable.

The firm affirmed that report of process validation studies including assessment of (b) (4) of drug product intermediates, e.g., (b) (4) beads and revised acceptance criteria for the dissolution testing of treated beads would be submitted to the NDA upon completion.

Since the pending dissolution specification has been resolved, this NDA is recommended for approval, pending satisfactory cGMP recommendation by the Office of Compliance.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: D. Christodoulou
ChemistryTeamLeaderName/Date: Ali Al-Hakim
ProjectManagerName/Date: K. Davies

C. CC Block

5 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

Danae Christodoulou
12/2/2008 04:32:57 PM
CHEMIST

Ali Al-Hakim
12/2/2008 05:00:42 PM
CHEMIST

NDA (b) (4)

CIP-TRAMADOL ER CAPSULES

Cipher Pharmaceuticals LTD

Danae D. Christodoulou
and
Ted Chang
Office of New Drug Quality Assessment
Division of Premarketing Assessment III and Manufacturing Science (Branch V and VI)

CMC Review of NDA (b) (4)
For the Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)

Table of Contents

Chemistry Review Data Sheet

1. NDA or ANDA: (b) (4)

2. REVIEW #: 2

3. REVIEW DATE: 04/27/07

4. REVIEWER: Danae D. Christodoulou and Ted Chang

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
ORIGINAL SUBMISSION N-000	26-JUN-2006
AMENDMENT BZ	11-AUG-2006
AMENDMENT BC	12-OCT-2006
AMENDMENT BL	15-NOV-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
AMENDMENT BC	20-APR-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Cipher Pharmaceuticals LTD

Address: 409 Matheson Blvd. East, Mississauga, Ontario L4Z 2H2, Canada

Representative:	Arthur M. Deboeck, Galephar P.R., Road 198, km 14.7 #100, Juncos Industrial Park, Juncos 00777-3873, Puerto Rico
Telephone:	787-713-0340

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: CIP-TRAMADOL ER CAPSULES
b) Non-Proprietary Name (USAN): Tramadol HCl
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2). RLD: ULTRAM® (tramadol HCl tablets) by Ortho-McNeil Pharmaceuticals Inc.

10. PHARMACOL. CATEGORY: Analgesic

11. DOSAGE FORM: Extended-release capsules

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

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

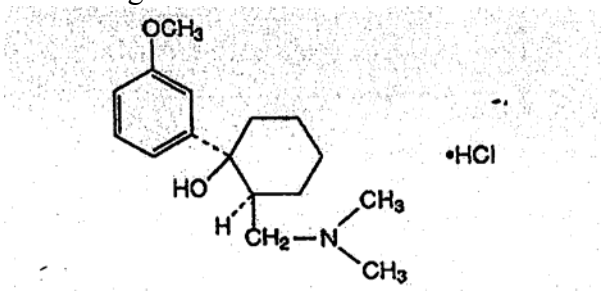
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

RR,SS-2-(dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexan-1-ol hydrochloride

Mol. Formula: $C_{16}H_{25}NO_2.HCl$

Mol. Weight: 299.84



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1, 4	Adequate	4/4/07	Review #6, D. Christodoulou DMF deemed adequate in previous reviews.
	IV		(b) (4)	4	N/A		
	IV		(b) (4)	4	N/A		
	IV		(b) (4)	4	N/A		
	IV			4	N/A		
	IV		Fill this	4	N/A		
	IV		Fill this	4	N/A		
	IV		(b) (4)	4	N/A		
	IV			4	N/A		
	IV			4	N/A		

(b) (4)		(b) (4)				
	IV		4	N/A		
	IV		4	N/A		
	IV		4	N/A		
	IV		4	N/A		
	IV		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		

[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)	(b) (4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted: Sufficient long term real time stability data to assess expiration dating provided.		
EES	Pending		
Pharm/Tox	Not consulted: Impurities are qualified/meet ICH Q3A Guidelines.		
Biopharm	AP. Provided feedback on in vitro drug release specifications.	3/26/2007	Lei Zhang
LNC	Not consulted: Conventional dosage form.		
Methods Validation	Not recommended for validation; methods do not meet ONDQA Criteria for MV.		
DMETS	Revisions proposed	2/22/07	M. Safarik
EA	N/A Categorical exclusion claimed; deficient: EIC based on the 5th year projected sales calculation not provided.		
Microbiology	N/A Solid oral dosage form which does not promote microbial growth.		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA (b) (4)

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

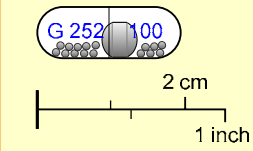
Approvable pending satisfactory resolution of the acceptance criteria for in vitro drug release and upon acceptable cGMP recommendation from the Office of Compliance. The comments listed at the end of the review should be included in the action letter.

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

II. Summary of Chemistry Assessments

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

CIP-TRAMADOL ER (tramadol hydrochloride) extended-release) capsules are a new formulation of tramadol HCl for analgesia. The drug product consists of extended release film coated white beads and an immediate release tablet encapsulated in white opaque, size 1, 0 and 00, hard gelatin capsules. Strengths are 100 mg, containing a 25 mg immediate release tablet, and 200 mg and 300 mg containing a 50 mg tablet and the appropriate amount of film coated beads (b) (4). The drug product is an extended release oral dosage form with (b) (4) in-vitro drug release within 1h, (b) (4) within 7-8h and (b) (4) after 24h. The capsules are packaged in white HDPE round bottles with CR closures.



CIP-Tramadol ER Capsule

Tramadol ER Capsule Configuration

Capsule Strength	IR-Tablet Strength	ER-Beads Strength
100 mg	25 mg	75 mg
200 mg	50 mg	150 mg
300 mg	50 mg	250 mg

Tramadol is a CNS acting analgesic with a combined effect on opioid receptors, noradrenergic and serotonergic neurotransmission and inhibition of monoamine uptake. Tramadol HCl is isolated as a single polymorph from isopropanol and it is a chiral molecule with 2 asymmetric centers. The drug substance is used as the racemate, since both optical isomers exhibit pharmacological activity. The (+) enantiomer binds to the μ-opioid receptor and preferentially inhibits serotonin reuptake, whereas the (-) enantiomer inhibits norepinephrine reuptake. The effects of both enantiomers are complementary and synergistic and result in the analgesic effect of tramadol. O-desmethyl tramadol, the major active metabolite, also has two enantiomers, shows higher affinity for the μ -opioid receptor and has at least twice the analgesic potency of the parent drug.

Tramadol HCl is a white to off-white crystalline solid, highly soluble in water (b) (4) and MeOH (b) (4) with a pH of about 5 in (b) (4) aqueous solution. The high water solubility of tramadol impacted development of this extended release formulation; drug release is effected via diffusion through an impermeable polymeric membrane.

The drug substance is stable to light and moisture. The observed identified impurities are the (b) (4) Identified impurities are not detectable in the drug product and unidentified impurities remain below ICH Q3A acceptable limits through the product's shelf-life. Retest date for the drug substance is (b) (4).

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

CIP-TRAMADOL ER (tramadol hydrochloride) extended-release 100, 200 and 300 mg capsules are administered once daily. The drug product is supplied in three count-size configurations: 7 capsules in 30-ml and 75-ml bottles; 30 capsules in 40-ml and 75-ml bottles; 90 capsules in 75-ml and 200-ml bottles with desiccant. Expiration dating period of 36 months may be granted based on the evaluation of the primary stability data. The recommended storage conditions are: "Store at 25°C [77°F]; excursions permitted to 15°C to 30°C [59°F – 86°F]".

C. Basis for Approvability or Not-Approval Recommendation

Tramadol is a CNS acting analgesic with a combined effect on opioid receptors, noradrenergic and serotonergic neurotransmission and inhibition of monoamine uptake. The immediate release oral dosage form of tramadol achieves Cmax rapidly (1-2h), has a relatively short half life (4-6h) and as a result, requires four daily administrations of 50-100 mg to alleviate pain and does not provide adequate pain relief through the night. The development of the extended release CIP-TRAMADOL ER capsules aims at obtaining (b) (4).

To allow for rapid onset and prolonged drug release, the extended-release capsules contain an immediate release (IR) tablet and extended release (ER) beads. The 100 mg capsule contains a 25 mg IR tablet and coated ER beads and the 200 mg and 300 mg capsules a 50 mg IR tablet (corresponding to the currently marketed 50 mg ULTRAM) and coated ER beads. The formulations are compositionally proportional with immediate release to extended release (IR:ER) component ratio of 1:3 (100 and 200 mg strengths) and 1:5 (300 mg strength).

The pre-existing coated bead technology developed by Galephar, which provides reproducible plasma levels for soluble drugs, was utilized in the manufacture of the coated extended-release tramadol beads. The manufacturing process for the coated beads involves (b) (4) (b) (4)

(b) (4) The release of tramadol from Eudragit NE30D coated beads is based on the diffusion of a soluble substance through an insoluble permeable membrane and obeys Fick's Law of Diffusion. When the ER beads are in contact with gastrointestinal fluid, tramadol is solubilized by water, builds osmotic pressure inside the beads and gets transported across the membrane via diffusion. This process depends only on water availability and is pH independent.

The drug substance, Tramadol HCl, is manufactured by (b) (4) and referenced to DMF (b) (4). The DMF was reviewed and deemed adequate. The analytical methods and control of structurally related impurities are based on the Ph. Eur. Monograph for Tramadol HCl.

The drug product is controlled as finished capsules and drug product intermediates. (b) (4) . (b) (4) pivotal (clinical and primary stability) batches of bulk capsules were manufactured at pilot scale and packaged in the proposed commercial 30 and 90-count configurations in HDPE bottles with CR closures and desiccant. Production scale batches (b) (4) are not available but planned for manufacture after approval of the NDA.

The drug product is supported by sufficient stability data on the primary batches: longest up to 36-month under normal storage, 24-month under intermediate and 6-month under accelerated storage conditions. No significant degradation is observed (no individual impurities detected and total impurities remain (b) (4)). (b) (4) However, a resolution on the in vitro drug release acceptance criteria was not reached in this review cycle. This is an approvability issue, since the applicant supported their revised acceptance criteria with justification based on limited IVIVC data. After discussion with the clinical pharmacology reviewer, it was decided to ask the applicant to provide detailed IVIVC data to support their revised acceptance criteria.

Responses to CMC deficiencies amended on April 20, 2007 were reviewed and most of the deficiencies were resolved, except for the one pertaining to the acceptance criteria for the in vitro drug release discussed above. Issues resolved were related to minor drug substance deficiencies (robustness of the HPLC method for the determination of impurities used by Galephar, supporting Certificates of Analysis for drug substance sublots used in the manufacture of pivotal drug product batches). Drug product deficiencies pertained to key manufacturing operations, e.g., (b) (4) (b) (4) (b) (4) , clarifications on lot numbers and clarity on the use of drug product batches in various clinical studies, and sufficient justification for the request of Categorical Claim from Environmental Assessment, etc. were resolved. The sponsor stated that dissolution is the (b) (4)

and provided revised batch records and adequate justification for the critical attributes of the key drug product intermediates.

An overall compliance recommendation is still pending for this application. The commercial manufacturing site, Galephar PR is pending inspection, and communications with the Office of Compliance indicate that the site has not been planned for inspection at this time (see Attachments 1 and 2-EER). However, every effort is being made to correspond with the Office of Compliance to resolve this pending issue. Thus, based on the CMC assessment, the NDA is approvable pending resolution of the acceptability of the dissolution specification, and acceptable recommendation from the Office of Compliance regarding cGMP status.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: D. Christodoulou
ChemistryTeamLeaderName/Date: R. Harapanhalli
ProjectManagerName/Date: K. Davies

C. CC Block

17 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

Danae Christodoulou
4/27/2007 06:38:29 PM
CHEMIST

Ted Chang
4/27/2007 06:40:02 PM
CHEMIST

Ravi Harapanhalli
4/27/2007 06:46:57 PM
CHEMIST

NDA (b) (4)

CIP-TRAMADOL ER CAPSULES

Cipher Pharmaceuticals LTD

Danae D. Christodoulou
and
Ted Chang
Office of New Drug Quality Assessment
Division of Premarketing Assessment III and Manufacturing Science (Branch V and VI)

CMC Review of NDA (b) (4)
For the Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)

Table of Contents

Chemistry Review Data Sheet

1. NDA or ANDA: (b) (4)

2. REVIEW #: 1

3. REVIEW DATE: 03/30/07

4. REVIEWER: Danae D. Christodoulou and Ted Chang

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ORIGINAL SUBMISSION N-000	26-JUN-2006
AMENDMENT BZ	11-AUG-2006
AMENDMENT BC	12-OCT-2006
AMENDMENT BL	15-NOV-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Cipher Pharmaceuticals LTD

Address: 409 Matheson Blvd. East, Mississauga, Ontario L4Z 2H2, Canada

Chemistry Review Data Sheet

Representative: Arthur M. Deboeck, Galephar P.R., Road 198, km 14.7 #100, Juncos Industrial Park, Juncos 00777-3873, Puerto Rico

Telephone: 787-713-0340

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: CIP-TRAMADOL ER CAPSULES
b) Non-Proprietary Name (USAN): Tramadol HCl
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2). RLD: ULTRAM® (tramadol HCl tablets) by Ortho-McNeil Pharmaceuticals Inc.

10. PHARMACOL. CATEGORY: Analgesic

11. DOSAGE FORM: Extended-release capsules

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

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

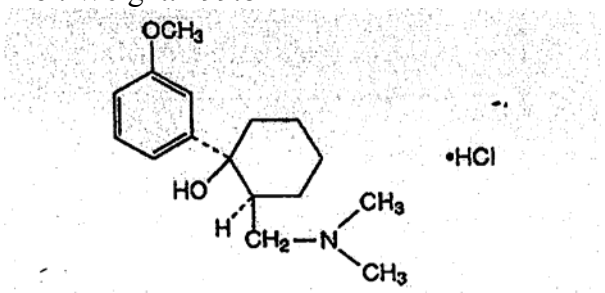
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

RR,SS-2-(dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexan-1-ol hydrochloride

Mol. Formula: $C_{16}H_{25}NO_2.HCl$

Mol. Weight: 299.84



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, 4	Adequate	4/4/07	Review #6, D. Christodoulou DMF deemed adequate in previous reviews.
	IV			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	IV			4	N/A		

(b) (4)		(b) (4)				
	IV		4	N/A		
	IV		4	N/A		
	IV		4	N/A		
	IV		4	N/A		
	IV		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		

[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)	(b) (4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted: Sufficient long term real time stability data to assess expiration dating provided.		
EES	Pending		
Pharm/Tox	Not consulted: Impurities are qualified/meet ICH Q3A Guidelines.		
Biopharm	AP. Provided feedback on in vitro drug release specifications.	3/26/2007	Lei Zhang
LNC	Not consulted: Conventional dosage form.		
Methods Validation	Not recommended for validation; methods do not meet ONDQA Criteria for MV.		
DMETS	Revisions proposed	2/22/07	M. Safarik
EA	N/A Categorical exclusion claimed; deficient: EIC based on the 5th year projected sales calculation not provided.		
Microbiology	N/A Solid oral dosage form which does not promote microbial growth.		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA (b) (4)

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable pending satisfactory resolution of the CMC deficiencies and acceptable cGMP recommendation from the Office of Compliance.

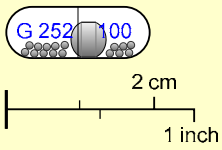
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Provide the process validation report and executed batch records for the commercial batches upon completion in a Annual Report to the NDA.

II. Summary of Chemistry Assessments

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

CIP-TRAMADOL ER (tramadol hydrochloride) extended-release) capsules are a new formulation of tramadol HCl for analgesia. The drug product consists of extended release film coated white beads and an immediate release tablet encapsulated in white opaque, size 1, 0 and 00, hard gelatin capsules. Strengths are 100 mg, containing a 25 mg immediate release tablet, and 200 mg and 300 mg containing a 50 mg tablet and the appropriate amount of film coated beads (b) (4). The drug product is an extended release oral dosage form with (b) (4) in-vitro drug release within 1h, (b) (4) within 7-8h and (b) (4) after 24h. The capsules are packaged in white HDPE round bottles with CR closures.



CIP-Tramadol ER Capsule

Tramadol ER Capsule Configuration

Capsule Strength	IR-Tablet Strength	ER-Beads Strength
100 mg	25 mg	75 mg
200 mg	50 mg	150 mg
300 mg	50 mg	250 mg

Tramadol is a CNS acting analgesic with a combined effect on opioid receptors, noradrenergic and serotonergic neurotransmission and inhibition of monoamine uptake. Tramadol HCl is isolated as a single polymorph from isopropanol and it is a chiral molecule with 2 asymmetric centers. The drug substance is used as the racemate, since both optical isomers exhibit pharmacological activity. The (+) enantiomer binds to the μ-opioid receptor and preferentially inhibits serotonin reuptake, whereas the (-) enantiomer inhibits norepinephrine reuptake. The effects of both enantiomers are complementary and synergistic and result in the analgesic effect of tramadol. O-desmethyl tramadol, the major active metabolite, also has two enantiomers, shows

higher affinity for the μ -opioid receptor and has at least twice the analgesic potency of the parent drug.

Tramadol HCl is a white to off-white crystalline solid, highly soluble in water (b) (4) and MeOH (b) (4) with a pH of about 5 in (b) (4) aqueous solution. The high water solubility of tramadol impacted development of this extended release formulation; drug release is effected via diffusion through an impermeable polymeric membrane.

The drug substance is stable to light and moisture. The observed identified impurities are the (b) (4) (b) (4) . Identified impurities are not detectable in the drug product and unidentified impurities remain below ICH Q3A acceptable limits through the product's shelf-life. Retest date for the drug substance is (b) (4).

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

CIP-TRAMADOL ER (tramadol hydrochloride) extended-release 100, 200 and 300 mg capsules are administered once daily. The drug product is supplied in three count-size configurations: 7 capsules in 30-ml and 75-ml bottles; 30 capsules in 40-ml and 75-ml bottles; 90 capsules in 75-ml and 200-ml bottles with desiccant. Expiration dating period of 36 months may be granted based on the evaluation of the primary stability data. The recommended storage conditions are: "Store at 25°C [77°F]; excursions permitted to 15°C to 30°C [59°F – 86°F]".

C. Basis for Approvability or Not-Approval Recommendation

Tramadol is a CNS acting analgesic with a combined effect on opioid receptors, noradrenergic and serotonergic neurotransmission and inhibition of monoamine uptake. The immediate release oral dosage form of tramadol achieves Cmax rapidly (1-2h), has a relatively short half life (4-6h) and as a result, requires four daily administrations of 50-100 mg to alleviate pain and does not provide adequate pain relief through the night. The development of the extended release CIP-TRAMADOL ER capsules aims at obtaining (b) (4) .

To allow for rapid onset and prolonged drug release, the extended-release capsules contain an immediate release (IR) tablet and extended release (ER) beads. The 100 mg capsule contains a 25 mg IR tablet and coated ER beads and the 200 mg and 300 mg capsules a 50 mg IR tablet (corresponding to the currently marketed 50 mg ULTRAM) and coated ER beads. The formulations are compositionally proportional with immediate release to extended release (IR:ER) component ratio of 1:3 (100 and 200 mg strengths) and 1:5 (300 mg strength).

The pre-existing coated bead technology developed by Galephar, which provides reproducible plasma levels for soluble drugs, was utilized in the manufacture of the coated extended-release tramadol beads. The manufacturing process for the coated beads involves: (b) (4)
(b) (4)

(b) (4)

(b) (4) The release of tramadol from Eudragit NE30D coated beads is based on the diffusion of a soluble substance through an insoluble permeable membrane and obeys Fick's Law of Diffusion. When the ER beads are in contact with gastrointestinal fluid, tramadol is solubilized by water, builds osmotic pressure inside the beads and gets transported across the membrane via diffusion. This process depends only on water availability and is pH independent.

The drug substance, Tramadol HCl, is manufactured by (b) (4) and referenced to DMF (b) (4). The DMF was reviewed and deemed adequate. The analytical methods and control of structurally related impurities are based on the Ph. Eur. Monograph for Tramadol HCl.

The drug product is controlled as finished capsules and drug product intermediates. (b) (4) (b) (4) pivotal (clinical and primary stability) batches of bulk capsules were manufactured at pilot scale and packaged in the proposed commercial 30 and 90-count configurations in HDPE bottles with CR closures and desiccant. Production scale batches (b) (4) are not available but planned for manufacture after approval of the NDA.

The drug product is supported by sufficient stability data on the primary batches: longest up to 36-month under normal storage, 24-month under intermediate and 6-month under accelerated storage conditions. No significant degradation is observed (no individual impurities detected and total impurities remain (b) (4)). (b) (4) Per the Meeting Minutes from September 9, 2005, in-vitro alcohol dissolution data were requested which were provided in an amendment to the NDA. The 100 and 300 mg dissolution rates accelerate significantly at low EtOH concentrations (b) (4) with complete dissolution at 4h and no apparent difference in the comparative dissolution profiles for the two strengths. These results were expected; based on the alcohol solubility of the polymer Eudragit NE 30D, corrosion of the diffusion membrane would result in rapid tramadol release and loss of the extended-release profile.

Drug substance manufacturing and controls information referenced to (b) (4) DMF (b) (4) was reviewed and found adequate. Purity profile, analytical methods and stability were included in the NDA. Minor drug substance deficiencies pertained to inadequate robustness of the HPLC method for the determination of impurities used by Galephar and lack of supporting Certificates of Analysis for drug substance sublots used in the manufacture of pivotal drug product batches. In addition to our recommendation to tighten the dissolution acceptance criteria as discussed above, drug product deficiencies included lack of clarity for key manufacturing operations e.g., (b) (4)

(b) (4)

(b) (4) clarifications on lot numbers and use of drug product batches, and sufficient justification for the request of Categorical Claim from Environmental Assessment.

The firm should be reminded to provide a report of process validation along with executed production batch records for the commercial batches in future Annual Report of the NDA. Based on the CMC assessment, the NDA is approvable pending satisfactory resolution of the CMC Deficiencies (communicated to the sponsor March 21, 2007) and acceptable recommendations from the Office of Compliance regarding cGMP status.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: D. Christodoulou
ChemistryTeamLeaderName/Date: R. Harapanhalli
ProjectManagerName/Date: K. Davies

C. CC Block

90 Page(s) has (have) been Withheld in Full immediately following this page as B4 (CCI/ TS)

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

/s/

Danae Christodoulou
4/16/2007 05:55:00 PM
CHEMIST

Ted Chang
4/17/2007 10:04:36 AM
CHEMIST

Ravi Harapanhalli
4/17/2007 02:10:47 PM
CHEMIST