

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022370Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Sharon Hertz, M.D.
<b>Subject</b>	Deputy Division Director Summary Review
<b>NDA/BLA #</b>	22-370/000
<b>Applicant Name</b>	Cipher Pharmaceuticals, Ltd.
<b>Date of Submission</b>	March 5, 2010
<b>PDUFA Goal Date</b>	May 8, 2010
<b>Proprietary Name / Established (USAN) Name</b>	To Be Determined
<b>Dosage Forms / Strength</b>	Extended-Release Capsules/ 100 mg, 200 mg, 300 mg
<b>Proposed Indication(s)</b>	Management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time
<b>Action/Recommended Action for NME:</b>	Approval

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review, first cycle	Keith Burkhart, M.D.
Statistical Review, first cycle	Joan Buenconsejo, Ph.D.
Pharmacology Toxicology Review, first cycle	Asoke Mukherjee, Ph.D. R. Daniel Mellon, Ph.D.
CMC Review/OBP Review	Danae D. Christodoulou, Ph.D.
Microbiology Review	
Clinical Pharmacology Review, first cycle	Lei Zhang, Ph.D.
DSI, first cycle	Xikui Chen, Ph.D. Jacqueline A. O'Shaughnessy, Ph.D
CDTL Review, first cycle	Suresh Doddapaneni, Ph.D.
OSE/DMEPA Review, first cycle	Cathy A. Miller, M.P.H., R.N. Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director

OND=Office of New Drugs  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DSI=Division of Scientific Investigations  
 CDTL=Cross-Discipline Team Leader

# Signatory Authority Review Template

## 1. Introduction

Cip-Tramadol is an (b) (4) capsule filled with (b) (4) extended-release (b) (4) beads. The application is a 505(b)(2) application referencing the agency's prior finding of efficacy and safety for Ultram (20-281) and Ultram ER (21-692).

The current application represents a complete response to a tentative approval action dated February 13, 2009, for an extended-release tramadol product first reviewed under NDA (b) (4). The product does not have an accepted tradename and will be referred to as Cip-Tramadol in this review. The deficiencies found in NDA (b) (4) that precluded approval have been discussed in the Director Memo, dated May 2, 2007, that can be found in Appendix 1, (b) (4). The second period of review for Cip-Tramadol took place under a new NDA number NDA 22-370, originally submitted on April 14, 2008 and the memo supporting the action, dated February 13, 2009, and can be found in Appendix 2. The new NDA number was assigned because the applicant chose to change the products referenced for the purposes of the 505(b)(2) requirements. (b) (4)

(b) (4) the applicant referenced added a reference to the Agency's prior findings for Ultram ER and submitted a relative bioavailability study that demonstrated bioequivalence for the Cip-Tramadol to Ultram ER. This was found to be adequate to support the application. However, a tentative approval was taken, rather than approval, as the listed reference drug product upon which the application was based still had a period of patent protection so that final approval of the application under section 505(c)(3)(B) of the Act (21 U.S.C. 355(c)(3)(B)) could not be made effective until the period has expired, i.e., May 10, 2014.

## 2. Background

The first tramadol product approved was Ultram (NDA 20-281, March 3, 1995), an immediate-release formulation, for the indication of moderate to moderately severe pain in adults. This was followed by Ultracet (NDA 21-123, August 15, 2001), an immediate-release tramadol and acetaminophen combination product, for short term ( $\leq 5$  days) management of acute pain, and Ultram ODT (NDA 21-693, May 5, 2005), an immediate-release, orally disintegrating tramadol, for moderate to moderately severe pain in adults.

The first extended-release tramadol product was Ultram ER (NDA 21-692), a tablet, approved on September 8, 2005, for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time. This was a 505(b)(2) application that referenced the Agency's prior finding of safety and efficacy for Ultram (NDA 20-281) and included a clinical efficacy study to support approval.

Ultram ER was granted 3 years of exclusivity based on the clinical study that has subsequently expired, but two patents are listed in the Orange Book that expire on May 10, 2014.

Ryzolt (21-745) was the next extended-release tramadol product approved on December 30, 2008, also a tablet. This was a 505(b)(2) application that also referenced the Agency's prior finding of safety and efficacy for Ultram (NDA 20-281) and included a clinical efficacy study to support approval. Ryzolt was granted 3 years of exclusivity due to expire on December 30, 2011 and has patents that expire on May 10, 2014 and Jun 29, 2020. Ryzolt differs from Ultram ER in that it has a core of tramadol with excipients that result in an extended-release profile and an outer coat of immediate-release tramadol.

(b) (4)

### **3. CMC/Device**

The 100 mg capsule of Cip-Tramadol contains a 25 mg IR tablet and coated ER beads. The 200 mg and 300 mg capsules contain a 50 mg IR tablet and coated ER beads. The 100 and 200 mg strength formulations are compositionally proportional with an immediate-release to extended-release (IR:ER) component ratio of 1:3. The 300 mg strength, however, has an IR:ER component ratio of 1:5.

No new CMC data were submitted in this response and there are no outstanding CMC issues that preclude approval.

### **4. Nonclinical Pharmacology/Toxicology**

No new nonclinical pharmacology or toxicology data were submitted in this submission and there are no outstanding pharm/tox issues that preclude approval.

### **5. Clinical Pharmacology/Biopharmaceutics**

No new clinical pharmacology data were submitted in this response and there are no outstanding clinical pharmacology issues that preclude approval.

### **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical-Efficacy**

There were no new efficacy data in this submission.

## **8. Safety**

There were no new safety data in this submission.

## **9. Advisory Committee Meeting**

There was no need for an Advisory Committee Meeting for this reformulation.

## **10. Pediatrics**

The applicant [REDACTED] <sup>(b) (4)</sup> was asked during the prior action to initiate studies as soon as feasible. The post marketing requirement for pediatric studies and the time line are described below.

## **11. Other Relevant Regulatory Issues**

There are no other unresolved relevant regulatory issues.

## **12. Labeling**

No proprietary name had been submitted for this product.

The package insert has been reviewed. In the course of the review of this submission it came to our attention that the applicant has included the following graph:

(b) (4)

### 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

Based on bioequivalence to Ultram ER, there is an adequate regulatory basis to support the approval of Cip-Tramadol, (b) (4)

Given the bioequivalence between Cip-Tramadol and Ultram ER, and the very similar PK profiles, a scientific bridge has been created for relying on the Agency's prior findings of efficacy for Ultram ER. There is both adequate safety data from the Cip-Tramadol trials as well as from the safety data from Ultram ER to describe the safety profile. There is no apparent clinical relevance for any differences in the PK profiles of Cip-Tramadol and Ultram ER, (b) (4)

- Recommendation for Postmarketing Risk Management Activities  
None.

- Recommendation for other Postmarketing Study Commitments

**PMR/PMC Title:**

A clinical trial to study the pharmacokinetics, efficacy and safety of tramadol extended-release capsules for the management of moderate to moderately severe chronic pain in pediatric patients ages  $\geq 2$  to 17 years.

**PMR/PMC Schedule Milestones:**

Protocol Submission: December 2013  
Study Start Date: December 2014  
Final Report Submission: December 2016

Appendix 1



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

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**DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION**

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**DATE:** May 2, 2007

**DRUG:** Cip-Tramadol ER (tramadol HCl) ER, 100, 200, 300 mg capsules

**NDA:** (b) (4)

**SPONSOR:** Cipher Pharmaceuticals Limited

**INDICATION:** For the management of moderate to moderately severe chronic pain in adults

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Cipher Pharmaceuticals submitted NDA (b) (4) on June 26, 2006 in support of marketing approval for Cip-Tramadol ER, for the management of moderate to moderately severe chronic pain in adults. This product is a new formulation of tramadol which incorporates both immediate-release (IR) and extended-release (ER) components. The 100-mg capsule contains a 25-mg IR tablet and 75 mg of coated beads that provide the ER component. The 200-mg capsule contains a 50-mg IR tablet and 150 mg of coated beads; and the 300-mg capsule contains a 50-mg IR tablet and 250 mg of coated beads. It is important to note that the 100- and 200-mg capsules are not dose proportional to the 300-mg capsules.

The CMC sections of this application were reviewed by Danae D. Christodoulou, Ph.D and Ted Chang, Ph.D. The Clinical Pharmacology and Biopharmaceutics information was reviewed by Lei K. Zhang, Ph.D. A clinical safety and efficacy review was completed by Keith K. Burkhart, M.D.; a statistical review and evaluation was completed by Joan Buenconsejo, Ph.D.; and a secondary review was provided by the Clinical Team Leader for this application, Mwango A. Kashoki, M.D. Consultation on this application was obtained from the Controlled Substances Staff, the Office of Surveillance and Epidemiology, and the Division of Drug Marketing, Advertisement and Communications.

***Clinical Safety:***

The safety profile for Cip-Tramadol ER based on the clinical study database was essentially unchanged from that of previously approved tramadol products. There was no increased incidence of adverse events commonly seen with exposure to tramadol, nor were there any unexpected, clinically concerning adverse events.

***Clinical Pharmacology and Biopharmaceutics:***

The pharmacokinetic profile of Cip-Tramadol ER shows two peaks presumably representing the  $C_{max}$  of the IR and ER components. While the  $C_{max}$  (ER peak) and  $AUC_{0-24}$  of Cip-Tramadol ER 200 mg QD were equivalent to Ultram 50 mg QID at steady-state, the  $C_{min}$  was lower by approximately 25%. When a single dose of Cip-Tramadol ER 200 mg and Ultram 50 mg QID were compared, there was a relative lack of exposure for Cip-Tramadol ER during the period from 18 to 24 hours. (b) (4)

It is important to note that the IR peak for the Cip-Tramadol ER 100- and 200-mg capsules are not dose proportional to the same peak for the 300-mg capsules. Thus, multiple 100- or 200-mg strength capsules are not interchangeable with 300-mg strength capsules.

***Pharmacology/Toxicology and Chemistry, Manufacturing and Controls:***

The only outstanding issue related to the pharmacology, toxicology or drug manufacturing and quality for this product is that several deficiencies were noted during the inspection of one of the manufacturing sites for the drug product which led to a withhold recommendation from the Office of Compliance. Demonstration of adequate cGMP compliance will be required before the application can be approved.

***Discussion:***

(b) (4)

It will be necessary for the sponsor to perform at least one additional adequate and well-controlled clinical trial that clearly demonstrates efficacy for their drug product before I would be able to conclude that substantial evidence had been submitted to support an approval action.

In addition, demonstration of adequate cGMP compliance for the manufacturing site that received a “withhold approval” recommendation from the Office of Compliance will be required before the application can be approved.

*Action recommended by the Division:* Approvable

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Bob A. Rappaport, M.D.  
Director  
Division of Anesthesia, Analgesia and Rheumatology Products  
Office of Drug Evaluation II, CDER, FDA

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**This is a representation of an electronic record that was signed electronically  
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/s/  
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Bob Rappaport  
5/2/2007 11:55:41 AM  
MEDICAL OFFICER

Review dated 2.13.2009 can be found in Medical Review Section of this approval package.

9 Page(s) have been Withheld in Full immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22370	ORIG-1	CIPHER PHARMACEUTICA LS LTD	TRAMADOL HYDROCHLORIDE

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/s/

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SHARON H HERTZ  
05/07/2010