CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022370Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 022370	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: tramadol hydrochloride Dosage Form: extended release capsules Strengths: 100mg, 200mg, 300mg		
Applicant: Cipher Pharmaceuticals		
Date of Receipt: March 8, 2010		
PDUFA Goal Date: May 8, 2010	Action Goal Date (if different): May 7, 2010	
Proposed Indication(s): management of moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 020281 (Ultram IR)	**labeling**
NDA 021692 (Ultram ER)	**labeling**

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

BA/BE studies to Ultram IR and Ultram ER.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Ultram IR	020281	Y
Ultram ER	021692	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☒ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application: **Ultram ER**

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for both an IR and ER component in a modified release capsule.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☒

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): Ryzolt NDA 021745

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):
NDA 21692 Patent 6254887, expiry 5/10/14
Patent 7074430, expiry 5/10/14

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): *Patent 6254887, expiry 5/10/14*
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *October 30, 2009 (Kim Q has the jacket with the exact date if this is not correct)*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☒ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

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/s/

KATHLEEN M DAVIES
05/07/2010

PMR/PMC Development Template

This template should be completed by review management and included for ***each*** PMR/PMC in the Action Package.

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 ≥ 2 to 17 years.

PMR/PMC Schedule Milestones:

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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

   Assessment of dosing, safety, tolerance and efficacy in children is appropriate postmarketing because initial evidence of safety and efficacy in adults was needed before initiating trials in children.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to*** *3.*

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☒ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

     No dosing, efficacy or safety information are available for children.

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

     Not applicable

   - **If the PMR is a FDAAA safety study/clinical trial, does it:**
     - ☐ Assess a known serious risk related to the use of the drug?
     - ☐ Assess signals of serious risk related to the use of the drug?

☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable.

4. If not required by regulation, characterize the review issue leading to this **PMC**

Not applicable

5. What type of study or clinical trial is required or agreed upon (describe)?

Required:

☐ Pharmacoepidemiologic study (list risk to be evaluated)
☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)
☐ Subpopulation (list type)
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies

- ☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- ☐ Dose-response study performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other (provide explanation)

6. Is the PMR/PMC clear and feasible?
   - ☒ Are the schedule milestones and objectives clear?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Larissa Lapteva, M.D., M.H.S.
Deputy Director for Safety
CDER/OND/ODE II/DAAP

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

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/s/

KATHLEEN M DAVIES
05/07/2010

LARISSA LAPTEVA
05/07/2010

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Anesthesia and Analgesia Products

Application Number: 022370

Name of Drug: tramadol hydrochloride extended release capsules

Applicant: Cipher

Material Reviewed:

Submission Date(s): March 5, 2010

Receipt Date(s): March 8, 2010

Submission Date of Structure Product Labeling (SPL): March 8, 2010

Type of Labeling Reviewed: WORD

Background and Summary

Sponsor received tentative approval on February 13, 2009. Sponsor resubmitted their NDA on March 8, 2010 after addressing patent issues. This labeling review compares the tentatively approved label to any modifications made by the Division during this review process.

Label was also compared to pending NDA 21745/S-002 (Ryzolt PLR conversion) and to NDA 21692/S-010 (Ultram ER PLR conversion).

Review

RPM Review

Please note that a strikethrough indicates deletion and an underline indicates addition to the approved label. Throughout the label, the term "TRADENAME ER" was removed and replaced with the established name, "tramadol hydrochloride extended-release capsules" since there is no tradename at this time for the product.

17 Page(s) have been Withheld in Full as b4 (Draft Labeling) immediately following this page

(b) (4)

[redacted]

Recommendations

Approve NDA.

Kathleen Davies, RPM

Supervisory Comment/Concurrence:

Sara Stradley
Chief, Project Management Staff

Drafted: KMD/19Apr10
Revised/Initialed:
Finalized:

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

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/s/

KATHLEEN M DAVIES
05/07/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 29, 2010
To:	Bob Rappaport, M.D., Director Division of Anesthesia and Analgesia Products
Through:	Zachary Oleszczuk, PharmD, Acting Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis
From:	Cathy A. Miller, M.P.H., R.N. Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Tramadol Extended-release Capsules 100 mg, 200 mg and 300 mg
Application Type/Number:	NDA 022370
Applicant:	Cipher Pharmaceuticals, Ltd.
OSE RCM #:	2010-622

INTRODUCTION

This review was written in response to a request from the Division of Anesthesia and Analgesia Products dated March 17, 2010, to evaluate revisions made to labels and labeling for Tramadol Extended-release 100 mg, 200 mg and 300 mg capsules. These revisions reflect recommendations provided by the Division of Medication Error Prevention and Analysis (DMEPA) in our OSE Review #2008-1193 dated February 12, 2009. We note that the Applicant does not have a proprietary name for this product.

1.1 REGULATOR HISTORY

The new drug application (NDA 022370) for Tramadol Hydrochloride Extended-release Capsules, Cipher Pharmaceuticals, Inc., received approvable status on May 2, 2007. The Division of Medication Error Prevention and Analysis was consulted on April 19, 2007 to review proposed proprietary names, (b) (4) and (b) (4), along with container labels and package insert labeling (OSE Reviews 2007-923 and 2007-924 both dated May 9, 2007). At that time, we did not recommend either of the proposed proprietary names, (b) (4) or (b) (4) due to their similarities to other drug products in the marketplace. We also provided labeling recommendations for container labels and package insert labeling.

On March 20, 2008, the applicant added a new reference listed drug (RLD), Ultram ER tablets, to their application. This required a resubmission under a new drug application (NDA 022370) due to an administrative process as it relates to the addition of a new RLD. We note however, that the proposed Tramadol Hydrochloride Extended-release Capsules are not AB rated to that of Ultram ER (Tramadol Hydrochloride) Extended-release Tablets, and hence, should not be interchanged or substituted for one another without consent of a physician. On April 14, 2008, the Applicant submitted container labels and packaging insert labeling for review however, the submitted labels and labeling contained the previously objected to proprietary name, (b) (4), and on August 8, 2008, we requested that the Applicant submit revised labeling accordingly.

On October 22, 2008, the Applicant submitted revised container labels and package insert labeling for Tramadol Hydrochloride Extended-release Capsules. On November 19, 2008, the Division of Medication Error Prevention and Analysis was provided the revised labeling for review. We note that the Applicant has not submitted a proposed proprietary name and therefore, the revised container labels and package insert labeling submitted for review are presented with 'NO TRADENAME ER'.

On February 12, 2009, DMEPA completed our review of labels and labeling for Tramadol Hydrochloride Extended-release capsules (OSE #2008-1193) and on March 8, 2010, the Applicant submitted revised labels and labeling which reflected recommendations provided by DMEPA in our review. DMEPA confirmed with DAAP when revised labels and labeling were resubmitted, that the Applicant does not have a proprietary name for this product.

2 METHODS AND MATERIALS

The Applicant submitted container labels (See Appendix A) and package insert labeling (no image) on March 17, 2010. DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels and insert labeling.

3 CONCLUSION AND RECOMMENDATIONS

We have provided recommendations on the insert labeling in Section 3.1 *Comments to the Division*. Section 3.2 *Comments to the Applicant* contains our recommendations for the container labels. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Abolade Adeolu (301) 796-4264.

3.1 COMMENTS TO THE DIVISION

We note that the labels and labeling submitted to DMEPA on March 17, 2010 are presented with 'TRADENAME ER'. In an email communication dated March 22, 2010, DAAP stated that there is no proposed proprietary name submission for this product. Additionally, we note that the warning statement on the container labels "Warning: cannot be interchanged with other Tramadol Extended-release products" does not appear in the insert labeling. DMEPA has the following recommendations for revision to the insert labeling:

1. Delete 'Tradename ER' from the insert labeling wherever it is referenced. If the Applicant is not planning to market this product with a proprietary name, labels and labeling should reflect the established name only.
2. Because Tramadol Hydrochloride Extended-release capsules cannot be interchanged with other Tramadol Extended-release products, revise the Dosage and Administration section of the insert labeling to include the statement "Cannot be interchanged with other Tramadol Extended-release products."

3.2 COMMENTS TO THE APPLICANT

Delete 'Tradename ER' from labels and labeling wherever it is referenced. If you market this product without a proprietary name, labels and labeling should reflect the established name only.

4 REFERENCES

Previous OSE Reviews:

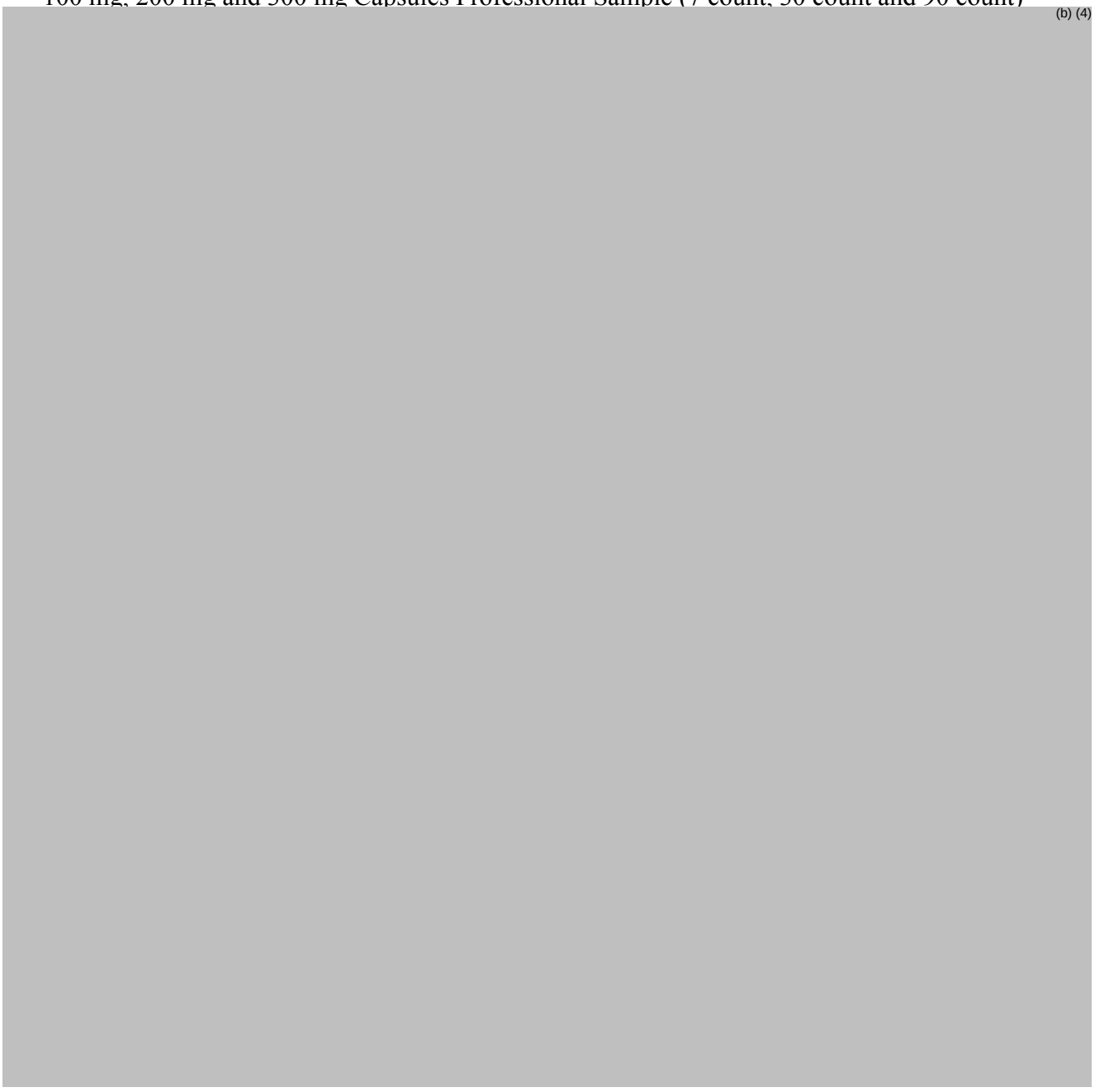
-Pedersen, K., OSE Review #2007-923 and 2007-924 dated May 9, 2007, (b) (4) and (b) (4) Proprietary Name Review

-Miller, C., OSE Review #2008-1193 dated February 12, 2009, Tramadol ER Labeling Review.

APPENDICES

Appendix A: Container Label for Tramadol Hydrochloride Extended-release 100 mg, 200 mg and 300 mg Capsules Professional Sample (7 count, 30 count and 90 count)

(b) (4)



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

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/s/

CATHY A MILLER
04/29/2010

ZACHARY A OLESZCZUK
04/29/2010

DENISE P TOYER
04/29/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 12, 2009
To:	Bob Rappaport, M.D., Director Division of Anesthesia, Analgesia and Rheumatology Products
Through:	Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Cathy A. Miller, M.P.H., R.N. Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Tramadol Extended-release Capsules 100 mg, 200 mg and 300 mg
Application Type/Number:	NDA 22-370
Applicant:	(b) (4)
OSE RCM #:	2008-1193

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EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container labels for Tramadol Extended-release Capsules is vulnerable to confusion that could lead to medication errors. Specifically, we note that, as identified in previous Tramadol Hydrochloride Extended-release reviews, OSE Reviews 2007-923 and 2007-924, (b) (4) a dosing frequency statement such as "Once Daily" statement does not appear on the primary display panel of the container label. Additionally, the principal display panel of the container label does not contain a warning statement advising against substitution with other Tramadol products. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated, and provides recommendations in Section 6.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products dated April 15, 2008, to evaluate revised container labels and package insert labeling for Tramadol Hydrochloride Extended-release Capsules for the potential to contribute to medication errors. We note that the applicant has not submitted a proposed proprietary name for this submission and as such, we will refer to the established name, Tramadol Extended-release Capsules, for this review.

1.2 REGULATORY HISTORY

The new drug application (NDA (b) (4)) for Tramadol Hydrochloride Extended-release Capsules, Cipher Pharmaceuticals, Inc., received approvable status on May 2, 2007. The Division of Medication Error Prevention and Analysis was consulted on April 19, 2007 to review proposed proprietary names, (b) (4) and (b) (4), along with container labels and package insert labeling (OSE Reviews 2007-923 and 2007-924). At that time, we did not recommend either of the proposed proprietary names, (b) (4) or (b) (4), due to their similarities to other drug products in the marketplace. We also provided labeling recommendations for container labels and package insert labeling.

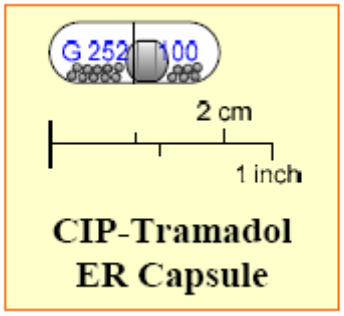
On March 20, 2008, the applicant added a new reference listed drug (RLD), Ultram ER tablets, to their application. This required a resubmission under a new drug application (NDA 22-370) due to an administrative process as it relates to the addition of a new RLD. We note however, that the proposed Tramadol Hydrochloride Extended-release Capsules are not AB rated to that of Ultram ER (Tramadol Hydrochloride) Extended-release Tablets, and hence, should not be interchanged or substituted for one another without consent of a physician. On April 14, 2008, the Applicant submitted container labels and packaging insert labeling for review however, the submitted labels and labeling contained the previously objected to proprietary name, (b) (4), and on August 8, 2008, we requested that the Applicant submit revised labeling accordingly.

On October 22, 2008, the Applicant submitted revised container labels and package insert labeling for Tramadol Hydrochloride Extended-release Capsules. On November 19, 2008, the Division of Medication Error Prevention and Analysis was provided the revised labeling for review. We note that the Applicant has not submitted a proposed proprietary name and therefore, the revised container labels and package insert labeling submitted for review are presented with 'NO TRADENAME ER', (b) (4)

1.3 PRODUCT INFORMATION

Tramadol Hydrochloride Extended-release Capsule is a centrally acting synthetic analgesic, in an extended-release formulation. Tramadol Hydrochloride Extended-release is indicated for the management of moderate to moderately severe chronic pain. Tramadol Hydrochloride Extended-release capsules are a new formulation of Tramadol Hydrochloride for analgesia, consisting of Extended-release film-coated white beads and an immediate release tablet encapsulated in white opaque 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 to provide the target strength (See Figure 1 below). The drug product is an Extended-release oral dosage form.

Figure 1



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 ER Capsules are not A-B bioequivalency rated to Ultram ER, and labeling states that Ultram ER and Tramadol ER should not be interchanged without consent of a physician.

The recommended dose is 100 mg once daily, which may be increased to a maximum 300 mg once daily dose. Tramadol Hydrochloride Extended-release is available in 100 mg, 200 mg and 300 mg capsules. The drug product is supplied in three count-size configurations: 7 Capsules, 30 Capsules and 90 capsules.

2 METHODS AND MATERIALS

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

On August 4, 2008, the Division of Medication Error Prevention and Analysis conducted a search of the FDA Adverse Event Reporting System (AERS) database to determine if any medication errors involving Tramadol ER have been reported. The following criteria were used: MedDRA High Level Group Term (HLGT) 'Medication Errors' and the Preferred term (PT) 'Pharmaceutical Product Complaint' with the active ingredient (tramadol hydrochloride), trade name (Ultram ER), and verbatim terms 'tramadol hydrochloride%'. Since the previous OSE Reviews #2007-923 and #2007-924 of Tramadol ER included

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

an AERS search performed for medication errors up to April 2007, our search was limited to the date ranges of May 2007 through December 2008.

The cases were manually reviewed to determine if medication errors occurred involving the label/labeling and/or nomenclature. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify contributing factors.

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because DMEPA analyze reported misuse of drugs, our staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use Failure Mode and Effect Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted the following labels and labeling for our review:

- Container Labels: 100 mg, 200 mg and 300 mg Tramadol Hydrochloride Extended-release Capsules Professional Sample (Quantity 7)
- Container Labels: 100 mg, 200 mg and 300 mg Tramadol Hydrochloride Extended-release Capsules (Quantity 30)
- Container Labels: 100 mg, 200 mg and 300 mg Tramadol Hydrochloride Extended-release Capsules (Quantity 90)
- Package Insert Labeling

3 RESULTS

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

The Adverse Event Reporting System (AERS) search retrieved a total of 44 cases, however, 43 of the cases were deemed not relevant to the labels, labeling or nomenclature for Tramadol Extended-release Capsules. These cases involved abuse or overdose of Ultram ER (n=4); overdose or abuse of Tramadol Hydrochloride tablets (n=21); accidental exposure of Tramadol Hydrochloride (n=3); product complaint that Ultram 50 mg tablets were not effective (n=1); product complaint that Tramadol Hydrochloride tablets were not effective (n=3); and various adverse event complaints for Tramadol Hydrochloride (n=11).

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

One relevant case was retrieved that involved a name confusion medication error between Tramadol Hydrochloride 50 mg Tablets and Trazodone Hydrochloride 50 mg Tablets. In this case, the patient's auto-faxed prescription order for Tramadol Hydrochloride 50 mg tablets was processed in the pharmacy but Trazodone Hydrochloride 50 mg tablets was dispensed. The error was discovered by the patient, who read the label and noted the wrong medication had been dispensed before administration. No additional information was provided regarding contributing factors for the medication error occurrence.

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the container labels and package insert labeling identified certain areas of vulnerability that could lead to medication error, specifically those issues identified in our previous OSE Reviews #2007-923 and #2007-924:

3.1.1 Container Labels

No dosing statement appears on the principal display panels of the container labels that would alert clinicians and patients that Tramadol Extended-release Capsules have a "Once Daily" dosing regimen.

(b) (4) does not appear in conjunction with the established name on the container labels. This is not in accordance with USP General Chapter on Nomenclature <1121>.

There is no information on the principal display panel of the container label warning against substitution of Tramadol ER with other Tramadol products. (Tramadol ER is not AB-rated to that of Ultram ER)

3.1.2 Package Insert Labeling

The established name (b) (4)

(b) (4)

4 DISCUSSION

4.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

We acknowledge that name confusion medication errors could create a source of confusion between Trazodone Hydrochloride Tablets and Tramadol Hydrochloride Extended-release Capsule due to similarities in the established names, as well as overlapping strengths (100 mg and 300 mg). We note, however, that our AERS search did not uncover any additional drug name confusion medication errors between Trazodone and the brand Ultram ER (Tramadol Hydrochloride Extended-release) or generic Tramadol Hydrochloride Extended-release. Additionally, these drug names appear on the Institute of Safe Medication Practices (ISMP) list of similar drug name pairs commonly confused.[3] This information has been widely distributed in the medical community in an effort to increase awareness amongst practitioners and minimize the potential for medication errors between the two drugs.

4.2 CONTAINER LABELS

The primary display panel for container labels of all Tramadol Hydrochloride Extended-release Capsule sizes and strengths does not include any statement regarding dosing frequency for the product. Because other Tramadol products are dosed differently (i.e. Tramadol Hydrochloride tablets are administered every four to six hours) and the proposed product, Tramadol Hydrochloride Extended-release Capsule, is dosed once daily, the potential for dosing frequency medication error exists. In an effort to reduce the

[3] Institute of Safe Medication Practices (ISMP) List of Confused Drug Names. http://www.ismp.org/tools/confuseddrugnames.pdf

potential for such confusion with the proposed product, we recommend that the Applicant include a dosing statement on the principal display panel of all bottles and any sample packages, such as "Once Daily".

As noted in their December 2, 2008 Chemistry Review of the proposed product, the Office of New Drug Quality Assessment, Division of Premarketing Assessment, the established name (b) (4) . Their recommendations included adding (b) (4) . We concur with the recommendations of the Office of New Drugs.

Lastly, we note that, as indicated in insert labeling, Tramadol ER is not 'AB-rated' to ULTRAM® ER and hence, the products should not be interchanged without consent of physicians. When dispensed, health care providers will unlikely look at the package insert and realize that these products are not interchangeable. Pharmacy personnel may assume that substitution of Tramadol ER with Ultram ER may be permitted due to the fact that the two products contain the same active ingredient (Tramadol Hydrochloride), are both available in the same strengths (100 mg, 200 mg and 300 mg), have the same dosing frequency (once daily) and are both extended-release dosage forms. Also, if the drug is marketed without a tradename, the assumption will be that it is a generic of Ultram ER. Therefore, a warning statement should appear on the principal display panel of the container label advising pharmacy personnel against substitution to minimize the risk of improper substitution medication errors.

4.3 INSERT LABELING

We note that in the 'Indications and Usage' section of the 'Highlights of Prescribing' portion of the Package Insert Labeling, (b) (4) with the established name (Tramadol Hydrochloride). As noted above, we have concerns (b) (4)

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed container labels and package insert labeling introduces vulnerability to confusion that could lead to medication errors. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

Based upon our assessment of the labels and labeling, the Division of Medication Error Prevention and Analysis has identified areas of needed improvement. We have provided label and labeling recommendations in section 5.2 and request this information be forwarded to the Applicant accordingly.

Regarding the Applicant's presentation of the established name (b) (4) we concur with the Office of New Drug Quality Assessment, Division of Premarketing Review recommendation dated December 2, 2008, that the proposed container labels should be revised (b) (4) (Tramadol Hydrochloride) Extended-release Capsules.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Chris Wheeler, Project Manager, at 301-796-0558.

5.2 COMMENTS TO THE APPLICANT

5.2.1 Container Labels:

1. Add a dosing frequency statement to the principal display panel of all container labels, such as "Once Daily" to minimize the risk of confusion among the currently marketed Tramadol products. Because other Tramadol products are dosed with differing frequencies (i.e. Tramadol Hydrochloride tablets are administered every four to six hours) and the proposed product, Tramadol Hydrochloride Extended-release Capsule, is dosed once daily. In an effort to reduce the potential for confusion with the proposed product, we recommend that the Applicant include a dosing statement on the principal display panel of all bottles and any sample packages, such as "Once Daily".

2. To avoid inadvertent substitution with other Tramadol products, add a warning statement on the principal display panel regarding substitution with other Tramadol products. We recommend adding a statement to the principal display panel of the Tramadol ER container label warning that your product cannot be interchanged with other Tramadol Extended-release products.

5.2.2 All Labels and Labeling:

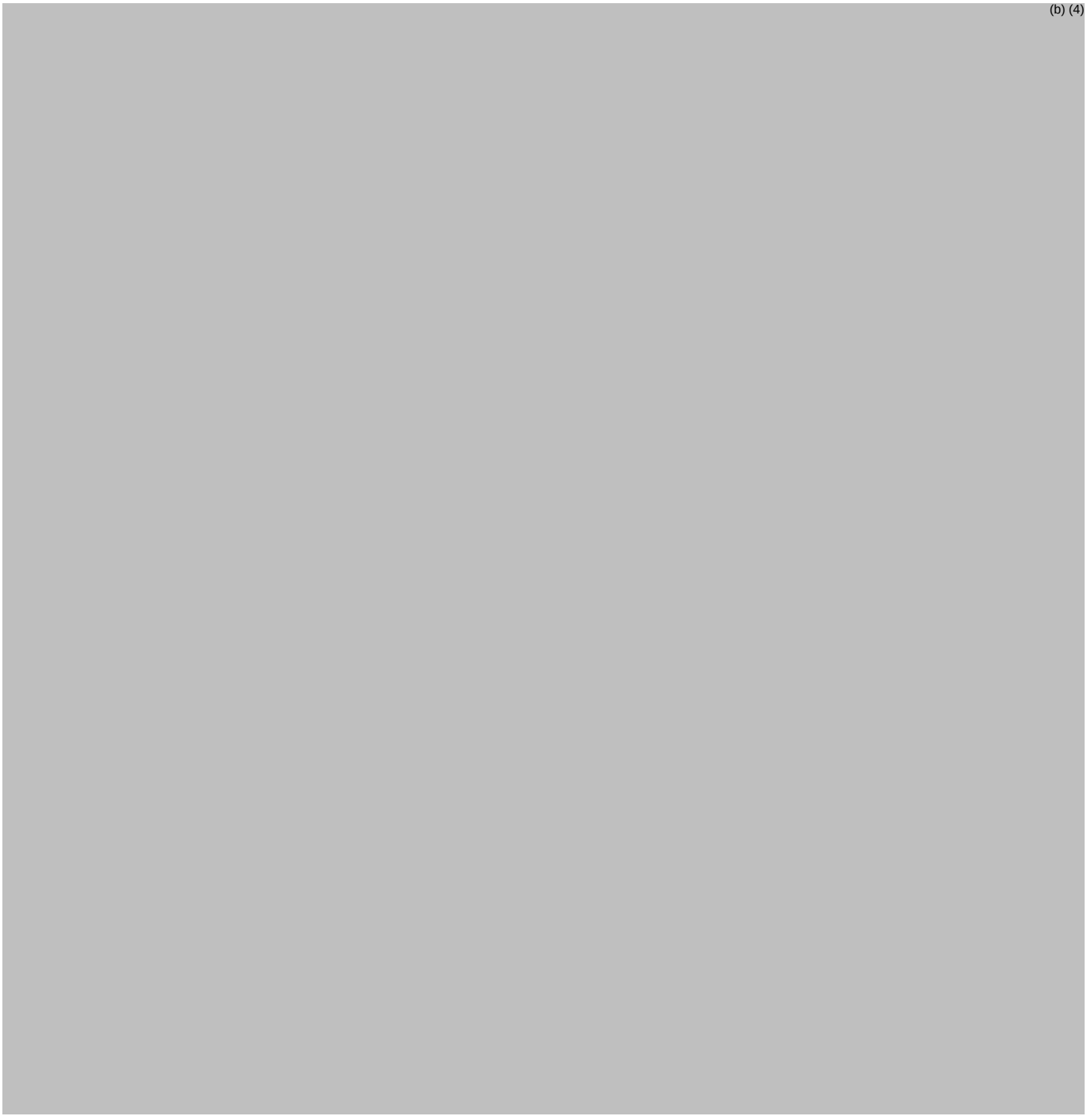
The established name (b) (4) This presentation does not comply with the USP General Chapter on Nomenclature<1121>. (b) (4).

Tramadol Hydrochloride Extended-release Capsules.

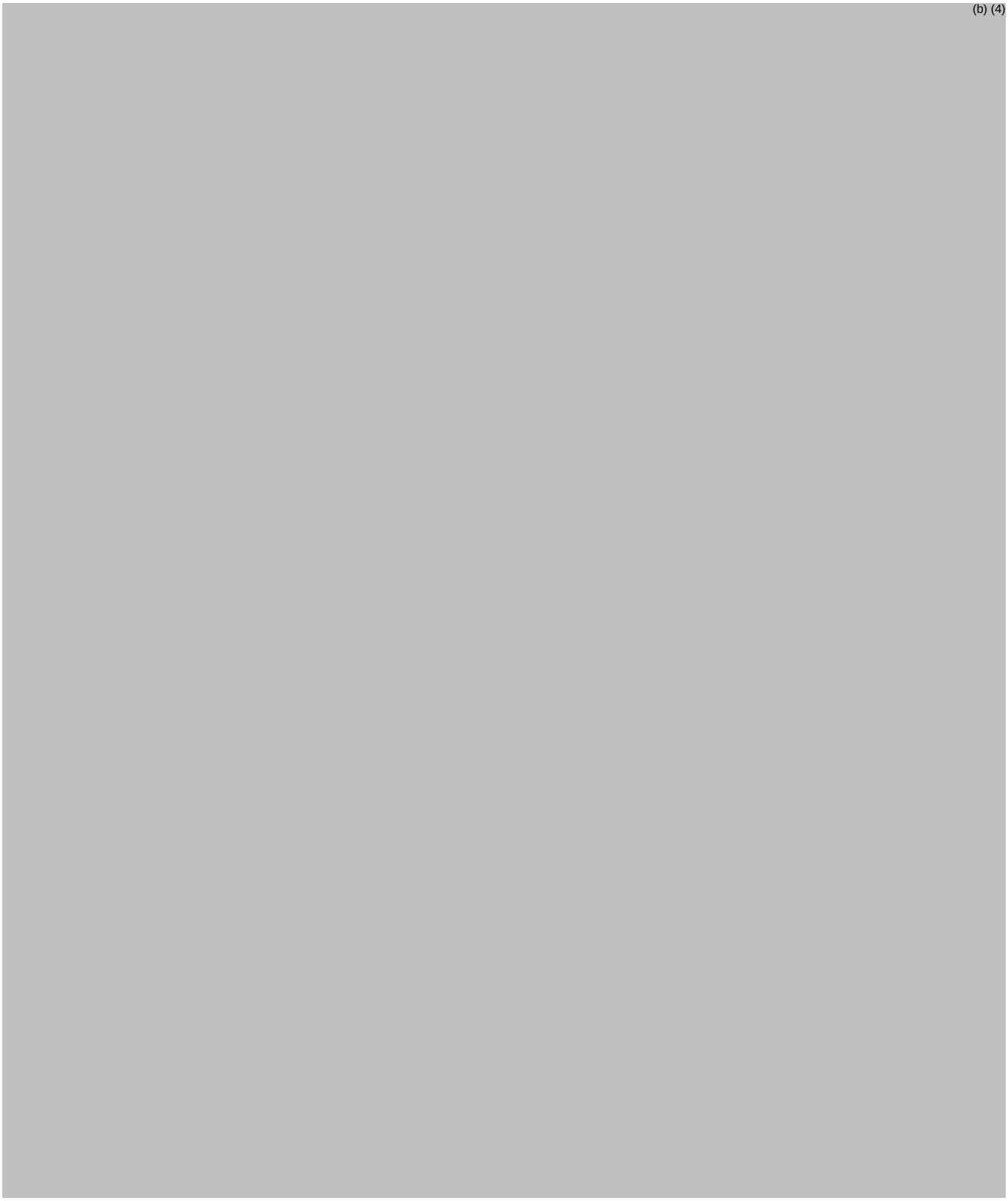
APPENDICES

Appendix A: Container Label for Tramadol Hydrochloride Extended-release 100 mg, 200 mg and 300 mg Capsules Professional Sample (Quantity 7)

Appendix B: Container Labels for Tramadol Hydrochloride Extended-release 100 mg, 200 mg and 300 mg Capsules (Quantity 30)



Appendix B: Container Labels for Tramadol Hydrochloride Extended-release 100 mg, 200 mg and 300 mg Capsules (Quantity 90)



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/s/

Cathy A Miller
2/12/2009 12:24:20 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/12/2009 01:26:45 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/12/2009 01:45:38 PM
DRUG SAFETY OFFICE REVIEWER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 30, 2008

FROM: Xikui Chen, Ph.D.
Jacqueline A. O'Shaughnessy, Ph.D
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D. _____
Associate Director, Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 22-370, Tramadol ER Capsules 300 mg, Sponsored by Cipher Pharmaceuticals, Inc.

TO: Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

As requested by DAARP, the Division of Scientific Investigations conducted inspections of the clinical and analytical portions of the following bioequivalence study:

> **Study TRAMPK.07.04**: An Open-Label, Single-Dose, Randomized, Four-Way, Comparative Bioavailability Study of Cipher Tramadol ER Capsules 300 mg Versus Biovail Ultram® ER Tablets 300 mg in Normal Healthy Subjects, Under Fed and Fasting Conditions

The clinical and analytical portions of Study TRAMPK.07.04 were conducted at Allied Research International-Cetero Research, Mississauga, Ontario, Canada and (b) (4) , respectively.

Following inspection of the clinical site (August 18-22, 2008), there were no significant inspectional findings and no Form 483 was issued.

Following inspection of the analytical site (July 14-18, 2008), Form 483 was issued. Our evaluation of the inspectional findings and the response from (b) (4) dated August 15, 2008 follows.

1. **The firm's SOP for evaluating incurred sample reproducibility (ISR) does not reflect the performance of the tramadol method. During method validation and Study TRAMPK.07.04, the QC precision was ≤6.8%. In contrast, the SOP states** (b) (4) (b) (4)

The firm's ISR criterion is liberal considering the tight performance of the tramadol assay during method validation and study conduct. Notwithstanding this issue, a majority (~77%) of the samples reassayed to evaluate ISR for Study TRAMPK.07.04 had differences less than 20% between the original and repeat values. For future ISR evaluations, the firm plans to revise their SOP to include an (b) (4)

2. **Samples with original tramadol concentrations above the upper calibration limit did not show similar results upon dilution and reanalysis. For example, six samples with original results >500 ng/ml had repeat results corrected for dilution ranging from approximately 350-400 ng/ml.**

The firm should have investigated this discrepancy. However, this issue was limited to few samples as only 8% of the samples that required dilution were affected (6 of 73).

3. **Failure to report all validation runs conducted for tramadol method LC/MS/MS 308.100 in that the matrix experiment on 12/6/07 was excluded from the validation report without assignable cause.**

The initial experiment was rejected because some of the matrix effect samples failed to meet the acceptance limit. Although the firm should have described this run in the validation report, the experiment was repeated with the same lots of matrix and no matrix effect was observed.

4. **Failure to document all aspects of study conduct. For example:**
   a. **Notebook entries to document the validation of tramadol method LC/MS/MS 308.100 were not contemporaneous with experimental conduct.**

The analyst stated that additional details were entered after the fact to address questions raised by the firm’s quality assurance unit.

b. There was no documentation to confirm that the autosampler injection sequence was verified.

The firm claimed that the sample sequence was checked but not documented in writing.

With respect to items 4a-b, the firm needs to improve their documentation practices to confirm that all aspects of study conduct are documented contemporaneously.

Conclusion:

Following the above inspections, DSI recommends that the clinical and analytical portions of Study TRAMPK.07.04 be accepted for review.

After you have reviewed this memo, please append it to the original NDA submission.

Xikui Chen, Ph.D.

Jacqueline A. O'Shaughnessy, Ph.D.

Final Classifications:
NAI - Allied Research International-Cetero Research
VAI - (b) (4)

cc:
DSI/Vaccari/Patague
DSI/O'Shaughnessy/Chen/Viswanathan/Yau
DAARP/Davies
HFR-CE6520/Yuscius
HFR-SW1580/Stone
Draft: JAO 9/26/08
Edit: SS 9/26/08, XC 9/29/08
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FACTS (b) (4)

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/s/

Jacqueline OShaughnessy
9/30/2008 02:02:33 PM
PHARMACOLOGIST

Xikui Chen
10/6/2008 03:15:23 PM
COMPLIANCE OFFICER

Martin Yau
10/6/2008 03:22:31 PM
CSO

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: May 30, 2008

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Bob Rappaport, MD
Director, Review Division, HFD-170

FROM: Kathleen Davies, Regulatory Project Manager, HFD-170

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 22-370
Tramadol ER Capsules

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study Code # TRAMPK.07 .04	Clinical Investigator: Deepen Patel, M.D., Allied Research International-Cetero Research, 4520 Dixie Road, Mississauga, ON, Canada, L4W1N2; Phone (905) 238-0599; Fax (905) 238-0682	Analytical Site (b) (4) (b) (4)

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **August 15, 2008**. We intend to issue an action letter on this application by **October 16, 2008**.

Should you require any additional information, please contact Kathleen Davies, 301-796-2205.

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/s/

Bob Rappaport

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 4/16/07

TO: Kathleen Davies, Regulatory Project Manager
Keith Burkhart, M.D., Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Carolanne Currier, CSO

SUBJECT: Evaluation of Clinical Inspections

NDA: (b) (4)

APPLICANT: Cipher Pharmaceuticals Limited

DRUG: Tramadol ER

THERAPEUTIC CLASSIFICATION: Standard review

INDICATION: (b) (4)

CONSULTATION REQUEST DATE: 8/24/07

DIVISION ACTION GOAL DATE: 4/30/07

PDUFA DATE:5/3/07

I. BACKGROUND:

Tramadol is a centrally acting analgesic approved in an immediate-release oral tablet formulation as Ultram. Tramadol, in the approved formulation, is rapidly absorbed into the bloodstream and remedication is recommended every 4 to 6 hours for continuous relief. Cipher Pharmaceuticals developed a capsulated form of tramadol using slow release beads along with immediate release (b) (4). It was hypothesized that the addition of the slow release beads would provide more continuous pain relief.

Cipher Pharmaceuticals has submitted studies using the slow (extended) release formulation in NDA (b) (4) (b) (4). The Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) determined that there were 4 protocols important to the review of this submission:

TRAMCT.02.01: A double-blind, randomized, placebo controlled, multi-dose, phase III, parallel group study of Tramadol ER in relief of signs and symptoms of osteoarthritis of the hip and knee

TRAMCT.02.02: A double-blind, parallel, randomized, placebo-controlled, multi-dose, phase III, parallel group study of Tramadol ER in the relief of signs and symptoms of osteoarthritis of the hip and knee

TRAMCT.02.03: An open-label, phase III, Follow-on study of Tramadol ER 300 mg, taken once-daily for the relief of signs and symptoms of osteoarthritis of the hip and knee

TRAMCT.02.04: A double-blind, randomized, placebo-controlled, phase III. Efficacy and safety study of Tramadol ER 300 mg, taken once-daily for the management of moderate to moderately severe chronic pain in osteoarthritis of the hip and knee in adults

Four clinical sites using these protocols were selected for inspection. Each site conducted studies with multiple protocols. Two of the selected sites were in Canada. These Canadian sites were selected by DAARP because there were insufficient domestic data for an adequate review of the NDA, plus the foreign data showed different results than the domestic sites.

II. RESULTS (by protocol/site):

Name of CI	City, State	Country	Protocol	Inspection Date	EIR Received Date	Final Classification
R. Lynn Magargle, M.D.	Camp Hill, PA	US	TRAMCT02.01 TRAMCT02.03 TRAMCT02.04	10/23-31/06	11/20/06	NAI
William P. Maier, M.D.	Eugene, OR	US	TRAMCT02.01 TRAMCT02.03	10/10-20/06	12/5/06	VAI
Kenneth Skeith, M.D.	Edmonton, AB	CA	TRAMCT02.02 TRAMCT02.03 TRAMCT02.04	2/5-9/06	4/2/07	NAI
Allan L. Bailey, M.D.	Spruce Grove, AB	CA	TRAMCT02.02 TRAMCT02.03 TRAMCT02.04	2/12-15/06	4/2/07	Pending (VAI*)

*Preliminary classification

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations.

A. Protocol # TRAMCT02.01

1. R. Lynn Magargle, Camp Hill, PA

a. What was inspected: Dr. Magargle screened 70 subjects and enrolled 58. Study records for 19 subjects were reviewed during the inspection. Study records reviewed included all source documents, case report forms, (b) (4) data listings provided by the sponsor, informed consent forms, drug accountability records, and communications with the sponsor and IRB.

b. Limitations of inspection: None

c. General observations/commentary: Dr. Magargle's records were organized and complete. All subjects whose records were reviewed met entry criteria. Data from all protocol-required tests were accurately reported in the case report forms and data listings. Drug accountability was adequate. The only problem found during the inspection was that a minor adverse event (AE) of a finger abscess was not reported on the case report form for subject 02012. The omission of the AE appears to be a simple record keeping error since the subject experienced additional AEs that were accurately reported.

d. Data acceptability: The study appears to have been conducted adequately (b) (4)

2. William P. Maier, M.D., Eugene, OR.

a. What was inspected: Dr. Maier screened 104 subjects and enrolled 84. Study records for 26 subjects were reviewed during the inspection. Study records reviewed included all source documents, case report forms, (b) (4) data listings provided by the sponsor, informed consent forms, drug accountability records, and communications with the sponsor and IRB.

b. Limitations of inspection: None

c. General observations/commentary: Dr. Maier's records were organized and complete. All subjects whose records were reviewed met entry criteria. Data from all protocol-required tests were accurately reported in the case report forms and data listings. Drug accountability was adequate. Three minor problems with recordkeeping were found during the inspection; 1) source documents indicated that subject 09023 was allergic to codeine however the case report form indicated the subject was allergic to caffeine; 2) subject 09051 was taking the prohibited medication digoxin before and during the study. The subject was terminated mid-study when the error was found and listed as a treatment failure; and 3) source documents indicated subject 09003 experienced nausea, vomiting, dizziness, sleepiness and headache after visit 3, however the case report form indicated only nausea. None of these deficiencies would adversely impact the study data or outcome.

d. Data acceptability: In general, the study appears to have been conducted adequately (b) (4)

B. Protocol # TRAMCT02.02

1. Kenneth Skeith, M.D., Edmonton, Alberta, Canada.

a. What was inspected: Dr. Skeith screened and enrolled 98 subjects. Study records for 30 subjects were reviewed during the inspection. Study records reviewed included all source documents, case report forms, (b) (4) data listings provided by the sponsor, informed consent forms, drug accountability records, and communications with the sponsor and IRB.

b. Limitations of inspection: None

c. General observations/commentary: Dr. Skeith's records were organized and complete. All subjects whose records were reviewed met entry criteria. Data from all protocol-required tests were accurately reported in the case report forms and data listings. Drug accountability was adequate. There was no evidence of under-reporting of adverse events.

d. Data acceptability: The study appears to have been conducted adequately (b) (4)

2. Allan L. Bailey, M.D., Spruce Grove, Alberta, Canada.

a. What was inspected: Dr. Bailey screened and enrolled 68 subjects. Study records for 20 subjects were reviewed during the inspection. Study records reviewed included all source documents, case report forms, (b) (4) data listings provided by the sponsor, informed consent forms, drug accountability records, and communications with the sponsor and IRB.

b. Limitations of inspection: None

c. General observations/commentary: Dr. Bailey's records were organized and complete. All subjects whose records were reviewed met entry criteria. Data from all protocol-required tests and procedures were accurately reported in the case report forms and data listings. Drug accountability was adequate. There was no evidence of under-reporting of adverse events.

d. Data acceptability: It appears the study was conducted adequately (b) (4) The observations noted above are based on the Form FDA 483, communications with the field investigator, and a preliminary review of the EIR. If additional problems are noted and/or conclusions change upon final review of the EIR, an inspection summary addendum will be generated.

C. Protocol # TRAMCT02.03 (follow-on study from protocol TRAMCT02.01)

1. Name: R. Lynn Magargle, Camp Hill, PA

a. What was inspected: Dr. Magargle enrolled 20 subjects from the TRAMCT02.01 study. Study records for 10 subjects were reviewed during the inspection. Study records reviewed included all source documents, case report forms (b) (4) data listings provided by the sponsor, informed consent forms, drug accountability records, and communications with the sponsor and IRB.

b. Limitations of inspection: None

c. General observations/commentary: Dr. Magargle's records were organized and complete. All subjects whose records were reviewed met entry criteria. Data from all protocol-required tests and procedures were accurately reported in the case report forms and data listings. Drug accountability was adequate. There was no evidence of under-reporting of adverse events.

d. Data acceptability: The study appears to have been conducted adequately (b) (4) (b) (4)

2. William P. Maier, M.D., Eugene, OR.

a. What was inspected: Dr. Maier enrolled 46 subjects from study TRAMCT02.01. Study records for 26 subjects were reviewed during the inspection. Study records reviewed included all source documents, case report forms, (b) (4) data listings provided by the sponsor, informed consent forms, drug accountability records, and communications with the sponsor and IRB.

b. Limitations of inspection: None

c. General observations/commentary: Dr. Maier's records were organized and complete. All subjects whose records were reviewed met entry criteria. Data from all protocol-required tests were accurately reported in the case report forms and data listings. Drug accountability was adequate. There was no evidence of under-reporting of adverse events.

d. Data acceptability: In general, the study appears to have been conducted adequately (b) (4)

3. Kenneth Skeith, M.D., Edmonton, Alberta, Canada.

a. What was inspected: Dr. Skeith enrolled 57 subjects from protocol TRAMCT02.01. Study records for 18 subjects were reviewed during the inspection. Study records reviewed included all source documents, case report forms, (b) (4) data listings provided by the sponsor, informed consent forms, drug accountability records, and communications with the sponsor and IRB.

b. Limitations of inspection: None

c. General observations/commentary: Dr. Skeith's records were organized and complete. All subjects whose records were reviewed met entry criteria. Data from all protocol-required tests and procedures was accurately reported in the case report forms and data listings. Drug accountability was adequate. There was no evidence of under-reporting of adverse events.

d. Data acceptability: The study appears to have been conducted adequately (b) (4)

4. Allan L. Bailey, M.D., Spruce Grove, Alberta, Canada.

a. What was inspected: Dr. Bailey enrolled 24 subjects from protocol TRAMCT02.01. Study records for 12 subjects were reviewed during the inspection. Study records reviewed included all source documents, case report forms, (b) (4) data listings provided by the sponsor, informed consent forms, drug accountability records, and communications with the sponsor and IRB.

b. Limitations of inspection: None

c. General observations/commentary: Dr. Bailey's records were organized and complete. All subjects whose records were reviewed met entry criteria. Data from all protocol-required tests and procedures were accurately reported in the case report forms and data listings. Drug accountability was adequate. There was no evidence of under-reporting of adverse events.

d. Data acceptability: It appears the study was conducted adequately (b) (4) The observations noted above are based on the Form FDA 483, communications with the field investigator, and a preliminary review of the EIR. If additional problems are noted and/or conclusions change upon final review of the EIR, an inspection summary addendum will be generated.

D. Protocol # TRAMCT02.04

1. Name: R. Lynn Magargle, Camp Hill, PA

a. What was inspected: Dr. Magargle screened 62 subjects and enrolled 49. Study records for 17 subjects were reviewed during the inspection. Study records reviewed included all source documents, case report forms, (b) (4) data listings provided by the sponsor, informed consent forms, drug accountability records, and communications with the sponsor and IRB.

b. Limitations of inspection: None

c. General observations/commentary: Dr. Magargle's records were organized and complete. All subjects whose records were reviewed met entry criteria. Data from all protocol-required tests and procedures were accurately reported in the case report forms and data listings. Drug accountability was adequate. The only problem found during the inspection was that a minor adverse event of a headache was not reported on the case report form for subject 02423. The omission of the AE appears to be a simple record keeping error since the subject experienced additional AEs that were accurately reported.

d. Data acceptability: The study appears to have been conducted adequately (b) (4)

2. Kenneth Skeith, M.D., Edmonton, Alberta, Canada.

a. What was inspected: Dr. Skeith screened and enrolled 27 subjects. Study records for 7 subjects were reviewed during the inspection. Study records reviewed included all source documents, case report forms, (b) (4) data listings provided by the sponsor, informed consent forms, drug accountability records, and communications with the sponsor and IRB.

b. Limitations of inspection: None

c. General observations/commentary: Dr. Skeith's records were organized and complete. All subjects whose records were reviewed met entry criteria. Data from all protocol-required tests

and procedures was accurately reported in the case report forms and data listings. Drug accountability was adequate. There was no evidence of under-reporting of adverse events.

d. Data acceptability: The study appears to have been conducted adequately (b) (4)

3. Allan L. Bailey, M.D., Spruce Grove, Alberta, Canada.

a. What was inspected: Dr. Bailey screened 30 subjects and enrolled 20. Study records for 15 subjects were reviewed during the inspection. Study records reviewed included all source documents, case report forms, (b) (4) data listings provided by the sponsor, informed consent forms, drug accountability records, and communications with the sponsor and IRB.

b. Limitations of inspection: None

c. General observations/commentary: Dr. Bailey's records were organized and complete. All subjects whose records were reviewed met entry criteria. Data from all protocol-required tests and procedures were accurately reported in the case report forms and data listings. Drug accountability was adequate. There was no evidence of under-reporting of adverse events.

d. Data acceptability: It appears the study was conducted adequately (b) (4) The observations noted above are based on the Form FDA 483, communications with the field investigator, and a preliminary review of the EIR. If additional problems are noted and/or conclusions change upon final review of the EIR, an inspection summary addendum will be generated.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

All studies with all protocols at all sites appear to have been conducted adequately. Source (b) (4) data were accurately transcribed to case report forms and matched data provided by the sponsor in data listings. With the exceptions of the three missing AEs (two in protocol TRAMCT02.01 and one in protocol TRAMCT02.04) as discussed above, all adverse events were appropriately reported to the sponsor and the IRB. It appears that, from the records reviewed, there were no problems found that would adversely impact the study data acceptability. The observations from the Bailey site are based on the FDA Form 483, communications with the field investigator, and a preliminary review of the EIR. If significant problems are noted and/or conclusions about the data at the Bailey site change upon final review of the EIR, DAARP will be notified immediately and an inspection summary addendum will be generated.

{See appended electronic signature page}

Carolanne Currier, CSO

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Carolanne Currier
4/18/2007 08:22:14 AM
CSO

Constance Lewin
4/18/2007 11:37:27 AM
MEDICAL OFFICER

M E M O R A N D U M
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: April 11, 2007

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology Products
(HFD-170)

Through: Deborah Leiderman, M.D., Director
Michael Klein, Ph.D., Team Leader

From: Geoffrey Zeldes, M.D., Pharm.D., Medical Officer
Controlled Substance Staff (HFD-009)

Subject: Review of Sponsor's meeting package for NDA (b) (4) CIP-Tramadol ER Capsules (100 mg, 200 mg, 300 mg)
Proposed Indication: "Management of moderate to moderately severe chronic pain in adults"
Date of Submission: July 23, 2006
Sponsor: Cipher Pharmaceuticals Ltd.
PDUFA Date: May 3, 2007

Background

CSS was asked by the Division to review and compare the Sponsor's proposed label on CIP-Tramadol ER Capsules abuse potential and interaction with MAO inhibitors and SSRIs. In preparing this consult the proposed labeling for CIP-Tramadol ER was compared to the labeling for Ultram ER (revised and approved as of 08/03/2006).

The proposed product will be available in three dosage strengths (100 mg, 200 mg, and 300 mg) of tramadol as extended release beads and an immediate release (IR) tablet together in a capsule. The 100 mg capsule has 25 mg of IR tramadol and 75 mg of the extended release (ER) beads. The 200 mg capsule has 50 mg IR and 150 mg ER, while the 300 mg has 50 mg IR and 250 mg ER.

The proposed dosing regimen for treatment of moderate to moderately severe chronic pain in adults is 100 mg once daily that can be titrated up to 300 mg once daily. The dosing regimen is consistent with that of Ultram ER, except Ultram ER has a more rapid titration to the next higher dose of 5 days compared to the CIP-Tramadol ER titration period of 7 days.

Conclusions and Recommendations

When the proposed CIP-Tramadol ER label is compared to the marketed Ultram ER label major differences are found. If approval of the NDA is granted, these labeling differences must be resolved.

The side by side comparisons of the labeling for CIP-Tramadol ER and Ultram ER for each section are listed in the attached **Appendix**.

The proposed CIP-Tramadol ER label has very little information regarding the opioid properties and effects associated with tramadol compared to the Ultram ER label. This information must be included in the final labeling.

The content of the Ultram ER label should be used in the CIP-Tramadol ER label for the following sections: **Withdrawal**; **Drug Abuse and Dependence (**in place of the proposed **Physical Dependence and Abuse & Drug Abuse and Dependence** sections**)**; and **Interactions with Alcohol and Drugs of Abuse**.

The extensive **SSRI and MAO inhibitors** sections for CIP-Tramadol ER are considerably more detailed than that for Ultram ER. The Sponsor's label for this section is adequate.

In addition, the following sections from the Ultram ER label should be added to the CIP-Tramadol ER label: **Suicide Risk**; **Misuse, Abuse and Diversion**; and **Use in Drug and Alcohol Addiction**.

Appendix

Because the active ingredient in CIP-Tramadol ER is an opioid, users of this product are at risk for both withdrawal and abuse potential. Tramadol is not a scheduled drug under the CSA. In the initial Pre-IND meeting with the Agency, the Sponsor was informed that they were to address abuse and dependence potential. Both abuse and dependence potential or withdrawal are addressed in the reference labeled drug, Ultram and Ultram ER. The Sponsor's proposed label does not adequately address these concerns.

The following are side by side comparisons of the labeling for CIP-Tramadol ER and Ultram ER.

Withdrawal	
Proposed CIP-Tramadol ER Label	Ultram ER Label
(b) (4)	**Withdrawal** Withdrawal symptoms may occur if ULTRAM ER is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be reduced by tapering ULTRAM ER.

Physical Dependence and Abuse	
Proposed CIP-Tramadol ER Label	
(b) (4)	

Drug Abuse and Dependence / Addiction	
Proposed CIP-Tramadol ER Label	Ultram ER Label
9 DRUG ABUSE AND DEPENDENCE (b) (4)	**DRUG ABUSE AND ADDICTION** **ULTRAM® ER is a mu-agonist opioid. Tramadol, like other opioids used in analgesia, can be abused and is subject to criminal diversion.** Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. ULTRAM ER, like other opioids, may be diverted for non-medical use. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs. ULTRAM ER is intended for oral use only. The crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Suicide Risk	
Proposed CIP-Tramadol ER Label	Ultram ER Label
(b) (4)	**WARNINGS** **Suicide Risk** **• Do not prescribe ULTRAM ER for patients who are suicidal or addiction-prone.** **• Prescribe ULTRAM ER with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess.** **• Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.** Tramadol products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. Tramadol should not be taken in doses higher than those recommended by the physician. The judicious prescribing of tramadol is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic

	analgesics. Patients should be cautioned about the concomitant use of tramadol products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, tramadol should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations. Many of the tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of tramadol alone or in combination with other drugs. Patients taking tramadol should be warned not to exceed the dose recommended by their physician.

Misuse, Abuse and Diversion	
Proposed CIP-Tramadol ER Label	Ultram ER Label
(b) (4)	**Misuse, Abuse and Diversion of Opioids** Tramadol is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Tramadol can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ULTRAM ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. ULTRAM ER could be abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**). Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse	
Proposed CIP-Tramadol ER Label	Ultram ER Label
(b) (4)	Tramadol may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

SSRI and MAO inhibitors	
Proposed CIP-Tramadol ER Label	Ultram ER Label
(b) (4)	**Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors** Use ULTRAM ER with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of ULTRAM ER with MAO inhibitors or SSRIs increases the risk of adverse events, including seizure and serotonin syndrome.

Use in Drug and Alcohol Addiction	
Proposed CIP-Tramadol ER Label	Ultram ER Label
(b) (4)	**Use in Drug and Alcohol Addiction** ULTRAM ER is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

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/s/

Geoffrey Zeldes
4/11/2007 02:12:34 PM
MEDICAL OFFICER

Michael Klein
4/11/2007 02:32:45 PM
CHEMIST

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: February 22, 2007

To: Kathleen Davies, MS, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products

From: Michelle Safarik, PA-C, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications

Subject: NDA (b) (4)
DDMAC labeling comments for CIP-Tramadol ER (tramadol hydrochloride) Capsules, 100/200/300 mg

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Per your consult request dated January 8, 2007, DDMAC has reviewed the proposed product labeling (PI) and proposed carton and container labeling for CIP-Tramadol ER (tramadol hydrochloride) Capsules, 100/200/300 mg (CIP-Tramadol ER Capsules), and we offer the following comments.

DDMAC notes that review of proposed trade names is done by consulting the Division of Medication Errors and Technical Support (DMETS), who evaluates proposed trade names from a safety perspective. DMETS then consults DDMAC to evaluate proposed trade names from a promotional perspective. DDMAC provides its comments to DMETS, and DMETS relays DDMAC's comments to the review divisions.

DDMAC also notes that the proposed carton and container labeling for CIP-Tramadol ER Capsules was provided in the June 26, 2006, EDR submission, and revised product labeling was provided in the November 15, 2006, EDR submission.

PI

Highlights

General

1. For consistency with the proposed trade and established names, we recommend adding the word "Capsules" to "CIP-Tramadol ER" throughout the proposed PI.

Indications and Usage

1. “Management of moderate to moderately severe chronic pain.”

   For consistency with the Ultram ER indication and to avoid misleadingly broadening the indication, we recommend adding the following to the above proposed indication: “in adults who require around-the-clock treatment of their pain for an extended period of time.”

Warnings and Precautions

1. For ease of readability, we recommend grouping the bullet points discussing seizure risk together, and recommend separating out each warning and precaution that follows as a separate subsection.

2. We recommend adding “Acute abdominal conditions” and “Use in renal and hepatic disease” to this section for consistency with the proposed PI and to avoid misleadingly minimizing the risks associated with the drug.

Drug Interactions

1. “Inhibitors of CYP2D6.”

   We recommend adding “and CYP3A4” for consistency with the Drug Interactions section of the proposed PI.

Use in Specific Populations

1. (b) (4)

2.

3. Is it appropriate to include more information about patients who are pregnant, in labor and delivery, nursing, pediatric, and differences in gender in this section?

Full Prescribing Information

Indications and Usage

1. "CIP-Tramadol ER is indicated for the management of moderate to moderately severe chronic pain in adults."

   For consistency with the Ultram ER indication and to avoid misleadingly broadening the indication, we recommend adding the following to the above proposed indication: "who require around-the-clock treatment of their pain for an extended period of time."

Dosage and Administration

1. For consistency with the Ultram ER PI, is it appropriate to include language about how the drug must be swallowed whole and must not be chewed, crushed, or swallowed?

2. We recommend including the specific dosage adjustments of the drug for those with renal and hepatic disease for consistency with the Use in Specific Populations section of the proposed PI.

Warnings and Precautions

1. For consistency with the Ultram ER PI, we recommend bolding all the text in the Seizure Risk subsection.

2. For consistency with the Ultram ER PI and if appropriate, we recommend adding a Suicide Risk subsection.

3. (b) (4)

   For consistency with the Ultram ER PI and to avoid misleadingly minimizing the risks associated with the drug, we recommend replacing (b) (4) with "reduced."

4. We recommend that the language of the Physical Dependence and Abuse subsection be made stronger and more closely follow that in the Misuse, Abuse and Diversion of Opioids and Drug Abuse and Addiction sections of the Ultram ER PI.

5. Is it appropriate to include language from the Precautions – Use in Drug and Alcohol Addiction section of the Ultram ER PI in this section of the proposed PI?

Adverse Reactions

1. [redacted] (b) (4)

   While these claims may be accurate, they misleadingly minimize the risks associated with the drug. Therefore, we recommend deletion.

2. [redacted] (b) (4)

   Is it necessary to include the sponsor's name (Cipher) when discussing the double-blind studies? If not, we recommend deletion.

3. It is unclear what [redacted] (b) (4) stands for in the table (double-blind?) We recommend replacing [redacted] (b) (4) with "CIP-Tramadol ER Capsules" and "Placebo" as appropriate.

Drug Abuse and Dependence

1. "CIP-Tramadol ER is not a controlled substance."

   [redacted] (b) (5)

Overdosage

1. Is it appropriate to include more information about overdosage of the drug as is done in the Overdosage section of the Ultram ER PI?

Clinical Pharmacology

1. [redacted] (b) (4)

   These terms are promotional in tone; we recommend deletion since context is provided later in the sentences.

2. [redacted] (b) (4)

   This phrase is highly promotional in tone and implies clinical benefit from pharmacokinetic studies, which is inappropriate. Therefore, we recommend deletion.

3. This section includes an extensive discussion of CIP-Tramadol ER Capsule pharmacokinetics compared to those of (b) (4)

4. (b) (4)

   While we acknowledge that this is a 505(b)(2) application, the above claim is highly promotional, repetitive, and implies clinical benefit from pharmacokinetics studies, which is inappropriate. Therefore, we recommend deletion.

5. "Therefore, CIP-Tramadol ER Capsules can be administered without regard to meals (b) (4)" (emphasis added).

   The phrase (b) (4) is promotional in tone and is an unsubstantiated claim. Therefore, we recommend deletion.

Clinical Studies

1. (b) (4) and "long-term" are promotional in tone; we recommend deletion.

2. (b) (4)

   Would it be possible to specify the exact number of patients in each treatment arm for context?

3. Is it appropriate to include an open-label study as substantial evidence to demonstrate efficacy? If not, we recommend deletion.

4. (b) (4)

   Would it be possible to specify the exact mean age for context?

5. (b) (4)

(b) (4)

6. (b) (4)

This claim is extremely promotional as it goes beyond pain relief and makes an extrapolation (b) (4) Is this claim supported by substantial evidence to be included in labeling? If so, we recommend providing more details about the study. If it is not supported by substantial evidence, we recommend deletion.

Patient Counseling Information

1. Is the information in this section adequate? For example, unlike the Precautions-Information for Patients section of the Ultram ER PI, it contains no discussion of how the drug is for oral use only and should be swallowed whole, and how it should not be chewed, crushed, or split.

Carton and Container Labeling

1. (b) (4)

For consistency with the proposed trade and established names in the proposed PI, we recommend revising the above to (b) (4)

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/s/

Michelle Safarik
2/22/2007 02:59:26 PM
DDMAC REVIEWER

Date: September 14, 2006

From: Robin Anderson, RN, MBA
Label Initiatives Specialist
Study Endpoint and Label Development (SEALD)
Office of New Drugs, CDER

Through: Laurie B. Burke, RPh, MPH
Director, SEALD

To: Kathleen Davies
Regulatory Project Manager
Division of Analgesic, Anesthetics and Rheumatology Products

Subject: Proposed Labeling Format Review
NDA (b) (4) CIP-Tramadol ER (tramadol hydrochloride) Capsules

This memo provides a list of revisions for the proposed labeling that should be conveyed to the applicant in an Information Request letter. Please contact me at 796-0534 with questions or concerns.

Highlights:

- For the Highlights limitation statement, the last statement must read "See full prescribing information for CIP-Tramadol ER". [See 21 CFR 201.57(a)(1)]

- The preferred format for presenting the drug names is without all capital letters. [Best Practices] Also, the dosage form CAPSULES should not be in all capital letters. Please correct.

- For Initial U.S. Approval, delete "[Approval pending]". [See 21 CFR 201.57(a)(3)]

- Regarding Contraindications, (b) (4) possibilities must not be listed (b) (4). [See 21 CFR 201.57(a)(9)] If the contraindication is not (b) (4), then it must be reworded to explain the type and nature of the adverse reaction. The same applies to the FPI Contraindications section. [See 21 CFR 201.57(c)(5)]

- In the first statement under Warnings and Precautions, it should read "increase", not "increases". Please correct.

- Under Warnings and Precautions, you must provide a cross reference under (b) (4) for each bulleted item. [See 21 CFR 201.56(d)(3)]

- For the adverse reactions reporting statement, you list a company website (b) (4). Note that a general link to a company website or an email address cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. Please delete from Highlights. [See 21 CFR 201.57 (a)(11)].

- The revision date will be the month/year that the NDA is approved, not (b) (4). [See 21 CFR 201.57(a)(15)].
-
- A horizontal line must separate the Highlights, Contents, and Full Prescribing Information (FPI). [See 21 CFR 201.57(d)(2)]

- Please submit the completed Highlights Data Element Table. To complete the Highlights data elements, please refer to the following two documents at the FDA Data Standards Council website (http://www.fda.gov/oc/datacouncil) under Structured Product Labeling: "Companion Document for SPL Release 2 Implementation Guide for Highlights DRAFT" and "SPL Highlights Data Element Table". This table must be filled out with the terms that have been proposed for the Highlights data elements. The companion document provides information on the terminology to be used. If you need assistance completing the Highlights data elements portion of your application, please contact spl@fda.hhs.gov.

Full Prescribing Information: Contents:

- The word "Contents:" is missing from the header. Please add. [See 21 CFR 201.57(b)]

- For Drug Abuse and Dependence, the subsections are:

  9.1 Controlled substance, not 9.1 Physical Dependence and Abuse
  9.2 Abuse
  9.3 Dependence

  This also applies to section 9 in the FPI. Please correct. [See 21 201.56(d)(1) and 21 CFR 201.57(c)(10)]

Full Prescribing Information (FPI):

- The preferred presentation of cross-references in the FPI is the section heading followed by the numerical identifier. For example, *[see Warnings and Precautions (5.1, 5.10), Overdosage (10)]*, not [see WARNINGS, Seizure Risk and OVERDOSAGE (5.1, 5.10, 10)]. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Please correct your cross-references throughout the labeling. [Implementation Guidance]

- Under Adverse Reactions, the term "adverse event" is used instead of "adverse reaction". Refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/cder/guidance and revise the Adverse Reactions section accordingly.

- Delete unnecessary references. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

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/s/

Robin E Anderson
9/15/2006 10:00:24 AM
CSO

Laurie Burke
9/15/2006 05:16:09 PM
INTERDISCIPLINARY