CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022370Orig1s000

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA #	22-370/000
Applicant Name	Cipher Pharmaceuticals, Ltd.
Date of Submission	April 14, 2008
PDUFA Goal Date	February 15, 2009
Proprietary Name / Established (USAN) Name	To Be Determined
Dosage Forms / Strength	Extended-Release Capsules/ 100 mg, 200 mg, 300 mg
Proposed Indication(s)	Management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time
Action/Recommended Action for NME:	Tentative Approval

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

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

Signatory Authority Review Template

1. Introduction

The current application, although a new NDA, represents a complete response to a complete response action for an extended-release tramadol product first reviewed under NDA (b) (4). The product does not have an accepted tradename and will be referred to as Cip-Tramadol in this review. The problems with NDA (b) (4) that precluded approval will be discussed as will the rationale for the current submission and whether it has merit.

2. Background

The first tramadol product approved was Ultram (NDA2 20-281,March 3, 1995), an immediate-release formulation, for the indication of moderate to moderately severe pain in adults. This was followed by Ultracet (NDA 21-123,August 15, 2001), an immediate-release tramadol and acetaminophen combination product, for short term (≤ 5 days) management of acute pain, and Ultram ODT (NDA 21-693, May 5, 2005), an immediate-release, orally disintegrating tramadol, for moderate to moderately severe pain in adults. The first extended-release tramadol product Ultram ER (NDA 21-692), was approved on September 8, 2005, for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

NDA (b) (4) was originally submitted on June 26, 2006, as a 505(b)(2) application (b) (4) Cip-Tramadol is an extended-release formulation of tramadol with an immediate-release outer component. (b) (4)

(b) (4)

In an approvable letter dated May 2, 2007, the following deficiencies were identified:

1. (b) (4) Provide substantial evidence of efficacy from at least one adequate and well-controlled clinical trial.

2. You have failed to provide adequate data to support your revisions to the in vitro drug release specifications. We refer to the email correspondences between you and the Division on December 6, 2006 and April 27, 2007. Since the proposed revisions to the in vitro drug release specifications are now to be based on support from in vitro/in vivo correlation (IVIVC) studies, you will need to submit a full report of the IVIVC analysis for review.

3. You have failed to demonstrate satisfactory cGMP compliance for the manufacturing facilities. Several deficiencies noted during a recent inspection led to a withhold recommendation from the Office of Compliance. Demonstration of adequate cGMP compliance is required before the approval of the NDA.

A formal dispute resolution request (FDRR) was submitted on December 3, 2007. (b) (4) A meeting was also requested and held on December 17, 2007. (b) (4) Dr. Curtis Rosebraugh responded to this FDRR, noting that he supported the Division's findings (b) (4) (b) (4) .

(b) (4) .

The letter also stated that the applicant could [redacted] resubmit as a 505(b)(2) application that identifies Ultram ER as an additional listed drug.

The current submission represents a new NDA for Cip-Tramadol. In this 505(b)(2) application, the applicant has now listed both Ultram ER and Ultram as reference products. Ultram ER currently has patent protection listed in the Orange Book until May, 2014. The applicant is [redacted] but on the Agency's prior finding of efficacy for Ultram ER and bioequivalence of Cip-Tramadol with Ultram ER. The applicant is also referencing the data submitted in NDA [redacted] in support of this application.

3. CMC/Device

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

Two of the deficiencies in the original approvable action letter were failure to provide adequate data to support the in vitro drug release specifications and a finding of unsatisfactory cGMP compliance for the manufacturing facilities.

There is sufficient stability data on the primary batches including up to 36 months under normal storage, 24 months under intermediate and 6 months under accelerated storage conditions. To address the deficiency of insufficient data to support the in vitro drug release specifications, he applicant agreed to revise the drug release acceptance criteria for the dissolution method and to implement higher level testing, as needed, as per USP <711>. The dissolution specification was based on in-vitro dissolution profiles of the [redacted] primary pilot scale stability and clinical batches. In the current submission, the applicant proposed to revise the drug release acceptance criteria after production and evaluation of [redacted] commercial (production scale) batches. Dr. Christodoulou found this proposal to be acceptable.

In her review, Dr. Christodoulou found the application approvable pending satisfactory cGMP recommendation from the Office of Compliance.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Stability testing supports an expiry of 36 months.

To resolve the outstanding problem concerning the inspection of the manufacturing site, as noted by Dr. Christodoulou in an addendum to her review:

> The applicant withdrew the original packager, [redacted], in a communication submitted to NDA 22-370 on January 6, 2009. The EER was updated to reflect the change,

and the Office of Compliance gave an overall "Acceptable" cGMP recommendation for this application on 2/2/09. There are no CMC outstanding issues.

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

In her review of NDA (b) (4) Dr. Zhang found that the following Clinical Pharmacology items were adequately addressed by the sponsor.
(1) Extended release characteristics.
(2) Dose proportionality
(3) The drug product's steady-state performance relative to a currently marketed IR product
(4) Effect of food on the formulation
(5) Effect of alcohol on the formulation

The applicant did not perform any special population or drug interaction studies and is relying on the Agency's previous findings for Ultram to inform their labeling.

Dr. Zhang's review focused on four new relative bioavailability studies comparing Cip-Tramadol to Ultram ER conducted in support of this NDA. Study TRAMPK.08.02 compared the pharmacokinetic characteristics of Cip-Tramadol 200 mg to Ultram ER 200 mg at steady state under fasting conditions. Both drugs were dosed once daily for seven days. The results of this study are depicted in the figure below from Dr. Zhang's review.

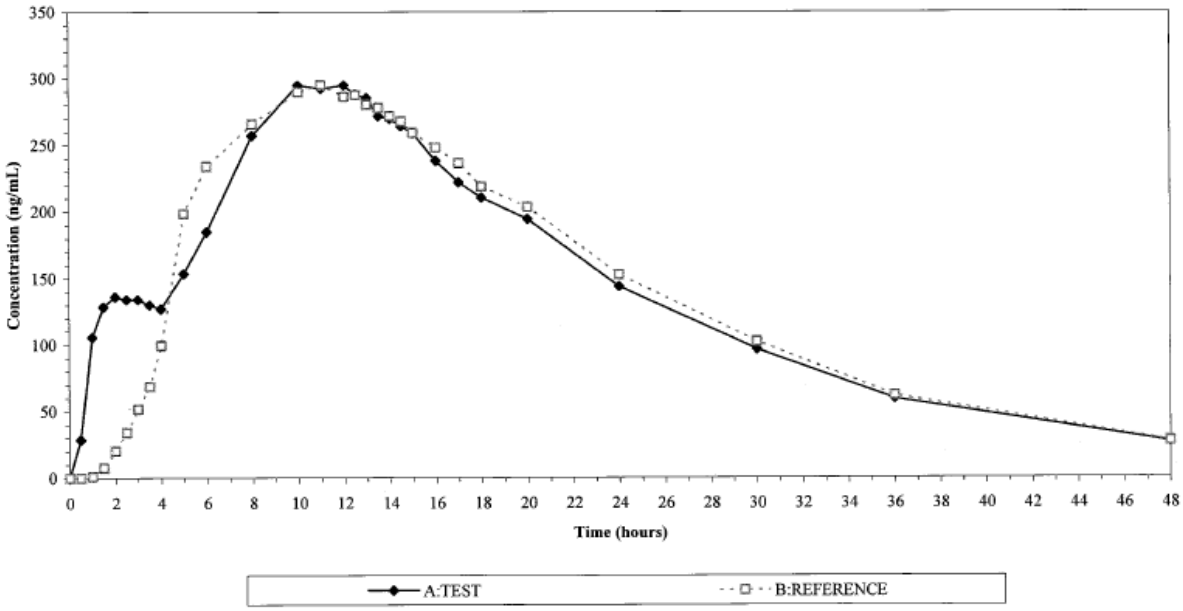
Figure 1 PK Profiles of Cip-Tramadol 200 mg and Ultram ER 200 mg at Steady State

(b) (4)

During the first four hours of the 24-hour period, Cip-Tramadol has an earlier rise in plasma levels than Ultram ER. This is a result of the immediate-release component of Cip-Tramadol. Even so, the two products met criteria for bioequlaence based on AUC and Cmax.

The remaining three studies were single-dose bioequivalence studies of the 300 mg doses. Study TRAMPK.07.01 was a pilot study and will not be considered further. Study TRAMPK.07.04 compared Cip-Tramadol 300 mg and Ultram ER 300 mg under fasting and fed conditions. TRAMPK.08.01 compared Cip-Tramadol 300 mg and Ultram ER 300 mg under fasting conditions. The two products were bioequivalent based on AUC and Cmax. The results of the single-dose PK for the 300 mg dose are provided in Figure 2 from Dr. Zhang's review. As with the steady state data from the 200 mg dose, there is a small peak following administration of Cip-Tramadol in the first four hours reflecting the immediate-release component. A high fat meal had no important effect on the PK of Cip-Tramadol 300 mg.

Figure 2 Single-Dose PK Profiles of Cip-Tramadol 300 mg and Ultram ER 300 mg, Study TRAMPK.08.01



Test = Cip-Tramadol Reference = Ultram ER

No bioequivalence studies were conducted with Cip-Tramadol 100 mg and Ultram ER 100 mg. As noted by Dr. Zhang, the following arguments were provided to support the 100 mg capsule: the bioequivalence of the 300 mg and 200 mg capsules with the corresponding Ultram ER tablets, the compositionally proportional formulations of the 100 mg and 200 mg capsules, the dose proportionality for the dose normalized Cmax and AUC for all three capsules, the similar dissolution for the 100 and 200 mg capsules of Cip-Tramadol, and the dose proportionality of the Ultram ER tablets. Taken together, they provide adequate support to conclude that the Cip-Tramadol 100 mg capsules and the Ultram ER 100 mg tablet will result in similar exposure.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical (b) (4)

There were no new efficacy studies submitted in this application.

8. Safety

The only new safety data in this application reflected data from healthy volunteers in pharmacokinetic studies. There were no new safety findings.

9. Advisory Committee Meeting

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

10. Pediatrics

(b) (4)

the product is ready for approval except for the 505(b)(2) issues with outstanding patent protection for Ultram ER. Therefore the applicant will be asked to initiate studies.

11. Other Relevant Regulatory Issues

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. No concerns were raised as a result of the inspection of the clinical site. However, a Form 483 was issued following inspection of the analytical site. All of the findings were adequately addressed by the applicant and it was noted that the firm needs to improve their documentation practices to confirm that all aspects of study conduct are documented contemporaneously. DSI recommended that the clinical and analytical portions of Study TRAMPK.07.04 be accepted for review.

There are no other unresolved relevant regulatory issues"

12. Labeling

No proprietary name had been submitted for this product. The package insert has been reviewed and changes submitted to and agreed upon by the applicant.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Tentative Approval

- Risk Benefit Assessment

Except for the outstanding issues concerning inspection of the manufacturing site, there is overall, adequate information to determine a favorable risk to benefit balance to support the approval of Cip-Tramadol. (b) (4)

Two modified-release tramadol products have been able to demonstrate efficacy and the applicant has referenced Ultram ER in this application. Given the bioequivalence between Cip-Tramadol and Ultram ER, and the very similar PK profiles, a scientific bridge has been created for referencing the Agency's prior findings of efficacy for Ultram ER. There is both adequate safety data from the Cip-Tramadol trials as well as the safety data from Ultram ER to determine the safety profile.

- Recommendation for Postmarketing Risk Management Activities

None.

- Recommendation for other Postmarketing Study Commitments

None.

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/s/

Sharon Hertz
2/13/2009 02:59:11 PM
MEDICAL OFFICER

Cross-Discipline Team Leader Review

Date	January 5, 2008
From	Suresh Doddapaneni, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	22-370
Applicant	Cipher Pharmaceuticals Ltd.
Date of Submission	April 14, 2008
PDUFA Goal Date	February 15, 2009
Proprietary Name / Established Name	To Be Determined/ (tramadol hydrochloride) extended-release capsules
Dosage forms / Strength	Extended Release Capsules/ 100 mg, 200 mg, 300 mg
Proposed Indication(s)	Management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time
Recommended	Tentative Approval

1. Introduction

CIP-Tramadol ER capsules 100 mg, 200 mg, and 300 mg is an extended-release product of tramadol formulated for once a day administration. The proposed indication is 'management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time'. Currently, two other single entity innovator tramadol products are approved for marketing. These are- Ultram® Tablets 50 mg (NDA 20-281) and Ultram® ER tablets 100 mg, 200 mg, and 300 mg (NDA 21-692). Initially, Cipher Pharmaceuticals submitted their 505(b)(2) NDA (b) (4), referencing the findings of safety and efficacy of Ultram® Tablets. (b) (4) An "Approvable" letter was sent to the sponsor on May 2, 2007. The specific deficiencies stated in the letter that needed to be addressed before the application may be approved were:

1. (b) (4) Provide substantial evidence of efficacy from at least one adequate and well-controlled clinical trial.

2. You have failed to provide adequate data to support your revisions to the in vitro drug release specifications. We refer to the email correspondences between you and the Division on December 6, 2006 and April 27, 2007. Since

the proposed revisions to the in vitro drug release specifications are now to be based on support from in vitro/in vivo correlation (IVIVC) studies, you will need to submit a full report of the IVIVC analysis for review.

3. You have failed to demonstrate satisfactory cGMP compliance for the manufacturing facilities. Several deficiencies noted during a recent inspection led to a withhold recommendation from the Office of Compliance. Demonstration of adequate cGMP compliance is required before the approval of the NDA."

A post-action meeting was held with the sponsor on May 30, 2007 to discuss the Division's concerns and what may be required to resolve the noted issues. (b) (4) A request for formal dispute resolution (FDRR) was made on December 3, 2007 (b) (4) The sponsor also requested a meeting to discuss the issues set forth in their FDRR document. This meeting was held on December 17, 2007. Subsequently, a response to FDRR was sent to the sponsor in the letter dated January 11, 2008 wherein the sponsor's request was denied and the need for additional clinical trial data was reiterated.

Subsequently, Cipher Pharmaceuticals changed their regulatory strategy and (b) (4) bioavailability study(s) demonstrating bioequivalence of CIP-Tramadol ER capsules to the approved Ultram® ER tablets were conducted and a Complete Response was submitted to the NDA. In doing so, Cipher Pharmaceuticals now relies on Ultram® ER tablets (NDA 21-692) for the 505 (b)(2) linkage. Since, a new Listed Drug is referenced in the complete response, per Agency's current practice, this submission was assigned a new NDA number 22-370. As such, in one sense this is a Complete Response to NDA (b) (4) while it is a new NDA in light of the reliance on a new Listed Drug. None the less, data from both NDA's (b) (4) and 22-370 go together for the Regulatory Action of NDA 22-370.

A proprietary name has not yet been determined for this product.

2. Background

There is no approved pharmaceutical equivalent to CIP-Tramadol ER capsules. The only extended-release tramadol product currently approved at the time of submission of NDA 22-370 is Ultram® ER tablets which is a tablet and is a pharmaceutical alternative. Both CIP-tramadol ER capsules and Ultram® ER tablets have identical strengths of 100, 200, and 300 mg and are meant for once daily dosing. As such, a 505 (b)(2) submission for CIP-Tramadol ER capsules relying on Ultram® ER Tablets through acceptable bioequivalence data is permissible. When NDA 22-370 was initially submitted, the sponsor submitted data demonstrating bioequivalence of CIP-Tramadol ER capsules and Ultram® ER Tablets at the highest strength of 300 mg. However, comparative dissolution data in different media for the lower strengths of 200 mg and 100 mg across the two products was not submitted (b) (4)

(b) (4). The Agency then requested the sponsor submit these comparative data. Subsequently, comparative dissolution data from *in vitro* study LES-096 and *in vivo* study TRAMPK.08.02 demonstrating bioequivalence of the 200 mg strength were submitted on June 27, 2008.

3. CMC/Device

Dr. Danae D. Christodoulou reviewed the Chemistry data of this NDA. The CMC deficiencies for NDA (b) (4) were related to the inadequate dissolution specifications for the drug product and a "Withhold" recommendation by the Office of Compliance for the NDA manufacturing facilities, due to unacceptable cGMP compliance of Galephar, Puerto Rico, the drug manufacturer (items 2 and 3 of the Approvable Letter for NDA (b) (4)). In this NDA, the same facilities have been resubmitted. Galephar, Puerto Rico, the drug manufacturing site and (b) (4), the packaging site, were re-assigned inspections. Inspection is pending at the Galephar, Puerto Rico site. (b) (4) the sole packaging site, was found "out of business" twice by inspectors during this review cycle. The Applicant was advised to designate an alternate packaging site by the Agency.

Related to the dissolution specifications, Cipher stated that the IVIVC had not been completed and instead proposed an alternative to their original specifications in NDA (b) (4) and further proposed to revise the dissolution specification, after production and evaluation of (b) (4) commercial scale batches. Since inadequate justification was provided in support of the alternative specifications, the Agency proposed revised dissolution specifications consistent with FDA dissolution guidances which the sponsor agreed to implement until additional data is generated. The Agency agreed to the sponsor's proposal to re-evaluate the dissolution specification after the production of (b) (4) commercial batches. (b) (4) Related to labeling, Dr. Christodolou recommends that in the carton and container labels, the established name should be revised to: (tramadol hydrochloride) extended-release capsules.

Overall, Dr. Christodoulou recommended an Approvable Action (review dated December 2, 2008) pending an acceptable cGMP recommendation from the Office of Compliance. Subsequent to completion of Dr. Christodoulou's review, Cipher submitted a new packaging site and the Office of Compliance completed the inspections of both the manufacturing and new packaging sites. The manufacturing site (Galephar facility) received "withhold" after the recent inspection on December 16 and the new package site passed the inspection. The overall acceptable CGMP recommendation from the Office of Compliance is still pending as of January 5, 2008. Further, the old packaging site (b) (4) has not been withdrawn by the sponsor.

4. Nonclinical Pharmacology/Toxicology

There were no unresolved or pending Pharmacology/Toxicology deficiencies from NDA (b) (4). For NDA 22-370, there is no Pharmacology/Toxicology review as no new data were submitted.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review of this NDA was completed by Dr. Lei K. Zhang. She recommends acceptance of the Clinical Pharmacology data provided acceptable labeling language can be worked out with the sponsor.

Previously, in NDA (b) (4), the sponsor had addressed a number of Clinical Pharmacology items that were deemed acceptable:

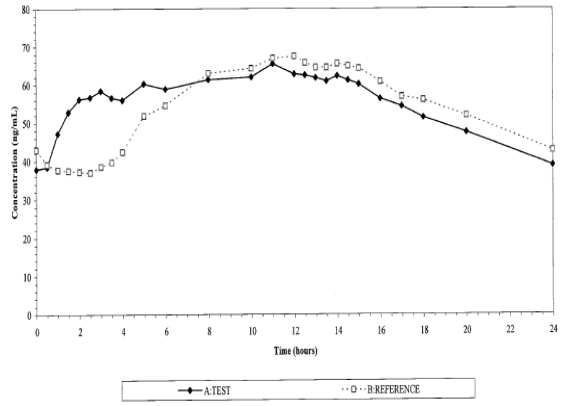
(1) Extended release characteristics.
(2) Dose proportionality
(3) The drug product's steady-state performance relative to a currently marketed IR product
(4) Effect of food on the formulation
(5) Effect of alcohol on the formulation

In NDA 22-370, *in vivo* data was available from four new BA/BE studies comparing CIP-Tramadol ER capsules 200 mg or 300 mg and Ultram® ER tablets 200 mg or 300 mg. Three single-dose studies assessed bioequivalence between 300 mg CIP-Tramadol ER capsules and 300 mg Ultram® ER tablet: one was considered a pilot study (Study TRAMPK.07.01), one had 4 arms including both fed and fasting conditions (Study TRAMPK.07.04), and one had 2 arms under fasting conditions (Study TRAMPK.08.01). Study TRAMPK.08.02 assessed relative bioavailability of CIP-Tramadol ER capsules 200 mg and Ultram® ER tablets 200 mg under steady-state fasting conditions.

Tables and figures shown here were extracted from Dr. Zhang's review

Results from Study TRAMPK.08.02 showed that compared to the steady-state PK profile of Ultram® ER (200 mg QD for 7 days), CIP-Tramadol ER (200 mg QD for 7 days) showed equivalent C_{max}, C_{min} and AUC (Figure 1 and Tables 1 and 2) for both tramadol and its active O-desmethylated metabolite, M1.

(b) (4)



b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations (0-24 hr) on Day 7 for 200-mg CIP-Tramadol ER Capsules QD (♦) or 200-mg Ultram® ER Tablets QD (□) (N=38).

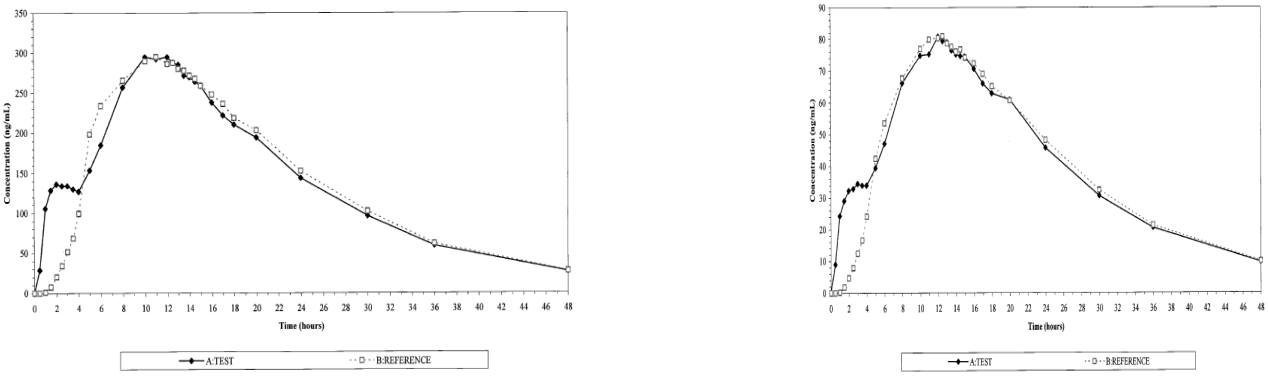
Table 1. Relative Bioavailability for Tramadol at Steady State (on Day 7) (A: 200 mg CIP-Tramadol ER vs. B: 200 mg Ultram ER).

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Tramadol N=38				
Parameter	**Test A**	**Reference B**	**% Ratio**	**90% CI**
$AUC_{0-\tau}$ (ss) (ng-hr/mL)	5504.67	5299.33	103.87	(97.36, 110.82)
$C_{max\ (ss)}$ (ng/mL)	322.74	334.96	96.35	(90.29, 102.83)
$C_{min\ (ss)}$ (ng/mL)	120.04	112.98	106.25	(96.25, 117.29)

Table 2. Relative Bioavailability for M1 at Steady State (on Day 7) (A: 200 mg CIP-Tramadol ER vs. B: 200 mg Ultram ER).

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data O-desmethyltramadol N=38				
Parameter	**Test A**	**Reference B**	**% Ratio**	**90% CI**
$AUC_{0-\tau}$ (ss) (ng-hr/mL)	1229.02	1191.10	103.18	(97.66, 109.01)
$C_{max\ (ss)}$ (ng/mL)	65.75	67.53	97.36	(92.08, 102.94)
$C_{min\ (ss)}$ (ng/mL)	32.72	29.93	109.31	(100.82,118.52)

Study TRAMPK.08.01 assessed the single-dose bioequivalence of CIP-Tramadol ER capsules 300 mg and Ultram® ER tablets 300 mg and was considered the pivotal BE study. Results from this study showed equivalent C_{max} and AUC (Figure 2 and Tables 3 and 4) for both tramadol and M1.



a. Tramadol b. M1

Figure 2. Mean Plasma Tramadol (a) and M1 (b) Concentrations (0-48 hr) Following a Single Dose of 300-mg CIP-Tramadol ER Capsule (♦) or a 300-mg Ultram® ER Table (□) (N=30).

Table 3. Relative Bioavailability for Tramadol after a Single Dose Administration (A: 300 mg CIP-Tramadol ER vs. B: 300 mg Ultram ER) (N=30).

Test Product A vs. Reference Product B Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Tramadol N=30				
Parameter	**Test A**	**Reference B**	**% Ratio**	**90% CI**
AUC_{0-t} (ng-hr/mL)	6394.21	6383.52	100.17	(95.81, 104.72)
AUC_{0-inf} (ng-hr/mL)	6776.94	6808.59	99.54	(95.77, 103.45)
C_{max} (ng/mL)	307.71	320.85	95.90	(88.27, 104.20)

Table 4. Relative Bioavailability for M1 after a Single Dose Administration (A: 300 mg CIP-Tramadol ER vs. B: 300 mg Ultram ER) (N=30).

Test Product A vs. Reference Product B Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data M1 (O-Desmethyltramadol) N=30				
Parameter	**Test A**	**Reference B**	**% Ratio**	**90% CI**
AUC_{0-t} (ng-hr/mL)	1826.33	1790.09	102.02	(97.87, 106.36)
AUC_{0-inf} (ng-hr/mL)	1981.83	1944.83	101.90	(97.58, 106.42)
C_{max} (ng/mL)	80.38	82.16	97.83	(90.89, 105.31)

CIP-Tramadol ER capsules contain an immediate-release (IR) tablet component and an ER beads component. The *in vivo* concentration-time profiles for tramadol and its metabolite, M1, showed that there was a lower Cmax peak (Peak 1) at around 2 hours and a higher Cmax peak (Peak 2) at around 10-12 hours. Peak 1 mainly represents the release of tramadol from the IR tablet and Peak 2 mainly represents the release of tramadol from the ER beads. Overall, peak 2 corresponds to the Cmax of the product. The sponsor in their pharmacokinetic analysis focused only on the major peak corresponding to the overall Cmax of the product. The Clinical Pharmacology review for NDA (b) (4) contained a discussion related to the potential lack of dose-proportionality (studies 02-406 and 02-556) and a potentially different food effect (study 02-405) for the early peak as compared to the main peak of the product based on an independent assessment by Dr. Zhang. However, assessment of the entire data (both submitted under NDA (b) (4) and NDA 22-370) shows that this peak is just a part of the overall pharmacokinetic profile. While this peak can be seen on a consistent basis under single-dose conditions, it is not reproducibly seen under multiple-dose conditions. Based on overall assessment of the entire database, there is no evidence to suggest that this first peak is associated with any specific safety concern. In the Medical Team Leader memo dated 4/25/07, Dr. Mwango Kashoki concluded that the use of Cip-Tramadol ER is associated with adverse events comparable to those reported with other tramadol products. Further, in the Action Letter dated 5/2/07, there were no identified safety related deficiencies. As such, this first peak is considered to be a part of the overall pharmacokinetic profile of CIP-Tramadol ER product and its contribution to the efficacy and safety is already captured in terms of (a) CIP-Tramadol ER being bioequivalent to Ultram® ER tablets at the 300 mg strength under single-dose conditions and to the 200 mg Ultram® ER tablets under multiple-dose conditions and (b) CIP-Tramadol being associated with adverse events that have been reported with other tramadol products.

The sponsor did not conduct an *in vivo* BE study for 100 mg dose strength. The *in vitro* dissolution comparative data for the 100 mg CIP-Tramadol ER capsules and 100 mg Ultram® ER Tablets did not show equivalence based on the f_2 criteria (f_2 criteria values of 47, 38, and 49 respectively in media with pH values of 1.2, 4.5, and 6.8, respectively).

However, this is not entirely unexpected since CIP-Tramadol ER capsules have a specific immediate-release component and Ultram ER® tablets do not. That the comparative dissolution data did not meet the f_2 criteria is mainly due to the differences in the release profiles in the first six hours of *in vitro* release. Based on the demonstrated bioequivalence between 300 mg strengths of CIP-Tramadol ER capsules and Ultram® ER tablets under single-dose conditions, demonstrated bioequivalence between the 200 mg strengths of CIP-Tramadol ER capsules and Ultram® ER tablets under multiple-dose conditions, formulation similarity between 100 and 200 mg CIP-Tramadol ER capsules, dose-proportionality across the three strengths (100, 200, and 300 mg) based on dose-normalized Cmax and AUC (studies 556 and 406), *in vitro* dissolution similarity between 100 and 200 mg CIP-Tramadol ER capsules (Study LES-096), and approximate dose-proportionality for Ultram® ER tablets (as stated in the Ultram ER package insert), Dr. Zhang concluded that 100 mg CIP-Tramadol ER capsules and 100 mg Ultram® ER tablets will have similar exposure.

Dr. Zhang recommends several labeling changes many of which are editorial and formatting related and to bring consistency in the language between the products.

6. Clinical Microbiology

Not applicable for this product.

7. Clinical/Statistical

The Statistical review for NDA (b) (4) (b) (4) (b) (4) However, the applicant now relied on the demonstration of bioequivalence of their product to Ultram® ER tablets, a Statistical review was not conducted for NDA 22-370.

The clinical review of NDA 22-370 was conducted by Dr. Keith K. Burkhart. However, (b) (4) his review does not have any new conclusions (b) (4) Overall, Dr. Burkhart recommends approval of CIP-Tramadol ER capsules for the proposed indication, management of moderate to moderately severe chronic pain in adult patients. Since the patent for Ultram® ER does not expire until May 10, 2014, he recommends a "tentative approval".

Dr. Burkhart recommends many labeling changes to the Sponsor's proposed label. Major recommended changes are (b) (4) to add the specific safety experience with CIP-Tramadol ER, and to add the AEs observed in geriatric population following the treatment with CIP-Tramadol ER capsules to the Geriartric Use section of the label.

8. Safety

In NDA (b) (4), the overall safety assessment showed that the use of Cip-Tramadol ER capsules was associated with adverse events that have been reported with other tramadol products. There were no new clinical trial data in NDA 22-370 and therefore the new safety database consisted of only pharmacokinetics studies conducted in healthy volunteers. In his Clinical review for NDA 22-370, Dr. Burkhart concluded that there were no new safety findings and that the safety profile of CIP-Tramadol ER capsules is similar to Ultram® ER tablets and is therefore acceptable.

9. Advisory Committee Meeting

This product was not discussed at an Advisory Committee meeting.

10. Pediatrics

The following assessment on Pediatrics is extracted from Dr. Keith K. Burkhart's review;

(b) (4)

(b) (4)

The Division did not agree with the Applicant's pediatric plan and considered it inadequate to meet requirements under the Pediatric Research Equity Act (PREA). The Division sent an Information Request (IR) on October 16, 2008. In this IR the Division stated that moderately severe chronic pain is prevalent in the pediatric population, and there are

only a limited number of analgesics approved for use in this population; therefore these patients could benefit from tramadol. The Division informed the Applicant that at least one randomized, double-blind, controlled study in pediatric patients would be required using an age-appropriate formulation, as necessary. In addition, determination of the pharmacokinetics of tramadol in patients aged less than 12 years should be performed, to assist with dosing of patients in the randomized study. In response, the Applicant, on October 20, 2008, (b) (4)

On November 5, 2008 the Division held a teleconference with the Applicant to discuss the pediatric plan. The Division reiterated the need for adequate pediatric studies, and informed the Applicant that studies in patients less than 2 years could be waived, since it is difficult to measure and thus diagnose chronic pain in this population. During this teleconference the Applicant (b) (4) (b) (4) (b) (4) The Applicant committed to providing a written summary of its pediatric plan. At the time of this review, the summary had not been submitted.

The Division discussed the (b) (4) pediatric plan with the Pediatric Review Committee (PeRC). PeRC recommended that pediatric studies not be deferred until Cip-Tramadol ER is finally approved. Rather, pediatric studies should be initiated prior to the issuance of a final approval.

11. Other Relevant Regulatory Issues

The patent for Ultram® ER tablets does not expire until May 10, 2014. As such, if this NDA is approved, a 'Tentative Approval' action has to be taken pending the expiration of Ultram® ER tablets patents.

Division of Scientific Investigation (DSI) inspection was performed for the pivotal bioequivalence Study TRAMPK.07.04. Even though Form 483 was issued at the analytical site, the identified issues were not thought by DSI as having an adverse effect on the acceptance of data. DSI recommended that data be accepted for review.

At this time, the following are pending;

(1) Consult from Office of Surveillance and Epidemiology regarding the label.
(2) cGMP recommendation from the Office of Compliance regarding the inspections of the manufacturing and packaging sites.

12. Labeling

In the initial submission of NDA 22-370, sponsor proposed label basing on the approved Ultram® ER Tablets label. It had new Clinical Pharmacology related language reflecting the bioequivalence data. The sponsor was requested to submit a new label reflecting the CIP-Tramadol ER capsules clinical trial experience where applicable.

At this time, the review team is making labeling changes and agreement with the sponsor on the labeling changes is pending.

Among other things, Dr. Keith Burkhart proposes a significant revision to the Clinical Trial's section as follows (extracted from his review);

In the Applicant's proposed label, Section 14 - Clinical Studies contains language describing the trial results for Ultram® ER the RLD. (b) (4) . Suggested language follows:

(b) (4)

13. Recommendations/Risk Benefit Assessment

The applicant provided adequate data demonstrating bioequivalence of CIP-Tramadol ER capsules 100 mg, 200 mg, and 300 mg to the currently marketed Ultram® ER tablets 100 mg, 200 mg, and 300 mg. There were no new safety findings from this database or in NDA (b) (4) with the overall safety profile being similar to other approved tramadol products. As such, CIP-Tramadol ER capsules has acceptable benefit to risk profile.

However, at the time of completing this memo, the following items are still pending;

(1) Consult from Office of Surveillance and Epidemiology regarding the label.
(2) Overall "Acceptable" cGMP recommendation from the Office of Compliance regarding the inspections of the manufacturing and packaging sites.
(3) Agreements on the label with the sponsor
(4) Commitment from the sponsor to initiate pediatric studies prior to final approval as recommended by PERC.

Once the above items are satisfactorily resolved, this NDA can be granted 'Tentative Approval'. A Tentative Approval as opposed to Approval is warranted because CIP-Tramadol capsules cannot be marketed until the expiry of Ultram® ER tablets patent on May 10, 2014.

In the action letter, the following ONDQA related agreements reached with the applicant should be reiterated;

(1) Report of process validation studies including assessment of (b) (4) of drug product intermediates, e.g., (b) (4) and revised acceptance criteria for the dissolution testing of (b) (4) beads should be submitted to the NDA upon completion.

(2) Revise the drug release acceptance criteria after production and evaluation of (b) (4) commercial (production scale) batches.

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/s/

Suresh Doddapaneni
1/5/2009 06:52:57 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**
Food and Drug Administration
Center for Drug Evaluation and Research
ODE II / DAARP
10903 New Hampshire Ave.
Silver Spring, MD 20993

Medical Officer Review

Date: December 2, 2008

Reviewer: Keith K. Burkhart, MD
Medical Officer, CDER/ODEII/DAARP

Application: NDA 22-370

Product: CIP-TRAMADOL ER

Background:

Cipher Pharmaceuticals Inc has submitted a new NDA (N 22-370) for their extended-release tramadol capsule that references their previous NDA (b) (4). A proprietary name for this product has not been determined. For the purposes of this review, the drug product will be referred to as Cip-Tramadol ER.

On May 2, 2007 the Division sent the Applicant an approvable letter for Cip-Tramadol ER Capsules, NDA (b) (4). The original submission comprised a 505(b) (2) NDA, and the reference labeled drug (RLD) was Ultram (immediate-release tramadol tablets). (b) (4)

Current Submission:

(b) (4) the Applicant has submitted a new NDA. (b) (4) the Applicant has opted to conduct bioequivalence studies against an alternate approved RLD, Ultram ER (extended-release tramadol) tablets. The Applicant considers their product a "pharmaceutical alternative" dosage form to Ultram ER, and is

citing the Agency's previous determination of safety and efficacy of Ultram ER as support of the safety and efficacy of the Cip-Tramadol ER capsule.

The new NDA initially contained two clinical studies, both of which were bioequivalence trials against Ultram ER. One study is a two-way crossover study of fasted subjects to compare the bioequivalence of Cip-Tramadol ER Capsules 300 mg to Ultram ER tablets 300 mg. A second study compares the bioequivalence to Ultram ER in a 4-way crossover fed/fasted study. This study design was intended to replicate the previous findings that Cip-Tramadol ER is bioequivalent to Ultram ER under fasted conditions, but does not have a food effect under fed conditions.

Shortly following receipt of the new NDA, the Division discussed with the Applicant its' concerns about the adequacy of the studies provided to determine bioequivalence of the product, specifically the limitation of the available data to show bioequivalence of the 100-mg and 200-mg dose strengths. Per agreement with the Division, additional in vitro and PK studies were performed and submitted to the amendment: Special Study LES-096 – Dissolution Profile Comparison studied the in vitro dissolution of Cip-Tramadol ER to Ultram ER at the respective 100 mg, 200 mg, and 300 mg strengths. The PK study, TRAMPK.08.02, was a multi-dose study comparing CIP-Tramadol ER 200 mg to the RLD, Ultram ER 200 mg. The review of all the studies has determined that Cip-Tramadol ER and Ultram ER are bioequivalent. Refer to the review by Clinical Pharmacologist, Dr. Lei Zhang, for details regarding the interactions between the Division and the Applicant over the NDA amendment, as well as FDA's assessment of these new clinical pharmacology studies.

Clinical Review

(b) (4)

(b) (4)

(b) (4)

The reference labeled drug, Ultram ER, is approved for doses up to 300 mg taken once daily. Efficacy was based in both fixed dose and flexible dose trials. Per the Ultram ER label, a responder analysis of the fixed dose trial demonstrated statistically significant improvement as measured by the WOMAC Pain Scale for the 100 and 200 mg doses. The second trial of Ultram ER was a flexible-dosing trial in subjects with osteoarthritis of the knee. Daily doses of 100 to 300 mg were administered. In that study, an Ultram ER dose of 270 mg/day demonstrated a statistically different decrease in the mean VAS pain score.

All of the Applicant's studies of Cip-Tramadol ER were fixed-dose trials of 100, 200, and 300 mg/day in patients with osteoarthritis. The Applicant did not perform any flexible dosing clinical trials. (b) (4)

Safety
The only new safety data for Cip-Tramadol ER came from the new pharmacokinetic studies in healthy volunteers. These studies showed that there were no new safety findings for Cip-Tramadol.

Labeling Review:

In the initial submission of the current NDA, the Applicant proposed a label that was based on the approved one for Ultram ER. (b) (4) . The label included new language under the Clinical Pharmacology section that reflected the bioequivalence data.

My preliminary review of the label found that the proposed labeling required a number of modifications. Some sections that (b) (4) , such as the Adverse Reactions section and Clinical Studies section, should be modified to reflect (b) (4)

(b) (4). I also recommend that the Common Adverse Reaction Table should be modified to remove AEs where the rate of events in the Cip-Tramadol ER arm is not higher than the placebo rate. Additionally, I recommend that the order of the adverse events (AEs) should descend based upon the incidence in the 100 mg dose group, so as to reflect the types of reactions that can occur even at the lowest recommended dose.

The Applicant was asked to provide a new label reflecting the Applicant's clinical trial experience, including a new proposed AE table. The following comments are based on this new label:

(b) (4)
.

The Applicant proposed:

(b) (4)

(b) (4)

(b) (4)

I propose this modification:

Suicide Risk

(b) (4)

(b) (4)

the avoidance of the concomitant use of alcohol while taking an opioid is

justified. Alcohol is well known to impair judgment and many patients have difficulty regulating intake. Opioids and alcohol consumption both act upon the CNS and may act synergistically. Concomitant use may further impair judgment or aggravate CNS depression placing the patient and others at risk for injury.

The proposed wording for Section 5.10 - Withdrawal was changed in a manner that suggests a claim that Cip-Tramadol ER might produce less withdrawal than other tramadol formulations.

The Applicant proposed:

> **Clinical experience *with other formulations of tramadol* [emphasis mine] suggests that withdrawal symptoms may be reduced by tapering the dose of tramadol.**

The Applicant did not provide an explanation for this change.

The proposed language suggests that withdrawal symptoms will not occur with Cip-Tramadol ER. Adverse event data from the clinical trials suggests that withdrawal symptoms may occur following discontinuation of Cip-Tramadol ER (see my previous review of NDA (b) (4)). Comparative studies with other tramadol formulations were not done to demonstrate that withdrawal does not occur with Cip-Tramadol ER. Therefore the wording should reflect that of the RLD label.

I recommend that this wording be changed back to:

(b) (4)

In section 5.12 - Interactions with Alcohol and Drugs of Abuse, the Applicant has added a new sentence (underlined) at the end of the paragraph:

(b) (4)

I accept this addition based on the same justification provided in Section 5.2 above, “Suicide Risk.”

With respect to the Adverse Reactions section, the Applicant proposed the following Common AE (>5% patients) Table 1A:

(b) (4)

I recommend the following table (Table 1B), which modifies the Applicant's Table 1A. (b) (4)

Table 1B: Reviewer's Proposed Common Adverse Event Table

	CIP-TRAMADOL ER	CIP-TRAMADOL ER	CIP-TRAMADOL ER	PLACEBO
Preferred Term	100 mg (N=429) n (%)	200 mg (N=434) n (%)	300 mg (N=1054) n (%)	(N=646) n (%)
HEADACHE	99 (23.1)	96 (22.1)	200 (19.0)	128 (19.8)
NAUSEA	69 (16.1)	93 (21.4)	265 (25.1)	37 (5.7)
SOMNOLENCE	50 (11.7)	60 (13.8)	170 (16.1)	26 (4.0)
DIZZINESS	41 (9.6)	54 (12.4)	143 (13.6)	31 (4.8)
CONSTIPATION	40 (9.3)	59 (13.6)	225 (21.3)	27 (4.2)
VOMITING	28 (6.5)	45 (10.4)	98 (9.3)	12 (1.9)
ARTHRALGIA	23 (5.4)	20 (4.6)	53 (5.0)	33 (5.1)
DRY MOUTH	20 (4.7)	36 (8.3)	138 (13.1)	22 (3.4)
SWEATING	18 (4.2)	23 (5.3)	71 (6.7)	4 (0.6)
ASTHENIA	15 (3.5)	26 (6.0)	91 (8.6)	17 (2.6)
PRURITUS	13 (3.0)	25 (5.8)	77 (7.3)	12 (1.9)
ANOREXIA	9 (2.1)	23 (5.3)	60 (5.7)	1 (0.2)
INSOMNIA	9 (2.1)	9 (2.1)	53 (5.0)	11 (1.7)

(b) (4)

Based on my review of the data, I propose the following AE listings which have removed AEs that are not greater than the placebo rate, any duplicate listings, and have added missing AEs.

Reviewer's Proposal: Adverse events with incidence rates of 1.0% to <5.0%

Cardiac disorders: hypertension
Gastrointestinal disorders: dyspepsia, flatulence, tooth disorder
General disorders: abdominal pain, accidental injury, chills, fever, flu syndrome, neck pain, pelvic pain
Investigations: hyperglycemia, urine abnormality
Metabolism and nutrition disorders: peripheral edema, weight loss
Musculoskeletal, connective tissue and bone disorders: myalgia
Nervous system disorders: paresthesia, tremor, withdrawal syndrome
Psychiatric disorders: agitation, anxiety, apathy, confusion, depersonalization, depression, euphoria, nervousness
Respiratory, thoracic and mediastinal disorders: bronchitis, pharyngitis, rhinitis, sinusitis

Skin and subcutaneous tissue disorders: rash
Urogenital disorders: prostatic disorder, urinary tract infection
Vascular disorders: vasodilatation

Adverse events with incidence rates of 0.5% to <1.0% at any dose and serious adverse events reported in at least two patients.
Cardiac disorders: EKG abnormal, hypotension, tachycardia
Gastrointestinal disorders; gastroenteritis
General disorders: neck rigidity, viral infection
Hematologic/Lymphatic disorders; anemia, ecchymoses
Metabolism and nutrition disorders: blood urea nitrogen increased, GGT increased, gout, SGPT increased
Musculoskeletal disorders: arthritis, arthrosis, joint disorder, leg cramps
Nervous system disorders: emotional lability, hyperkinesia, hypertonia, thinking abnormal, twitching, vertigo
Respiratory disorders; pneumonia
Skin and subcutaneous tissue disorders: hair disorder, skin disorder, urticaria
Special Senses: eye disorder, lacrimation disorder
Urogenital disorders: cystitis, dysuria, sexual function abnormality, urinary retention

In the Applicant's proposed label, Section 14 - Clinical Studies (b) (4) [redacted] Suggested language follows:

(b) (4) [redacted]

(b) (4)

The Special Population section of the initially proposed label describes the geriatric experience (b) (4) The label should reflect the experience with Cip-Tramadol ER in older patients.

An analysis of AEs by age 65 and less or over 65 for Cip-Tramadol and noted the AEs that had a higher incidence rate in patients over 65 years of age. This analysis adds nausea, somnolence, dry mouth, vomiting, asthenia, and pruritus, (b) (4) as the rates of these events are at least 2% higher than in patients younger than 65. See Table 2 below.

Table 2. AE Incidence Rates in Elderly Patients > 65 compared to ≤ 65 years old

PREFERRED TERM	100 %		200 %		300 %		PBO %	
AGE GROUP	> 65	≤ 65	> 65	≤65	> 65	≤ 65	> 65	≤ 65
NAUSEA	15.38	11.16	19.15	14.34	28.87	18.98	4.87	3.38
CONSTIPATION	12.09	8.76	18.09	13.55	27.46	18.06	6.37	4.42
HEADACHE	12.64	9.16	11.17	8.37	14.32	9.41	13.86	9.61
SOMNOLENCE	10.44	7.57	14.36	10.76	19.01	12.50	4.49	3.12
DIZZINESS	9.34	6.77	12.23	9.16	14.55	9.57	5.62	3.90
DRY MOUTH	2.75	1.99	11.17	8.37	12.91	8.49	4.49	3.12
VOMITING	6.04	4.38	8.51	6.37	10.56	6.94	2.25	1.56
ASTHENIA	5.49	3.98	4.26	3.19	9.62	6.33	4.49	3.12
PRURITUS	3.30	2.39	7.98	5.98	7.98	5.25	3.00	2.08
INFECTION	5.49	3.98	5.32	3.98	2.58	1.70	8.99	6.23

Other Regulatory Issues:

(a) Patent Certification
The Applicant references Ultram ER, in this 505(b)(2) NDA. The Applicant included a Paragraph III patent certification as part of its NDA. The patent for Ultram ER, #6254887, expires on May 10, 2014. Therefore, should the bioequivalence data be found acceptable and the application is approved, the Applicant's product cannot be marketed until Ultram ER's patent expires.

(b) (4)

The Division did not agree with the Applicant's pediatric plan and considered it inadequate to meet requirements under the Pediatric Research Equity Act (PREA). The Division sent an Information Request (IR) on October 16, 2008. In this IR the Division stated that moderately severe chronic pain is prevalent in the pediatric population, and there are only a limited number of analgesics approved for use in this population; therefore these patients could benefit from tramadol. The Division informed the Applicant that at least one randomized, double-blind, controlled study in pediatric patients would be required using an age-appropriate formulation, as necessary. In addition, determination of the pharmacokinetics of tramadol in patients aged less than 12 years should be performed, to assist with dosing of patients in the randomized study. In response, the Applicant, on October 20, 2008, (b) (4)

(b) (4)

On November 5, 2008 the Division held a teleconference with the Applicant to discuss the pediatric plan. The Division reiterated the need for adequate pediatric studies, and informed the Applicant that studies in patients less than 2 years could be waived, since it is difficult to measure and thus diagnose chronic pain in this population. During this teleconference the Applicant

(b) (4)

(b) (4) (b) (4) . The Applicant committed to providing a written summary of its pediatric plan. At the time of this review, the summary had not been submitted.

The Division discussed the (b) (4) pediatric plan with the Pediatric Review Committee (PeRC). PeRC recommended that pediatric studies not be deferred until Cip-Tramadol ER is finally approved. Rather, pediatric studies should be initiated prior to the issuance of a final approval.

Conclusions/Recommended Regulatory Action:

The Applicant has demonstrated bioequivalence of Cip-Tramadol ER capsules to Ultram ER tablets. Therefore this reviewer recommends approval of Cip-Tramadol ER for the proposed indication, management of moderate to moderately severe chronic pain in adult patients (i.e. a "complete response" for this NDA). (b) (4) The safety profile for Cip-Tramadol ER is similar to the reference labeled drug, and is therefore acceptable.

The patent for Ultram ER does not expire until May 10, 2014. Therefore, a "tentative approval" action is recommended for the NDA.

Many labeling changes are recommended for the Applicant's proposed label. (b) (4) . Also, the label should be modified to add the specific safety experience with Cip-Tramadol ER, with addition to the Geriatric Use of the AEs observed in this population following treatment with Cip-Tramadol ER. Additionally the Common AE Table and AE listings should be changed to remove duplication and to display events in order of descending frequency in the 100 mg/day group.

With regard to pediatric studies, the Applicant has verbally agreed to perform (b) (4) (b) (4) . At this time, however, the Applicant has not formally submitted its pediatric plan. Pediatric studies should not be deferred until after the expiration of Ultram ER's patent in 2014 (i.e. until after Cip-Tramadol can be marketed).

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/s/

Keith K Burkhart
12/2/2008 05:20:47 PM
MEDICAL OFFICER

As reviewed two minor edits

Mwango Kashoki
12/3/2008 05:30:34 PM
MEDICAL OFFICER
I concur

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS
HFD-170, 10903 New Hampshire Avenue, Silver Spring MD 20993

CLINICAL TEAM LEADER MEMORANDUM

DATE: April 24, 2007

TO: File, NDA (b) (4)

FROM: Mwango A. Kashoki, M.D., M.P.H
Medical Team Leader

RE: Supervisory Review of NDA (b) (4)
Tramadol ER Capsules
Cipher Pharmaceuticals, Inc.

Indication: "Management of moderate to moderately severe pain"

TABLE OF CONTENTS

1. Action

A "not-approvable" action is recommended.

2. Basis for Recommendation

2.1. Background

The NDA for Cip-Tramadol ER Capsules was submitted by Cipher Pharmaceuticals Ltc. on June 26, 2006. This is a 505(b)(2) application, which references Ultram (immediate-release tramadol) tablets. The desired indication for this product is the "treatment of moderate to moderately severe pain."

Cip-Tramadol ER is a capsule comprised of an immediate-release (IR) tablet and beads of extended-release tramadol. Three strengths have been developed: 100, 200, and 300 mg. The capsule strengths vary by the amount of tramadol content of the IR tablet and the amount of coated beads. The 100 mg capsule contains a 25 mg IR tablet and 75 mg of coated beads; the 200 capsule contains a 50 mg IR tablet and 150 mg of beads; and the 300 mg capsule contains a 50 mg IR tablet and 250 mg of coated beads.

Tramadol is a centrally acting analgesic that, together with its M1 metabolite, acts as an agonist at the mu opioid receptor. Tramadol has also been shown to weakly inhibit reuptake of neuronal serotonin and norepinephrine. There are five other formulations of tramadol that have been approved for marketing in the United States:

- Ultram – immediate release tramadol, 50 mg tablet (NDA 20-281). Approved 03/03/1995 for moderate to moderately severe pain in adults.
- Ultracet – immediate release tramadol (37.5 mg) and acetaminophen (325 mg) combination tablet (NDA 21-123). Approved 08/15/2001 for short term (≤ 5 days) management of acute pain.
- Ultram ODT – immediate release, orally disintegrating tramadol, 50 mg tablet (NDA 21-693). Approved 05/05/2005 for moderate to moderately severe pain in adults.
- Ultram ER – extended release tramadol; 100, 200, and 300 mg tablets (NDA 21-692). Approved 09/08/2005 for management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

(b) (4)

Initially, the regulatory responsibility for tramadol lay with the Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products (DAAODP) (b) (4)

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(b) (4)

The clinical studies of (b) (4) safety were reviewed by Dr. Keith Burkhart. The application was also reviewed by Drs. Joan Buenconsejo and Dionne Price (biostatistics), Dr. Lei Zhang (clinical pharmacology and biopharmaceutics), Dr. Danae Christodoulou (chemistry), Dr. Ted Chang (chemistry), and Dr. Asoke Mukherjee (pharmacology/toxicology).

2.2. Chemistry, Manufacturing, and Controls

As described in Section 2.1, Cip-Tramadol ER a capsule comprised of an immediate-release (IR) tablet and beads of extended-release tramadol. The extended-release beads consist of IR tramadol covered with a controlled-release polymer coating. There are three strengths (100, 200, and 300 mg) which vary by the tramadol content of the IR tablet and the amount of coated beads:

Strength	IR tramadol tablet	ER coated beads	Ratio of IR:ER tramadol
100 mg	25 mg	75 mg	1:3
200mg	50 mg	150 mg	1:3
300 mg	50 mg	250 mg	1:5

Sufficient data has been collected to support a 36-month expiration date.

At the time of the writing of this memorandum, the application acceptable for approval from a CMC perspective.

2.3. Non-clinical Pharmacology and Toxicology

All of the inactive ingredients in Cip-Tramadol ER are found in previously approved drug products at comparable exposure levels.

No other non-clinical studies were indicated for this product.

There were no pharmacology/toxicology issues and, from this perspective, the application can be approved.

2.4. Clinical Pharmacology

Bioavailability studies show that Cip-Tramadol has two peaks which represent the C_{max} of the IR and ER components. The C_{max} and AUC_{inf} of Cip-Tramadol ER 200 mg were equivalent to Ultram IR 50 mg QID, however the Cmin was lower by approximately 25%. The clinical relevance of this lower C_{min} value is uncertain.

The IR peaks of the Cip-Tramadol ER 100 and 300 mg doses, and the 200 and 300 mg were not dose proportional. This finding, together with the fact that the capsules vary in the total amount of the IR tramadol tablet that they contain, indicate the doses are not interchangeable. That is three 100 mg tablets are not equivalent to one 300 mg tablet, and one 100 and one 200 mg tablet are not equivalent to one 300 mg tablet.

Comparison of a single dose of Cip-Tramadol ER 200 mg to Ultram IR 50 mg QID showed that there is a relative lack of exposure of Cip-Tramadol ER during the terminal phase (18-24 h). Lack of adequate drug exposure towards the end of the dosing interval could impact the efficacy of the product.

A study of the effect of food on the kinetics of Cip-Tramadol ER showed a 1-hour delay in the first peak (the IR peak), and a 30 minute delay in the second peak (the ER peak). For this product intended to treat chronic pain, these delays are not considered clinically significant, and doses may be taken with or without food.

An *in vitro* study of the effects of alcohol on drug dissolution was performed. This study showed that alcohol does compromise the controlled-release characteristics of the Cip-Tramadol ER formulation, with immediate release of the tramadol content (i.e. dose-dumping). Although the clinical risks of an immediate exposure to the maximum dose of Cip-Tramadol ER (300 mg tramadol) are not fatal, the product label should apprise patients and prescribers of this effect of alcohol on the formulation.

Overall, from a clinical pharmacology perspective, the NDA is acceptable for approval.

2.5. Clinical (b) (4) Safety

(b) (4)

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(b) (4)

2.5.2. Clinical Safety

The primary sources of safety data came from 3 short-term (b) (4) (TRAMCT02.01, --02, and -05), and two long-term safety trials studies (TRAMCT02.03 and -04). Studies -01 and -02 have already been described. The remaining studies are summarized below:

Study ID	Study Design	Doses
TRAMCT.02.03	12-month, open label safety study	Tramadol ER 300 mg QD
TRAMCT.02.04	12-month, randomized, placebo-controlled, fixed-dose, parallel group safety and efficacy study	Tramadol ER 300 mg QD Placebo QD
TRAMCT02.05	12 week, randomized, placebo-controlled, fixed-dose, parallel group efficacy study	Cip-Tramadol ER QD (100, 200, and 300 mg) Placebo QD

As stated in Section 1 (Background), the results of study TRAMCT.02.05 were not included in the initial NDA submission, and were received by the division approximately two weeks before finalization of the primary NDA reviews. As such, the safety data from this trial were evaluated only for occurrences of deaths, serous adverse events (SAEs), and specific adverse events (AEs) of interest, namely seizures and serotonin syndrome. Consequently, the data from TRAMCT02.05 were not included in the division's evaluation of overall exposure, frequency of SAEs and non-serious AEs, and effects of treatment on laboratory values, ECG parameters, or vital signs.

2.5.2.1.Exposure

Based on the initial NDA data, 1474 subjects were exposed to Cip-Tramadol ER in the clinical trials: 130 subjects in the clinical pharmacology trials, 62 subjects in a phase 2 dental pain study, and 1282 subjects in the phase 3 trials. With respect to duration of exposure, the division found that 352 patients were treated for at least 6 months, and 144 were treated for at least 1 year. The applicant reported that 366 patients were treated with Cip-Tramadol 300 mg for 6 months, and 198 with the 300 mg dose for 12 months.

Overall, the size of the safety database was considered adequate to characterize the safety profile of Cip-Tramadol ER.

2.5.2.2.Deaths

There was one death reported in the submitted studies. The death, a myocardial infarction in a 55 year old male with risk factors for cardiovascular disease, occurred in study TRAMACT.02.04 approximately 48 days after initiation of treatment with Cip-Tramadol ER 300 mg/day. This death is considered unlikely to be due to study treatment, because of the patient's risk factors and the lack of a previous association of tramadol with cardiac effects.

2.5.2.3.Discontinuations due to Adverse Events

(b) (4)

In these trials, more patients in the Cip-Tramadol ER groups (29%) discontinued due to adverse events

compared to placebo patients (11%). (b) (4) Discontinuation due to adverse events increased with increasing dose of Cip-Tramadol ER: 12% of the 100 mg/day group, 24% of the 200 mg/day group, and 35% of the 300 mg/day group.

Medical Reviewer's Table 7.1.3.1 (adapted) – Patient disposition, 12-week double-blind trials (TRAMCT02.01, -02, and -04)

Disposition status	Cip- Tramadol ER 100 mg (N = 216) N (%)	Cip- Tramadol ER 200 mg (n = 217) N (%)	Cip- Tramadol ER 300 mg (N = 849) N (%)	Placebo (N = 430) N (%)
Completed	83 (38)	76 (35)	167 (20)	103 (25)
Withdrew				
Adverse Event	26 (12)	51 (24)	293 (35)	48 (11)
Treatment Failure	12 (5.6)	8 (3.7)	72 (8.5)	42 (10)
Worsening Pathology	0 (0)	0 (0)	1 (0.1)	0 (0)
Intercurrent Illness	0 (0)	3 (1.4)	8 (0.9)	1 (0.2)
Lost to Follow-up	1 (0.5)	0 (0)	27 (3.2)	9 (2.1)
Withdrew Consent	5 (2.3)	1 (0.5)	23 (2.7)	7 (1.6)
Non-Compliant	3 (1.4)	4 (1.8)	3 (0.5)	2 (0.5)
Protocol Violation	4 (1.9)	2 (0.9)	39 (4.6)	15 (3.5)
Not eligible	0 (0)	1 (0.5)	2 (0.5)	0 (0)
Patient's Best Interest	0 (0)	0 (0)	62 (7.3)	19 (4.4)

2.5.2.4.Serious Adverse Events (SAEs)

Altogether, 34 patients experienced an SAE in double-blind trials (21 patients treated with Cip-Tramadol ER, and 13 treated with placebo). The incidence of SAEs was greatest in the placebo group (13/430, 3%), followed by the Cip-Tramadol ER 300 mg/day group (20/849, 2%), and the 100 mg/day group (1/216, 1%).

Among all treated patients, the most frequent SAEs were non-fatal myocardial infarction and pneumonia (4/1782, 0.2%, each). The incidence of non-fatal myocardial infarction was greater in the placebo group (3/430, 0.7%) than in the Cip-Tramadol groups (1/1282,

0.08%). The incidence of pneumonia was also higher in the placebo group (1/430, 0.2%) than in the active group (1/1282, 0.08%). With respect to the other SAEs, only one patient each experienced these.

In the open-label safety study of Cip-Tramadol 300 mg/day, there were 14 patients who experienced an SAE. The most common SAEs were accidental injury and chest pain (n = 2, each). Similar to the double-blind studies, no pattern of SAEs was observed in the open-label trial.

Overall, the SAE profile for Cip-Tramadol ER groups was not different from that of the placebo group. No specific pattern of SAEs associated with active treatment was observed.

2.5.2.5.Other Significant Adverse Events

Tramadol is an opioid analgesic therefore, like other opioids, overdose with tramadol can cause respiratory depression, coma, and death. As a weak inhibitor of norepinephrine and serotonin reuptake, tramadol may interact with SSRIs, SSNIs or MOAIs to cause seizure and serotonin syndrome.

In the NDA, there were no reports of acute overdose or typical serotonin syndrome. There was one report of seizure in a 75 year old female (subject 93403, Study TRAMCT.02.04) that occurred 87 days after initiation of treatment with Cip-Tramadol ER 300 mg/day. The patient was hospitalized for a cerebrovascular accident and was found to have seizure activity. This event is considered not likely to be associated with treatment with Cip-Tramadol ER.

2.5.2.6.Common (non-serious) Adverse Events

In the placebo-controlled trials, 1225 patients experienced a non-serious AE. The incidence was greatest in the Cip-Tramadol 300 mg arm (694/849, 82%), followed by the 200 mg group (147/217, 68%), the 100 mg group (136/216, 63%), and the placebo group (245/430, 57%).

The most common non-serious AEs (occurring in > 5% of all patients and in order of frequency) were nausea, headache, somnolence, dizziness, dry mouth, vomiting, asthenia, and pruritus. The table below shows the incidence of these events by treatment group. AEs were more frequent in the Cip-Tramadol ER group than in the placebo group. The incidence of these AEs increased with increasing tramadol dose, with the exception of somnolence and headache.

These common AEs are similar to those that have previously been reported for other tramadol products.

Most frequently occurring non-serious AEs – All Phase 3 placebo-controlled trials

Preferred Term	Cip-Tramadol ER						Placebo (N = 430)	
	100 mg (N = 216)		200 mg (N = 217)		300 mg (N = 849)			
	N	%	N	%	N	%	N	%
NAUSEA	40	18.52	44	20.28	209	24.62	27	6.28
HEADACHE	37	17.13	33	15.21	138	16.25	63	14.65
CONSTIPATION	21	9.72	31	14.29	184	21.67	20	4.65
SOMNOLENCE	35	16.20	30	13.82	145	17.08	20	4.65
DIZZINESS	19	8.80	30	13.82	123	14.49	26	6.05
DRY MOUTH	12	5.56	18	8.29	125	14.72	15	3.49
VOMITING	19	8.80	25	11.52	84	9.89	8	1.86
ASTHENIA	8	3.70	16	7.37	80	9.42	10	2.33
PRURITUS	6	2.78	19	8.76	70	8.24	11	2.56

2.5.2.7.Laboratory Data

Clinical laboratory tests (hematology, chemistry, and urinalysis) were generally performed at baseline and study end. There were no significant changes in mean laboratory values, or shifts from normal to abnormal values for any of the tests.

2.5.2.8.Vital Signs

The submitted data showed that there were no remarkable changes in vital signs observed in patients treated with Cip-Tramadol ER compared to placebo-treated patients.

2.5.2.9.ECGs

There was no apparent pattern of differences in ECG parameters between the placebo and Cip-Tramadol ER groups.

2.5.2.10. Safety Update

As stated in the Background section, data from study TRAMCT.05 was submitted to the Agency approximately two weeks before the primary clinical review was due, and the applicant stated that the study was intended solely to support safety. As such the data were evaluated only for events of deaths and other serious adverse events. The sponsor's summary of common adverse events for TRAMCT.05 was also reviewed to determine whether the common AE profile was similar to that found for the (b) (4) safety (b) (4) studies.

There were 2 deaths during the trial, neither of which was related to treatment with Cip-Tramadol ER. A total of 21 patients experienced an SAE. There was no clear association between treatment with Cip-Tramadol and the SAEs. The common AE profile was similar to that observed in the previous studies of Cip-Tramadol.

2.5.2.11. Drug Abuse, Withdrawal, and Overdose Experience

No cases of Cip-Tramadol ER overdose were reported in any of the Phase 3 trials. The highest tested dose across the clinical studies was 300 mg/day.

Because tramadol is an opioid, discontinuation of treatment can be associated with opioid withdrawal symptoms including anxiety, sweating, insomnia, tremors, nausea, diarrhea, rhino rhea, piloerection, yawning, and hallucinations. In the long-term safety studies TRAMCT.02.03 and -04, Cipher evaluated patients for symptoms of withdrawal at the end of the study or upon premature discontinuation of the trial. The applicant used the (b) (4) which is the applicant's own scale that has not been validated. As described in Dr. Burkhart's review:

(b) (4)

Per its own analysis of the (b) (4) results, the applicant concluded that Cip-Tramadol ER 300 mg/day is associated with a low abuse potential, even with long-term use.

Cipher also assessed for opiate withdrawal using the validated Clinical Opiate Withdrawal Scale (COWS). The COWS was administered at the final study visit which was two weeks after drug discontinuation. The COWS data showed that most patients (> 95%) had no withdrawal symptoms. However, as Dr. Burkhart noted in his review, based on the half-life of Cip-Tramadol, signs and symptoms of tramadol withdrawal would be anticipated within 3 days of drug discontinuation. As such, the COWS assessment was performed too late to adequately capture any events of opioid withdrawal.

The Office of Surveillance and Epidemiology (OSE, formerly Office of Drug Safety) has noted that tramadol has been marketed for over ten years and has not, to date, required risk management tools beyond standard product labeling and post-marketing safety surveillance.

Finally, as an modified-release formulation, there is the potential that Cip-Tramadol ER, in the presence of alcohol or other solution, may undergo compromise of its modified-release mechanism, leading to immediate availability of the total tramadol dose (i.e. dose dumping). An *in vitro* alcohol interaction study was conducted and showed that in the presence of alcohol, dose-dumping of Cip-Tramadol ER does occur. This is probably because the polymer coating of the ER tramadol beads is soluble in ethanol (see Section 2.4, Clinical Pharmacology). An *in vivo* alcohol interaction study was not required. This is because dose-dumping effect does not raise considerable safety issues - a single dose of 300 mg tramadol (the maximum dose proposed) is not fatal. Rather, patients are more likely to experience considerable adverse effects such as nausea and vomiting.

Nevertheless, the effects of alcohol on the Cip-Tramadol ER formulation should be described in the product label, and the label should contain the language regarding alcohol-tramadol interactions that already exists for other tramadol products.

3. Proprietary Name

At the time of this memorandum, the applicant had not proposed a proprietary name for Cip-Tramadol ER capsules. A proprietary name is not required for an action to be taken on this NDA.

4. Conclusions and Recommendaitons

(b) (4)

The safety data show that use of Cip-Tramadol ER is associated with adverse events that have been reported with other tramadol products. The most common events are nausea, constipation, dizziness, somnolence, vomiting, and pruritus. SAEs varied considerably, with no demonstration of relationship to Cip-Tramadol ER dose. The three reported deaths were not considered to be related to Cip-Tramadol ER. There is no evidence of increased risk of overdose or withdrawal with Cip-Tramadol ER compared to what has been observed with other tramadol products.

Despite the comparability of the safety profile of Cip-Tramadol ER to that of the approved extended release tramadol product (Ultram ER), I recommend against approval

of this application for the desired indication, "treatment of moderate to moderately severe pain," (b) (4)

(b) (4)

The action letter should detail approaches to resubmission of the safety data to facilitate more definitive review. The resubmitted safety data should integrate the experience from all Phase 2 and 3 trials of Cip-Tramadol ER, and should describe all post-marketing experience with tramadol.

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/s/

Mwango Kashoki
4/25/2007 11:39:18 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	(b) (4)
Submission Code	N-000
Letter Date	6/26/2006
Stamp Date	7/05/2006
PDUFA Goal Date	5/03/2007
Reviewer Name	Keith K. Burkhart, MD
Review Completion Date	3/7/2007
Established Name	Cip-Tramadol ER Capsules
(Proposed) Trade Name	Not determined
Therapeutic Class	Opiates
Applicant	Cipher Pharmaceuticals Ltd
Priority Designation	S
Formulation	Capsules
Dosing Regimen	Once daily
Indication	Management of moderate to moderately severe chronic pain
Intended Population	Adults

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that a "not approvable" action be taken for the following reasons:

(b) (4)

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

A risk management plan is not indicated for Cip-Tramadol ER. Extensive post-marketing experience already exists for tramadol related products. Labels already warn about tramadol risks.

1.2.2 Required Phase 4 Commitments

Not applicable.

1.2.3 Other Phase 4 Commitments

Not applicable.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Cipher Pharmaceutical Ltd's product is an extended release formulation of tramadol. Tramadol is an opioid analgesic that blocks the reuptake of norepinephrine and serotonin. The product is an oral capsule with immediate and extended release components.

The proposed indication for Tramadol ER is "management of moderate to moderately severe chronic pain." (b) (4) studies were conducted in adult patients with osteoarthritis of the hip and knee.

Three pivotal (b) (4) studies were performed, TRAMCT02.01, TRAMCT02.02, and TRAMCT02.04. These were double-blind placebo-controlled trials. In addition there was one follow-on safety trial. Some subjects completing the first two (b) (4) trials continued into an open-label safety trial (TRAMCT02.03) for an additional 12 months of exposure. Therefore some patients remained on Tramadol ER for up to 15 months

There were 130 patients enrolled in the phase 1 pharmacology trials. There was one phase 2 study of Cip-Tramadol ER in an acute dental pain trial that enrolled 62 patients. (b) (4)

(b) (4)

(b) (4)

1.3.3 Safety

The safety of Cip-Tramadol ER was evaluated in six Phase 1 trials in healthy subjects, one phase 2 trial in post-operative acute dental pain patients, and four Phase 3 trials (multiple-dose treatment for up to 12 months) in patients with osteoarthritis of the hip and knee. Overall the

safety profile of Cip-Tramadol ER was similar to that of the approved tramadol products, Ultram and Ultram ER. No new safety signals were identified from Cip-Tramadol ER treatment.

In the Phase 3 trials, 1282 patients (Safety Population) with osteoarthritis were treated with at least one dose of Cip-Tramadol ER (100 to 300 mg). There were 1712 patients in the three placebo-controlled trials, of these 216 were treated at the 100mg dose, 217 at the 200 mg dose and 849 at the 300 mg dose. The open-label trial was a follow-on trial where subjects (no matter their previous dose from Trials 01 and 02) were given 300 mg Tramadol ER. The average age of the study population was about 64 years with approximately 40-45% of patients of age ≥ 65 years; 60-75% of patients were females and 80-90% of subjects were Caucasian. Altogether, 352 subjects remained on tramadol for over 6 months; of these subjects 144 took tramadol for 12 months or more.

There was one death reported during the clinical trials. One subject on Tramadol ER 300 mg died from a myocardial infarction. The MI was not considered to be related to the study medication.

A total of 47 other subjects reported serious adverse events (SAEs): 33 of the subjects with SAEs were in the placebo controlled-trials and the other 14 were in the follow-on open-label trial using the 300 mg dose. Twenty-nine of the subjects with SAEs were in the 12-month Trial 04, 15 (15/627, 2.4%) subjects were taking the 300 mg dose, while 14 (14/210, 6.7%) were placebo subjects.

The SAEs occurred in many different organ systems. The cardiovascular system accounted for the highest number of SAEs. Cardiovascular-related SAEs were reported by 12 subjects including the one death due to a myocardial infarction (5/1282, 0.4% all tramadol vs 7/430, 1.6% placebo). The incidence of cardiovascular SAEs was higher in the placebo subjects. The high rate of cardiovascular events is most likely related to the elderly patient population that was enrolled. There was only one seizure reported in a subject taking Cip-Tramadol ER. The subject developed a seizure after a cerebrovascular accident (stroke). Therefore the stroke would be the primary cause, although tramadol may have also contributed by lowering the seizure threshold. Otherwise, the SAEs were single cases across the study groups. No trend of an association with Tramadol ER treatment was evident. In almost all of the cases an underlying medical condition in this elderly population is considered most likely etiology. No pattern was seen that would suggest that Cip-Tramadol ER aggravates a specific disease or medical condition; causes a disease-drug interaction.

The gastrointestinal and nervous systems were the predominant systems for common adverse events (AEs). Within the gastrointestinal system the common AEs, in order of highest frequency, were nausea, constipation, dry mouth, vomiting, and anorexia. Except for vomiting, these GI AEs showed a dose dependent pattern. The common nervous system adverse events were somnolence and dizziness, the later showing a dose-dependent pattern.

Overall, the safety profile of Tramadol ER appears comparable to that of the previously approved tramadol products.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen includes a starting dose of 100 mg daily. After one week, the dose may by increased 100 mg weekly, to a maximum of 300 mg once daily. This was the dosing regimen studied in the trial. Some subjects did not tolerate the higher doses during the titration period and dropped out before reaching the higher doses (b) (4) The higher doses were associated with higher drop out rates due to AEs. Overall, the dosing regimen, however, is safe for those patients who tolerate the medication. The dosing regimen is consistent with that of Ultram ER, except Ultram ER has a more rapid titration phase of 5 days compared to the Cip-Tramadol ER titration to next higher dose period of 7 days.

1.3.5 Drug-Drug Interactions

Drug-drug interactions of Cip-Tramadol ER were not specifically studied for this NDA. However, information on drug interactions with tramadol is available from the approved tramadol products and literature. These drug-drug interactions are contained in the referenced Ultram labels. Pharmacokinetic interactions involving metabolism by the CYP2D6 and CYP3A4 isoenzymes have been described. The greatest pharmacodynamic drug-drug interaction risk is respiratory depression. The use of other central nervous system (CNS) depressants carries the risk to induce coma and respiratory arrest. Pharmacodynamic interactions may also result from the pharmacologic action of blocking the reuptake of serotonin and norepinephrine. Drug-drug combinations may result in enhanced serotonergic or noradrenergic activity that may increase the risk for seizures and the serotonin syndrome.

1.3.6 Special Populations

Special populations were not studied. (b) (4)

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Cip-Tramadol ER is the proposed trade name for this new dosage form. Tramadol hydrochloride is the established name. The pharmacologic class is a centrally acting synthetic opioid analgesic. Tramadol possesses opioid agonist properties and activates monoaminergic spinal inhibition of pain. Tramadol is a racemic mixture of 2 enantiomers. Both contribute to the analgesic effect. Tramadol has modest affinity for the μ-opioid receptors and weak affinity for δ and κ receptors.

Description of new formulation: The Applicant has licensed the product from Galephar PR Inc., as a unique extended release form of tramadol. The product comprises extended release beads of tramadol and an immediate release tablet together in a capsule. There are three dosage

strengths, 100 mg, 200 mg, and 300 mg. In the 100 mg capsule there is 25 mg of immediate release (IR) tramadol with 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.

Proposed Indication: Management of moderate to moderately severe chronic pain in adults. The proposed dosing regimen is 100 mg once daily that can be titrated up to 300 mg once daily.

2.2 Currently Available Treatment for Indications

There are numerous marketed analgesic products for the management of chronic pain. These include other long-acting opiate preparations such as morphine. In addition, non-opiate medications are available, such as non-steroidal anti-inflammatory drugs (NSAIDS) and acetaminophen. These later medications can be used as adjunctive treatment with tramadol products.

Non-pharmacotherapy (such as interventional procedure and acupuncture) is another alternative approach.

2.3 Availability of Proposed Active Ingredient in the United States

Tramadol hydrochloride is available in both immediate release and extended release dosage forms. For this NDA, the Applicant references the immediate-release oral tablets, Ultram. Ultram (NDA 20-281) was approved on March 3, 1995 and is indicated for 'the management of moderate to moderately severe pain in adults." The approved dose is 50-100 mg orally every four to six hours not to exceed 400 mg/day.

Ultram ER (21-692) Extended-Release Tablets are available in once daily 100 mg, 200 mg, and 300 mg tablets. The indication is for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time. The starting dose is 100 mg that can be titrated by 100 mg increments every five days to the 300 mg daily maximum. Ultram ER was approved in September of 2005.

The two other Ultram products are:

1) Ultracet (37.5 mg tramadol and 325 mg acetaminophen combination tablets) approved on August 15, 2001 under NDA 21-123 is indicated for "*the short-term (five days or less) management of acute pain.*"
2) Ultram ODT (tramadol orally disintegrating tablets 50 mg) approved May 5, 2005 under NDA 21-693 is indicated "*for management of moderate to moderately severe pain in adults.*"

2.4 Important Issues with Pharmacologically Related Products

Several safety concerns exist for the use of tramadol products. There are many safety warnings on the labels for Ultram and Ultram ER. These include seizure risks, risk for serotonin syndrome, and suicide risks.

The most recent safety addition has been warnings about the concomitant use of other drugs that inhibit the reuptake of serotonin and/or norepinephrine. The combination may result in serotonin syndrome.

Seizures have been a recognized risk with a black box warning in the product label for many years. Tramadol seems to have a narrow therapeutic window. Doses just beyond the recommended therapeutic dose appear to increase the seizure risk. Drug interactions with CYP3A4 and CYP2D6 that might increase levels of tramadol or its' active metabolite are described in the Precautions section of the label. Patients are warned that the seizure risk may increase with the concomitant use of other opioids, selective serotonin re-uptake inhibitors, SSRIs, and tricyclic antidepressants and other tricyclic compounds. Because of an enhanced seizure risk, there is a warning against the administration of tramadol with MAO inhibitors, neuroleptics and other seizure-threshold lowering drugs. In tramadol overdose, naloxone may also increase seizure risk.

Suicide risk is the second warning within the black box. Suicidal or addiction-prone patients are not to be prescribed tramadol ER. Cautious use of tramadol is recommended for patients taking tranquilizers or antidepressants, as well as patients who use alcohol in excess.

2.5 Presubmission Regulatory Activity

Cip-Tramadol ER was developed under IND (b) (4) and the former HFD-550 was the responsible review division. Key milestones in the clinical development program are highlighted below.

1. Pre-IND: (02/22/2001)

    - No additional animal and toxicology studies are needed, but a review of the published literature is required.
    - Proposed excipients in the formulation are acceptable.
    - Proposed tests and specifications are satisfactory.
    - Proposed PK studies of bioequivalence, dose proportionality and food effect compared to the referenced drug, Ultram, appear adequate.
    - It is necessary to differentiate between the isomers for tramadol and its metabolite.
    - Clinical study design: (b) (4)

2. Pre-IND: (12/04/2001)

- Dental extraction protocol submitted (b) (4) would provide safety information.
- (b) (4)

3. End of Phase 2 (EOP2) Meeting: 9/24/2002

- Proper biopharmaceutical studies completed or planned.
- (b) (4)
- (b) (4)
- A gender analysis will need to be done.
- (b) (4)
- Dose titration increasing from 100 mg by 100 mg after one week was acceptable.
- (b) (4)
- (b) (4)

4. Teleconference with Applicant 10/15/2003

- Ongoing TRAMCT.02.03 trial was accepted as an open label study for long-term safety.
- It was acceptable to amend TRAMCT.02.04, as a controlled 12 month study to provide long-term safety data.

5. EOP2 Meeting 7/16/2004

- (b) (4)

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(b) (4)

13. Pre-NDA meeting (11/21/2005)

- Ability of the product to be approved as a 505(b)(2) application required further regulatory consideration.

(b) (4)

- FDA asked Cipher to perform an interaction study of the 300 mg dose with alcohol.

(b) (4)

- A description of the overall format and presentation of the NDA was acceptable.

14. Teleconference (12/21/2005)

- Applicant may submit in vivo alcohol study with the 120 day safety update.

15. Letter sent 6/14/2006. Informed Applicant that in vivo alcohol study would not be required, as in vitro data would be adequate for characterization and labeling.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Dr. Danae Christodoulou was the primary CMC reviewer for the application. Dr. Ted Chang reviewed the manufacturing component. Per their preliminary review, there are no approvability issues. No aspects of the CMC review are critical to the clinical interpretation of the data.

3.2 Animal Pharmacology/Toxicology

This NDA filing is a 505(b)(2) application. No non-clinical studies were performed. The Applicant has relied upon data from the Ultram NDA 20-281. Dr. Asoke Mukherjee was the primary reviewer of the non-clinical pharmacology/toxicology issues. His finding was that there are no approvability issues. No new non-clinical studies are recommended. Changes are recommended to the non-clinical section of the proposed label regarding exposure ratios.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review relied upon summary reports and datasets provided by the Applicant. The reports included three bioavailability trials, three comparative bioavailability and bioequivalence trials, one phase 2 trial in post-operative dental pain, and four phase 3 safety (b) (4) trials. The Applicant's summaries of (b) (4) safety data these trials were examined. The datasets were utilized for confirmatory and exploratory data analyses.

4.2 Tables of Clinical Studies

Table 4.2A. Phase 1 and 2 Tramadol ER Studies

Study Type	Study ID	Objective	Study Design	Subject # Type	Dosage
Bio-availability	TRAMPK01.04	BA fed/fast Food effect	OL, 2-way Crossover One-day	18 Healthy Males	Tramadol ER 300 mg
Bio-availability	TRAMPK01.03	Dose proportionality	OL, 2-way cross-over One-day	20 Healthy Both sexes	Tramadol ER 200 and 300 mg
Bio-availability	TRAMPK02.02	Dose proportionality	OL, 2-way Crossover One-day	28 Healthy Both sexes	Tramadol ER 100 and 300 mg
Comparative Bio-availability	TRAMPK01.01	Compare Tramadol ER vs Ultram	OL, 2-way Crossover One-day	26 Healthy Both sexes	Tramadol ER 200 mg OD vs Ultram 50mg QID
Comparative Bio-availability	TRAMPK01.02	Compare Tramadol ER vs Ultram	OL, 2-way Crossover 7-days	16 Healthy Males	Tramadol ER 200 mg OD vs Ultram 50mg QID

Comparative Bio-availability	TRAMPK02.01	Compare Tramadol ER vs Ultram	OL, 2-way Crossover 7-days	22 Healthy Males	Tramadol ER 200 mg OD vs Ultram 50mg QID
Phase II (b) (4) Safety	TRAMCT01.05	Compare Tramadol ER vs Ibuprofen and Placebo (PBO)	2-phase, PBO-controlled, parallel group	62 Post-op dental pain Both sexes	Tramadol ER 200mg or 300 mg Ibuprofen 400 mg Placebo

Table 4.2B. Phase 3 Tramadol Safety (b) (4) Studies

Study ID	Objective	Study Design	Subject #	Dosage
TRAMCT.02.01	Safety (b) (4) @12 weeks osteoarthritis of knee or hip	Randomized, PBO-controlled, parallel group	433	Tramadol ER 100, 200 or 300 mg QD vs Placebo
TRAMCT.02.02	Safety (b) (4) @12 weeks osteoarthritis of knee or hip	Randomized, PBO-controlled, parallel group	450	Tramadol ER 100, 200 or 300 mg QD vs Placebo
TRAMCT.02.03	Safety for 12 months	Open label	260	Tramadol ER 300 mg QD
TRAMCT.02.04	Safety (b) (4) @12 weeks	Randomized, PBO-controlled, parallel group	856	Tramadol ER 300 mg QD vs Placebo

4.3 Review Strategy

(b) (4) The application also relies upon with the Agency's previous finding of efficacy for tramadol hydrochloride, Ultram. (b) (4). A Phase 1 trial was submitted to bridge the pharmacodynamics of Cip-Tramadol ER to the reference listed drug, Ultram.

Data from (b) (4) three (b) (4) trials, plus one follow-on open-label trial, TRAMCT02.03, provided the data for the Integrated Safety Analysis. The specific datasets are detailed in Section 7.1.

(b) (4)

Dr. Asoke Mukherjee, PhD of the Pharmacology and Toxicology staff reviewed the pharmacology/toxicology data.

Dr. Danae Christodoulou of the Chemistry, Manufacturing and Controls (CMC) staff reviewed the CMC data.

Dr. Lei Zhang of the Office of Clinical Pharmacology and Biopharmaceutics performed the primary review of the clinical pharmacology data.

4.4 Data Quality and Integrity

DSI was asked to review the following sites:

Indication(s)	Site (Name and Address)	Protocol #	Number of Subjects
Analgesia for chronic pain	R. Lynn Magargle 3335 Market Street Camp Hill, PA 17011	TRAMCT02.01 TRAMCT02.03 TRAMCT02.04	58 20 49
	William P Maier Rheumatology Pro Research Suite 450 401 E. 10th Avenue Eugene, OR 97401	TRAMCT02.01 TRAMCT02.03	84 46
	Kenneth Skeith Allin Clinic 10155-120 Street Edmonton, AB, Canada T5K 2A2	TRAMCT02.02 TRAMCT02.03 TRAMCT02.04	91 57 21
	Allan L. Bailey BioQuest Research #302, 131-1st Avenue Spruce Grove, AB, Canada T7X 2Z8	TRAMCT02.02 TRAMCT02.03 TRAMCT02.04	54 24 26

The above sites were selected because they were the highest enrolling sites. (b) (4) . In addition the TRAMCT02.02 trial was performed entirely outside of the United States. Therefore, these high enrolling sites were selected because of the conflicting study results and lack of sufficient domestic data.
The Division of Scientific Integrity (DSI) inspected two sites, Drs. Magargle and Maier. At Dr. Maier's site, DSI found minor problems with recordkeeping, the enrollment of one ineligible subject, and unreported adverse events. At Dr. Magargle's site DSI found only two minor

unreported AEs. DSI concluded that none of these deficiencies would adversely impact the study outcome.

The inspections of the international sites are pending at the time of this review.

4.5 Compliance with Good Clinical Practices

The clinical studies appear to have been conducted under Good Clinical Practices. The Applicant contracted with (b) (4), a CRO (Contract Research Organization), to provide data quality assurance. There were no reported issues. When protocol violations occurred subjects were discontinued in the trials. There were 60 (60/1712, 3.5%) such reported protocol violations. The distribution was 45 to 15 for study drug to placebo which matched the study drug to placebo subject ratio of 3:1. There is no evidence that these cases compromised the data.

4.6 Financial Disclosures

The applicant certified that there were no financial arrangements with all clinical investigators and sub-investigators.

5 CLINICAL PHARMACOLOGY

This review is based upon the preliminary findings by the primary pharmacology reviewer, Lei Zhang, PhD. The text is taken from her preliminary review with minor editing. Reviewer comments are added to stress points important to the clinical interpretation of data submitted in this application.

5.1 Pharmacokinetics

To support human PK and biopharmaceutics requirements, CIP-Tramadol ER was studied in a total of 6 *in vivo* PK studies. These studies assessed bioequivalence of CIP-Tramadol ER compared to Ultram IR after single and multiple doses, dose proportionality, and ingestion of food.

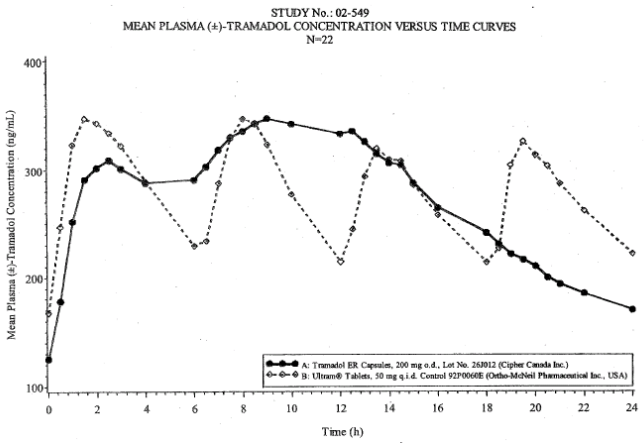
The extended-release capsule dosage form contains a tramadol HCI immediate release (IR) tablet and tramadol hydrochloride (HCI) ER beads. The *in vivo* concentration-time profiles for tramadol and its metabolite, M1, showed that there was a lower Cmax peak (Peak 1) at around 2 hours and a higher Cmax peak (Peak 2) at around 10 hours compared to Ultram IR (given QID). Peak 1 mainly represents the release of tramadol from the IR tablet and Peak 2 mainly represents the release of tramadol from the ER beads.

Relative Bioavailability Compared to Ultram (IR product):

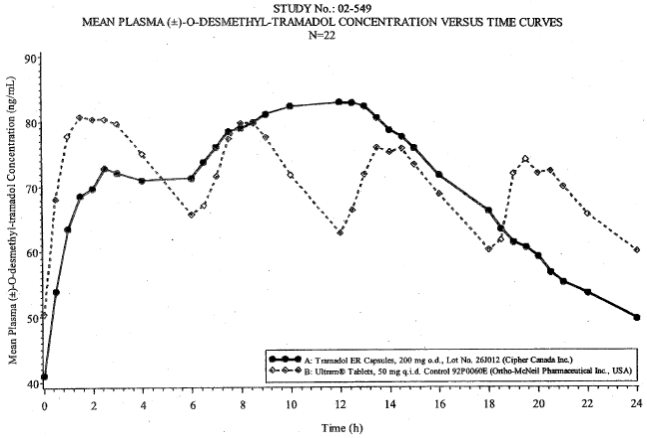
Compared to the steady-state PK profile of Ultram IR (50 mg QID), CIP-Tramadol ER (200 mg QD) showed equivalent C_{max} (Peak 2) and AUC (Figure 5.1 and Tables 5.1 and 5.2) for both tramadol and M1. However, C_{min} of tramadol and M1 for CIP-Tramadol ER was ~ 18-25%

lower than Ultram IR at steady-state. Lower concentrations of tramadol and M1 were observed between 18 and 24 hours following CIP-Tramadol ER once a day dosing compared to Ultram every 6 hour dosing.

Figure 5.1A. Mean Plasma Tramadol (a) and M1 (b) Concentrations on Day 7 for 200-mg CIP-Tramadol ER Tablets QD and 50-mg Ultram® Tablets Q6h.



a. Tramadol



b. M1

Table 5.1.1. Summary of PK Result Comparison for Tramadol at Steady State (on Day 7) (A: 200 mg Tramadol ER vs. B: Ultram).

Parameter	Test (A) / Reference (B) Geometric Mean Arithmetic Mean (CV%)		Ratio of Geom. Means (%)	90% Geom. Confidence Interval	Intra-Subject CV (%)
AUCtau (ng·h/mL)	6392.2 6600.0 (25)	6514.0 6712.9 (26)	98.13	94.83 – 101.55	7
Cmax (ng/mL)	355.9 363.8 (21)	368.9 378.9 (24)	96.47	92.97 – 100.10	7
Cmin (ng/mL)	154.7 164.9 (35)	205.0 212.9 (29)	75.45	69.64 – 81.73	15
Tmax [a] (h)	9.70 (18)	6.98 (68)		-	
DF [a] (%)	75.33 (29)	60.56 (17)		-	

[a] Presented as arithmetic mean (CV%) only.

Table 5.1.2. Summary of PK Result Comparison for M1 at Steady State (on Day 7) (A: 200 mg Tramadol ER vs. B: Ultram).

Parameter	Test (A) Geometric Mean Arithmetic Mean (CV%)	Reference (B) Geometric Mean Arithmetic Mean (CV%)	Ratio of Geom. Means (%)	90% Geom. Confidence Interval	Intra-Subject CV (%)
AUCtau (ng·h/mL)	1603.8 1683.2 (31)	1617.7 1703.8 (32)	99.14	95.46 – 102.96	7
Cmax (ng/mL)	83.0 87.4 (32)	81.0 85.4 (31)	102.48	98.10 – 107.04	8
Cmin (ng/mL)	49.0 51.5 (32)	59.4 62.5 (33)	82.47	77.00 – 88.32	13
Tmax [a] (h)	10.84 (22)	6.73 (71)		-	
DF [a] (%)	50.60 (33)	32.20 (23)		-	

[a] Presented as arithmetic mean (CV%) only.

(b) (4)

Dose Proportionality

CIP-Tramadol ER is intended to be administered at doses ranging from 100 mg to 300 mg per day. Exposure of tramadol and M1 from 100, 200 and 300 mg capsules were dose proportional in terms of total AUC and Cmax (Peak 2) (Figures 5.2 and 5.3). Because the IR tablet doses in 100, 200 and 300 mg ER capsules are 25, 50 and 50 mg, respectively, Peak 1 and early AUC (e.g., $AUC_{0\text{-}4\ hour}$) were not dose proportional between 100 and 300 mg capsules, and 200 and 300 mg capsules, respectively. The clinical relevance of non-dose proportionality for the early AUC between 100 and 300 mg, 200 and 300 mg capsules is not clear. The labeling needs to state that 100 and 300 mg capsules are not exchangeable.

Reviewer Comment: I agree with the pharmacology reviewer that the lack of exchangeability between the 100 and 300 mg doses must be communicated in the label.

Figure 5.1B. Mean Plasma Tramadol Concentrations Following Administration of 200 mg (●) and 300 mg (◊) ER Capsules.

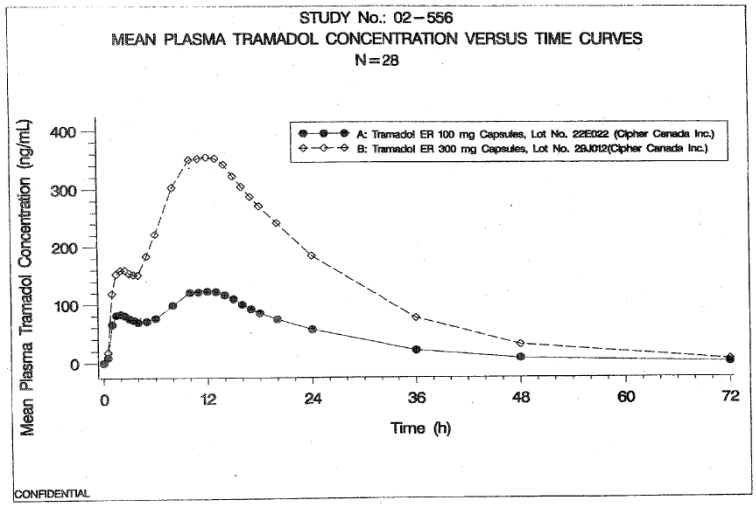
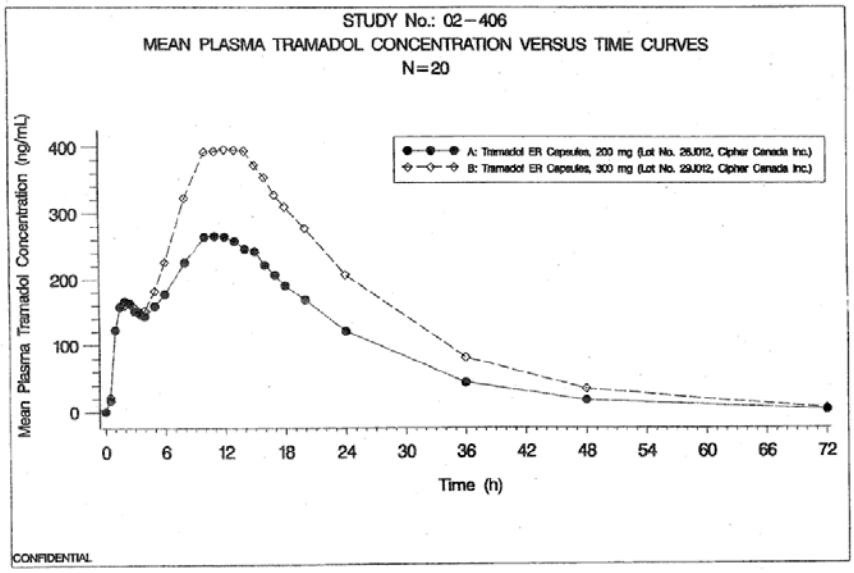


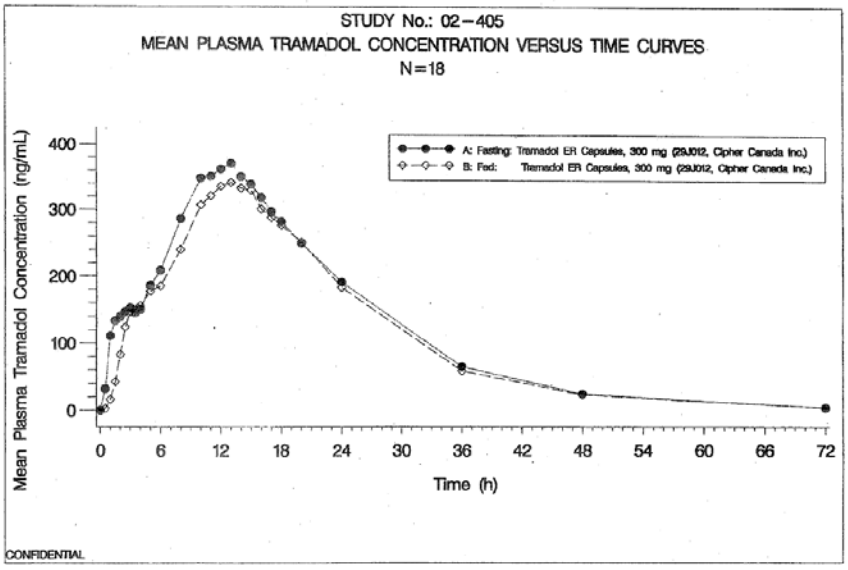
Figure 5.1C. Mean Plasma Tramadol Concentrations Following Administration of 200 mg (●) and 300 mg (◊) ER Capsules.



Food Effect

Food does not affect C_{max} or AUC following CIP-Tramadol ER dosing, however, there is a 30 min delay in T_{max} (Figure 5.1D).

Figure 5.1D. Mean Plasma Tramadol Concentrations under Fasting (●) and Fed (◊) Conditions.

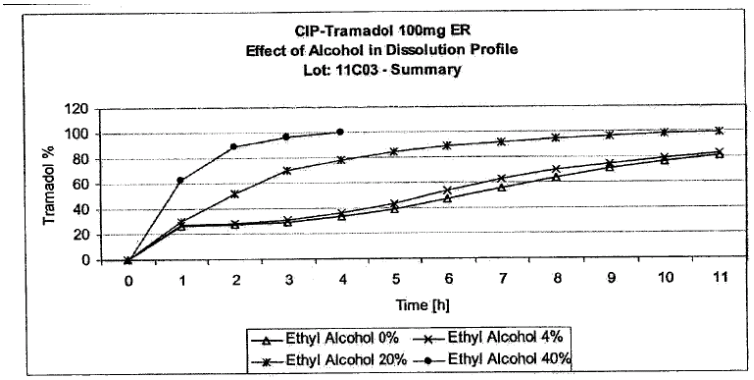


Reviewer comment: This food effect of a 30 minute delay in Tmax is not considered likely to have an adverse impact on the clinical management of chronic pain. A more important question would be if food affects the tolerability of this drug that causes significant gastrointestinal adverse effects (nausea and vomiting).

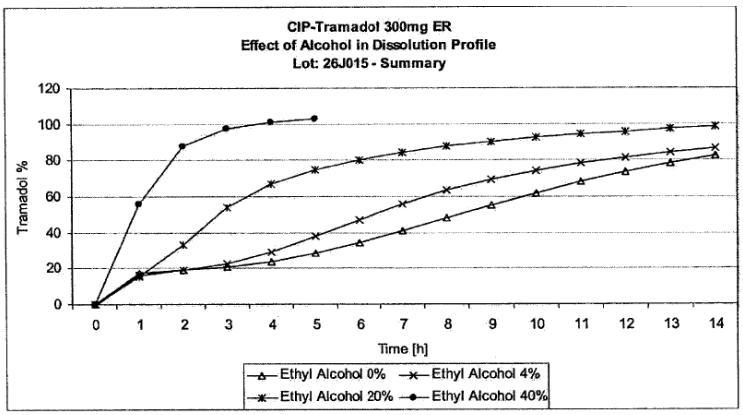
Effect of Alcohol

The effect of alcohol concentration on capsule dissolution performance was determined to evaluate the potential for dose dumping in the presence of alcohol. The rate of tramadol release increased in proportion to the ethyl alcohol concentration (0, 4, 20 and 40% ethanol) so that when 40% alcohol was used, complete dissolution occurred in approximately 4 hours. The effect of alcohol on the release of tramadol is similar for both 100 and 300 mg capsules (Figure 5.5E). The effect of alcohol is anticipated because the polymer coating for the beads is soluble in ethanol. Although an *in vivo* evaluation study is not required, dose dumping potential in the presence of alcohol for this drug product needs to be taken into consideration for proper labeling.

Figure 5.1E. CIP-Tramadol ER Dissolution Profile in the Presence of Alcohol (Above: 100 mg capsule; Bottom: 300 mg capsule).



100 mg



300 mg

Reviewer Comment: Dose dumping of Cip-Tramadol ER 300 mg in the presence of alcohol should not create a safety issue.

5.2 Pharmacodynamics

No pharmacodynamic studies were performed for this 505(b)(2) application.

5.3 Exposure-Response Relationships

No exposure-response assessments were studied. The Applicant relied upon the referenced drug Ultram and Ultram ER for the dosing determination. The sponsor did not conduct PK studies in special populations (e.g., renal and hepatic impairment patients, elderly patients). Drug-drug interaction studies were not done. Instead, the Applicant is relying on the Agency's previous findings for Ultram to construct their labeling.

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(b) (4)

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety database comprised three phase 3 double-blind trials, TRAMCT02.01, TRAMCT02.02 and TRAMCT02.04, and one open-label study (TRAMCT02.03). The first two trials, 01 and 02, were 12 weeks in duration. These trials incorporated a 2-week titration phase with doses starting from 100 mg. The titration resulted in the 200 mg patients at their dose for 11 weeks, and the 300 mg group being at their dose for 10 weeks. The Trial 04 had two groups, 300 mg and placebo. After the 2 week titration to the 300 mg dose, subjects were then continued for 52 weeks or 12 months. The three double-blind trials comprised the safety database for this review.

Some subjects in Trials 01 and 02 were rolled over into TRAMCT02.03, Trial 03. This trial was a follow-on open label trial with subjects treated with 300 mg for up to 12 additional months for a total for some subjects to be on study drug for up to 15 months. This trial had no titration phase to the 300 mg dose. This review focuses on the Serious Adverse Events reported from Trial 03.

The safety assessments performed in all four trials included laboratory tests, vital signs and electrocardiograms (ECGs). Vital signs, including pulse and blood pressure, were taken at every study visit. ECGs and laboratory tests were done at the beginning of the trial and then at the end

or at early termination. The laboratory tests included hematology, serum chemistry, and urinalysis. The specific hematologic measurements were RBC count, hemoglobin, hematocrit, WBC count with a differential, and platelets. Serum chemistry tests included glucose, BUN, SGOT (AST), SGPT (ALT), alkaline phosphatase, GGT, total bilirubin, sodium, potassium, chloride and calcium. Urinalysis included pH, specific gravity, glucose, ketones, bilirubin, protein, occult blood and microscopy. In addition for females of child-bearing potential a pregnancy test was performed at every study visit.

Adverse events (AEs) were to be spontaneously reported by the patient. The investigator was also charged with the detection and recording of adverse events. AEs were to be followed to completion. Any subject suffering a serious adverse event was to be terminated from the study. (Definitions for severity of AE are specified by FDA regulations.)

The ISS database contained datasets for all safety assessments made during all four trials. Separate datasets were also available depending on whether studies were for short-term (3 month) and long-term (12 month) exposure. The ISS also contained datasets for patient exposure to drug.

The safety population (Table 7.1) comprised all patients enrolled and who received at least one dose of study medication. The total exposure safety population (both double-blind and open label studies) is 1712 subjects (1282 all tramadol subjects and 430 placebo subjects). The open-label 300 mg trial enrolled 244 subjects from Trials 01 and 02.

Table 7.1 Safety Population by dose

Dose	100 mg	200 mg	300 mg	Placebo
Number of subjects	216	217	849	430

7.1.1 Deaths

One death from a myocardial infarction occurred in the Phase 3 trials. The mortality rate is therefore 1/1712, 0.06%.

The patient, a 55 yo male (PID #50454), was randomized to Tramadol ER 300 mg in Trial 04. His PMH was significant for hypertension and cardiovascular disease. The subject had undergone CABPG about 10 years earlier. His concomitant medications were aspirin, acetaminophen, and atenolol. The death occurred on day 48 of therapy. This event occurred when the subject undertook a trip to Thailand. It is unclear if the patient had discontinued this medication prior to this event. The autopsy in Thailand ruled the cause of death to be coronary heart disease on the death certificate.

Reviewer's Comment: A determination of relatedness to study drug is difficult. Withdrawal from opiates may result in increased sympathomimetic release. In a susceptible individual this might

precipitate a coronary event including a myocardial infarction. However, such a drug-disease interaction can not be determined in this case.

7.1.2 Other Serious Adverse Events (SAEs)

A total of 47 (47/1712, 2.7%) subjects reported SAEs. Thirty-three subjects (33/1712, 1.9%) were reported in the double-blind randomized trials, while 14 (14/244, 5.7%) subjects were in the open label Trial 03. There were four subjects with SAEs in the 3-month trials, TRAMCT02.01 and TRAMCT02.02; 3 subjects (3/222, 1.4%) were taking 300 mg and one (1/216, 0.5%) subject was taking 100 mg. TRAM CT02.04 was 12 months in duration and included 29 (29/837, 3.5%) subjects with SAEs. Of these, 15 (15/627, 2.4%) subjects were taking the 300 mg dose, while 14 (14/210, 6.7%) were in placebo subjects. The randomization was 1:1:1:1. Therefore, there were three times as many patients on active drug as there was for placebo.

Central nervous system-related SAEs are of interest because of the CNS effects of tramadol. Seizures have occurred in subjects taking tramadol. One seizure was reported in a patient taking 300 mg in Trial 04 (1/1282, 0.08% all tramadol vs 0/430 placebo). This 75 year old female was hospitalized for a cerebrovascular accident and found to have seizure activity. The seizure is most likely related to the stroke rather than study medication. There was one case (1/1282, 0.08% all tramadol vs 0/430 placebo) each of cerebral ischemia, vertigo and paralysis in subjects taking 300 mg. Since tramadol can alter the level of consciousness subjects might be at risk for falls and injuries. The only serious accidental injury, however, occurred in one subject on placebo.

Cardiovascular-related SAEs were reported by 12 subjects including the one death due to a myocardial infarction (5/1282, 0.4% all tramadol vs 7/430, 1.6% placebo). Another subject on 100 mg also had an MI. Three subjects on placebo also suffered from a myocardial infarction. Therefore the incidence of MI is 2/1282, 0.2% in all tramadol vs 3/430, 0.7% in placebo subjects. Three other subjects on 300 mg also had chest pain or angina (3/1282, 0.2% vs 0 placebo subjects). Subjects on chronic opiates may be at risk for cardiovascular events, if they are non-compliant. Abrupt withdrawal may cause a sympathomimetic excess state that could precipitate an arrhythmia or vasospastic event in the setting of preexisting cardiovascular disease.

There were seven subjects with pulmonary SAEs: Two cases of asthma occurred, one each for 300 mg (1/1282, 0.08%) and placebo (1/430, 0.2%). Four cases of pneumonia were reported, with two each for subjects on 300 mg (2/1282, 0.2%) and placebo (2/430, 0.5%).

Regarding other body systems, there was one case of gastric perforation in a subject taking the 300 mg dose (1/1282, 0.08%), while a case of intestinal obstruction occurred in a placebo subject (1/430, 0.2%). One case of blood urea nitrogen elevation occurred in a subject on 300 mg (1/1282, 0.08%).

Of the SAEs reported in the double-blind trials the SAE of elevated BUN was considered probably related to study medication by the clinical investigator. This patient had a history of prostatic cancer and a urinary tract infection. There was no vomiting or diarrhea that might have contributed to dehydration. The patient's baseline serum BUN was 22 mg/dL. It rose to 44 mg/dL and on repeat was 32 mg/dL. The determination of this derangement being related to study medication is questionable in my opinion.

In the open label trial six (6/244, 2.4%) of the 14 (5.7%) subjects with SAEs were cancer related. Two (0.8%) subjects had accidental injuries, motor vehicle accident and fall. Three subjects (1.2%) developed cardiovascular SAEs including two cases of chest pain and one myocardial infarction. There were single SAE reports for pneumonia and constipation. There was one subject who developed severe withdrawal when he discontinued from therapy at the end of the one year study period. This subject developed visual hallucinations, insomnia for four nights, chest pain, and tachycardia.

Details of the case summaries of the SAEs are provided in Appendix 10.1.4.

Table 7.1.2 summarizes the SAEs by body system and preferred term for the three double blind studies. No 200 mg subject had an SAE. Some subjects had two or three SAEs, so the column totals exceed the number of patients, 33, who had at least one SAE.

Table 7.1.2: Serious Adverse Events in all Double-Blind Studies.

Body System	**Preferred Term**	**100 mg N = 216 N - %**	**300 mg N = 849 N**	**300 mg %**	**Placebo N = 430 N**	**Placebo %**
BODY AS A WHOLE	ACCIDENTAL INJURY	0	0	0.00	1	0.23
	CARCINOMA	0	0	0.00	1	0.23
	CELLULITIS	0	2	0.24	0	0.00
	CHEST PAIN	0	2	0.24	0	0.00
	SPONDYLOLISTHESIS	0	1	0.12	0	0.00
CARDIOVASCULAR	ANGINA PECTORIS	0	1	0.12	0	0.00
	ATRIAL FIBRILLATION	0	0	0.00	1	0.23
	CHF	0	0	0.00	1	0.23
	CAD	0	0	0.00	1	0.23
	DVT	0	1	0.12	0	0.00
	HYPERTENSION	0	1	0.12	0	0.00
	HYPOTENSION	0	0	0.00	1	0.23
	MI	1 – 0.5%	0	0.00	3	0.70
DIGESTIVE	COLITIS	0	1	0.12	0	0.00
	GASTRITIS	0	1	0.12	0	0.00
	GI CARCINOMA	0	1	0.12	0	0.00
	GI PERFORATION	0	1	0.12	0	0.00
	INTESTINAL	0	0	0.00	1	0.23

	OBSTRUCTION					
METAB / NUTRITION	BUN INCREASED	0	1	0.12	0	0.00
	HYPERCALCEMIA	0	1	0.12	0	0.00
NERVOUS	CEREBRAL ISCHEMIA	0	1	0.12	0	0.00
	CONVULSION	0	1	0.12	0	0.00
	PARALYSIS	0	1	0.12	0	0.00
	VERTIGO	0	1	0.12	0	0.00
RESPIRATORY	ASTHMA	0	1	0.12	1	0.23
	LUNG DISORDER	0	0	0.00	1	0.23
	PNEUMONIA	0	2	0.24	2	0.47
SKIN / APPENDAGES	ANGIOEDEMA	0	1	0.12	0	0.00
UROGENITAL	CERVIX NEOPLASM	0	1	0.12	0	0.00
	KIDNEY CALCULUS	0	0	0.00	1	0.23
	PYELONEPHRITIS	0	0	0.00	1	0.23

Overall, there is no pattern seen in the review of these SAEs. The predominant organ system is the cardiovascular system. The placebo incidence rate, however, is higher than the tramadol rate. Otherwise, there is an incidence rate of one or two in any one preferred term SAE. The clinical investigators reported two of these SAEs as being related to tramadol. The one unequivocal case in my opinion is the case of severe withdrawal described above. The remainder of the SAEs could be considered exacerbations of the underlying medical conditions of an elderly population. Pharmacologically, a drug-disease interaction is not evident in my review of these SAEs.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

A large percentage of patients discontinued secondary to adverse events (AEs). The adverse event discontinuation rate increased with the higher doses. The rates rose from 12% to 24% to 35% from the 100 to 200 to 300 mg dose. The placebo AE discontinuation rate was 25%. The placebo group had the highest rate of discontinuation for treatment failure at 10%. In comparison, rates of discontinuation for treatment failure were 5.6%, 3.7% and 8.5% for the 100 mg, 200mg, and 300 mg groups respectively.

Only one subject was lost to follow-up in the 100 and 200 mg groups. Percentages were higher in the placebo and 300 mg groups which included the 12 month long-term subjects. The lost to follow-up rate was 3.2% for the 300 mg group, slightly higher that the 2.1% rate for the placebo group.

Table 7.1.3.1. Reasons for discontinuation by treatment group in double-blind studies.

	Tramadol			
Termination Reason	100 mg 216 subjects N - (%)	200 mg 217 subjects N - (%)	300 mg 849 subjects N - (%)	Placebo 430 subjects N - (%)
Completed	83 – (38)	76 – (35)	167 – (20)	103 – (25)
Adverse Event	26 – (12)	51 – (24)	293 – (35)	48 – (11)
Treatment Failure	12 – (5.6)	8 – (3.7)	72 – (8.5)	42 – (10)
Worsening Pathology	0	0	1 – (0.1)	0
Intercurrent Illness	0	3 – (1.4)	8 – (0.9)	1 – (0.2)
Lost to Follow-up	1 – (0.5)	0	27 – (3.2)	9 – (2.1)
Withdrew Consent	5 – (2.3)	1 – (0.5)	23 – (2.7)	7 – (1.6)
Non-Compliant	3 – (1.4)	4 – (1.8)	3 – (0.5)	2 – (0.5)
Protocol Violation	4 – (1.9)	2 – (0.9)	39 – (4.6)	15 – (3.5)
Not eligible	0	1 – (0.5)	2 – (0.5)	0
Patient's Best Interest	0	0	62 – (7.3)	19 – (4.4)

7.1.3.2 Adverse events associated with dropouts

The adverse events that most commonly led to premature discontinuation were expected based upon the pharmacology of tramadol. The following discussion focuses on AEs that led to discontinuation in greater than 3% of the active drug groups. Table 7.1.3.2 includes AEs that were reported in $\geq$ 1% of subjects who discontinued because of an adverse event. Overall, the rate of dropout due to AEs was similar in the 100 mg and placebo groups (approximately 12%), and was greater for the 200 mg (24%) and 300 mg (35%) groups.

Gastrointestinal adverse effects are an opiate class effect. Nausea was the most common adverse event to result in early termination in the Tramadol ER trials. There was also evidence for a dose effect. The rate of discontinuation due to nausea increased from 5.6% for the 100 mg dose, to 16% for the 300 mg dose. Nausea was reported 2.3% of the placebo subjects. Vomiting, likewise, was much higher in tramadol drug groups when compared to the placebo group dropout rate of 0.9%. Discontinuation for vomiting, however, did not demonstrate a dose response. The

drop out rates for the 100 mg, 200 mg, and 300 mg doses were respectively, 4.2%, 8.8% and 6.2%. Drop out due to constipation also demonstrated a dose dependent pattern. In the high dose, Tramadol ER 300 mg group, 10.4% discontinued due to constipation. This rate was about half, 5.1%, for the Tramadol ER 200 mg group, while no Tramadol ER 100 mg subject discontinued for this reason. Dry mouth was another common reason for discontinuation: Tramadol ER 300 mg group, 7.2%; the placebo and Tramadol ER 100 mg groups had the same rate of 0.5%; while the rate in the Tramadol ER 200 mg group was 3.2%. Finally, anorexia was another reason for subjects discontinuing the trials. The anorexia discontinuation reporting rate was 3.7% for the Tramadol ER 300 mg dose compared to 0.9% for the 100 mg dose, and 1.8% for the 200 mg dose. No placebo subjects discontinued due to anorexia.

Opiate and norepinephrine/serotonin reuptake inhibiting drugs pharmacologically produce nervous system effects. These pharmacologic actions not surprisingly may produce dose-dependent effects that could lead to terminations due to adverse events. Somnolence was a reported reason for termination in 9.8% of the Tramadol ER 300 mg subjects, while 0.5% of the placebo subjects reported this AE. A much lower rate was seen for the 100 and 200 mg strength groups: 3.7% and 4.2%, respectively. Dizziness was another frequent adverse event associated with dropout. This rate was 7.8% at the 200 mg strength, and the 300 mg group rate was similar at 7.9%. These AE discontinuation rates are much higher than the 1.9% for the placebo group. The discontinuation rate was 3.2% at the 100 mg dose. Although considered under the "body system as a whole" category two other preferred term adverse event terminations - headache and asthenia - could also be considered nervous system related. The rate of discontinuation due to asthenia AE also appeared to demonstrate a dose-dependent pattern. Asthenia discontinuation for placebo was 0.5%. This AE rate rose from 1.9% to 4.2% to 5.2% with increasing tramadol dose. Headache was an AE that led to termination of 7.4% of Tramadol ER 300 mg patients. This rate ranged between 3.2 to 3.7% for the other groups.

Two skin-related adverse events were responsible for discontinuations in over 3% of the Tramadol ER 300 mg group. These AEs were pruritus (4.6%) and sweating (4.0%). Rates of dropout due to sweating were the same 0.5% rate in the other treatment groups, while pruritus manifested a dose-dependent increase. The pruritus AE reporting rate in dropouts was 0.5% for placebo. This rate was 0.9% in the 100 mg group and increased to 2.8% for the 200 mg group.

Table 7.1.3.2. Reporting rates of AEs leading to subject discontinuations reported at a rate above 1% in a treatment group in the double-blind trials.

BODY SYSTEM	**PREFERRED TERM**	**100 MG N = 216**		**200 MG N = 217**		**300 MG N = 849**		**PBO N = 430**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
BODY AS A WHOLE	HEADACHE	8	3.7	7	3.23	63	7.42	14	3.26
	ASTHENIA	4	1.85	9	4.15	44	5.18	2	0.47
	ABDOMINAL PAIN	2	0.93	4	1.84	15	1.77	5	1.16
	CHILLS	0	0	0	0	13	1.53	0	0

CARDIOVASCULAR	VASODILATATION	1	0.46	0	0	17	2.00	1	0.23
	HYPERTENSION	0	0	4	1.84	12	1.41	0	0
DIGESTIVE	NAUSEA	12	5.56	25	11.52	136	16.02	10	2.33
	CONSTIPATION	0	0	11	5.07	88	10.37	2	0.47
	DRY MOUTH	1	0.46	7	3.23	61	7.18	2	0.47
	VOMITING	9	4.17	19	8.76	52	6.12	4	0.93
	ANOREXIA	2	0.93	4	1.84	31	3.65	0	0
	DYSPEPSIA	0	0	0	0	24	2.83	4	0.93
	DIARRHEA	0	0	5	2.3	12	1.41	6	1.4
METABOLIC / NUTRITION	WEIGHT LOSS	0	0	0	0	11	1.30	0	0
MUSCULOSKELETAL	ARTHRALGIA	1	0.46	1	0.46	12	1.41	1	0.23
NERVOUS	SOMNOLENCE	8	3.7	9	4.15	83	9.78	2	0.47
	DIZZINESS	7	3.24	17	7.83	67	7.89	8	1.86
	NERVOUSNESS	0	0	0	0	23	2.71	1	0.23
	INSOMNIA	1	0.46	1	0.46	22	2.59	1	0.23
	DEPRESSION	2	0.93	2	0.92	13	1.53	1	0.23
	ANXIETY	0	0	2	0.92	12	1.41	1	0.23
	DEPERSONALIZATION	1	0.46	0	0	12	1.41	1	0.23
	APATHY	0	0	0	0	9	1.06	0	0
	CONFUSION	0	0	2	0.92	9	1.06	1	0.23
RESPIRATORY	RHINITIS	0	0	0	0	12	1.41	2	0.47
SKIN / APPENDAGES	PRURITUS	2	0.93	6	2.76	39	4.59	2	0.47
	SWEATING	1	0.46	1	0.46	34	4.00	2	0.47
	RASH	1	0.46	0	0	12	1.41	2	0.47
UROGENITAL	URINARY TRACT INFECTION	1	0.46	0	0	10	1.18	1	0.23

7.1.3.3 Other significant adverse events

None

7.1.4 Other Search Strategies

Using iReview, an attempt was made to determine if some adverse events were associated with non-compliance. Nervousness, insomnia, anxiety and sweating might represent signs of withdrawal in non-compliant patients. The coding of compliance was mostly greater than or less than 90% for the interval between study visits. Since the patient diary did not record the exact days when study medication may have been missed, our search could not correlate AEs with compliance.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events (AEs) were to be spontaneously reported by the patient. The investigator was also charged with the detection and recording of adverse events. These AEs were to be followed to completion.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The Applicant used the COSTART dictionary for reporting adverse events. A review of the investigator terms appeared to correlate well with the coding of the preferred terms.

7.1.5.3 Incidence of common adverse events

7.1.5.4 Common adverse event tables

Many of the common adverse events were similar to the adverse event related to discontinuation of treatment. The gastrointestinal and nervous systems again predominate.

Within the gastrointestinal system the common AEs, in order of highest frequency, were nausea, constipation, dry mouth, vomiting, and anorexia. Except for vomiting, these GI AEs showed a dose dependent pattern. The most common adverse event for Tramadol ER (all doses) was nausea, with a rate three to four times higher in the study drug groups compared to placebo. Nausea occurred almost four times more commonly in the 300 mg dose, 24.6%, compared to placebo, 6.3%. The AE rates in the lower doses were 17.6% for the 100 mg dose and 20.3% for the 200 mg dose group. Vomiting did not demonstrate a dose escalating effect but was markedly more common in the tramadol group than placebo, which had a rate of 1.9%. Comparatively, the vomiting AE rate was 7.9% (100 mg), 11.5% (200 mg), and 9.9% (300 mg). Constipation followed nausea as the second most commonly reported AE for active drug. In the high dose, 300 mg, group the rate was 21.7%, while the placebo group rate was 4.7%. A dose dependent rate was again apparent as demonstrated by a rate of 9.7% (100 mg) and 14.3% (200 mg). No placebo subject reported anorexia, while there was a dose increasing rate noted for study drug, rising from 3.2% to 4.6% to 6.5% at the 300 mg dose. Dry mouth evidenced an increasing rate

with higher doses. In the Tramadol ER 100 mg group the dry mouth rate was 5.6% compared to the lower placebo rate of 3.5%. The 200 mg group rate was 8.3% and a markedly higher rate of 14.7% rate was seen in the Tramadol ER 300 mg group.

The nervous system also had a high number of preferred term adverse events. Somnolence and dizziness were the most common nervous system AE dropouts. They are the two highest nervous system common adverse events. The somnolence AE rate for Tramadol ER 300 mg was 17.1%, notably higher than the placebo rate of 4.7%. Unlike AEs associated with discontinuations the common AE rate did not increase with dose; 16.2% (100 mg) versus 13.8% (200 mg). Dizziness did demonstrate evidence for a dose effect although this may plateau at the 200 mg dose. The placebo group rate was 3.5%, while the rate was 8.8% at the 100 mg dose group, the rate increased to 13.8% for the 200 mg group and was 14.4% in the 300 mg group.

The next four adverse events in order of highest frequency at the Tramadol ER 300 mg frequency rate are insomnia (5.7%), nervousness (5.0%), anxiety (3.5%), and withdrawal (2.7%). The frequency rates for the 100 mg and 200 mg groups did not significantly differ from the placebo group rates which were all less than 2%. Insomnia, nervousness, and anxiety may represent withdrawal symptoms.

An attempt was made to search the database to determine if poor compliance might have been associated with these adverse events that are suggestive of withdrawal. The database did include a compliance measure. At each visit a determination as to whether there was at least 90% compliance was recorded. A search of some patients who had these adverse events was attempted. In most cases it was difficult to determine if episodes of non-compliance preceded or followed a specific adverse event.

Skin was another body system with common adverse event rates different from placebo. Pruritus and sweating are the two most prevalent. These two skin adverse events resulted in a significant number of AE discontinuations. Pruritus, a known opiate adverse effect, was at the top of the list. The rates were different for the 200 mg (8.8%) and 300 mg (8.2%) groups compared to the similar rates of 2.8% and 2.6% for the 100 mg and placebo groups. The sweating common AE rate was highest for the Tramadol ER 300 mg subjects at 7.5% versus a 0.9% placebo rate. The 100 mg (4.6%) and 200 mg (3.2%) rates were intermediate. Rash was another common AE for the Tramadol ER 300 mg subjects at 2.8%, while the placebo rate was 0.9%. Tramadol ER 200 mg had the same rate as placebo, but the Tramadol ER 100 mg group had the higher rate of 1.9%. The etiology of the rash would be difficult to determine. Theoretically, rash might represent another manifestation of histamine release, e.g. similar to pruritus. The much lower rate seen in the Tramadol ER 200 mg group for rash relative to pruritus does not support this possible explanation.

Under body system as a whole headache was the most commonly reported AE, but the rate was not much higher than the placebo rate in any of the Tramadol ER groups. Asthenia which was associated with a significant number of discontinuations for AE demonstrated a dose dependent pattern. While 2.3% of the placebo group had this AE, the rate rose from 3.7% in the 100 mg

group to 7.4% in the 200 mg group to 9.4% in the 300 mg group. Asthenia most likely represents a pharmacologic opiate action. Accidental injury would not be an unexpected adverse event. Because of the CNS altering property of opiates, accidental injury is a recognized adverse event of opiates, especially reported in the elderly. Accidental injury was reported in 3% of the Tramadol ER 300 mg group. This compared to 1.4% for the Tramadol ER 100 mg and placebo groups, while Tramadol ER 200 mg was slightly higher at 1.8%.

Under respiratory system the most common adverse event was sinusitis. It was only noted at a higher rate from placebo in the Tramadol ER 300 mg group, 5.3% vs 2.6% for placebo. The etiology for this adverse event is not readily apparent. Opiates suppress secretions and might cause dryness to the sinuses. The second most common respiratory adverse event was rhinitis. The Tramadol ER 300 mg rate was higher than placebo, 3.4% vs 2.6%, which were both higher than the 100 and 200 mg dose groups. If rhinitis represented rhinorrhea, then it could be another withdrawal symptom, but this can not be separated from subjects who developed upper respiratory infections.

The cardiovascular system also had two common AEs with significant differences from placebo. These were hypertension and vasodilatation which can be again considered opposites of one another. Hypertension was a commonly reported adverse event in the 200 and 300 mg groups at 3.7% and 4.1% respectively compared to the rates of 0.9% for placebo and 0.5% for the Tramadol ER 100 mg groups. Mechanistically, hypertension might again be consistent with withdrawal from an opioid. Vasodilatation was noted as a common adverse event in the 300 mg group with the higher rate of 4.0% compared to the placebo rate of 0.9%.

In summary, the common adverse events are mostly consistent with known opioid class effects. Many of the gastrointestinal and nervous system effects also demonstrated a dose dependent effect.

Table 7.1.5.4.A. Common adverse events at a rate greater than 1% in treated subjects any dose group - double-blind trials.

BODY SYSTEM	**PREFERRED TERM**	**100 MG N = 216**		**200 MG N = 217**		**300 MG N = 849**		**PBO N = 430**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
BODY AS A WHOLE	HEADACHE	37	17.13	32	14.75	138	16.25	63	14.65
	ASTHENIA	8	3.70	16	7.37	80	9.42	10	2.33
	INFECTION	5	2.31	6	2.76	48	5.65	30	6.98
	ABDOMINAL PAIN	6	2.78	6	2.76	38	4.48	17	3.95
	BACK PAIN	5	2.31	3	1.38	28	3.30	16	3.72
	ACCIDENTAL INJURY	3	1.39	4	1.84	25	2.94	6	1.40
	PAIN	0	0.00	3	1.38	23	2.71	8	1.86
	CHILLS	0	0.00	1	0.46	28	3.30	2	0.47
	FLU SYNDROME	4	1.85	7	3.23	17	2.00	3	0.70

	FEVER	1	0.46	1	0.46	14	1.65	3	0.70
	CHEST PAIN	0	0.00	2	0.92	11	1.30	4	0.93
	PELVIC PAIN	0	0.00	0	0.00	10	1.18	1	0.23
CARDIOVASCULAR	HYPERTENSION	1	0.46	8	3.69	35	4.12	4	0.93
	VASODILATATION	1	0.46	1	0.46	34	4.00	3	0.70
	MIGRAINE	2	0.93	0	0.00	5	0.59	2	0.47
	ELECTROCARDIOGRAM ABNORMAL	3	1.39	0	0.00	4	0.47	0	0.00
DIGESTIVE	NAUSEA	38	17.59	44	20.28	209	24.62	27	6.28
	CONSTIPATION	21	9.72	31	14.29	184	21.67	20	4.65
	DRY MOUTH	12	5.56	18	8.29	125	14.72	15	3.49
	VOMITING	17	7.87	25	11.52	84	9.89	8	1.86
	ANOREXIA	7	3.24	10	4.61	55	6.48	0	0.00
	DYSPEPSIA	6	2.78	5	2.30	46	5.42	17	3.95
	DIARRHEA	6	2.78	8	3.69	37	4.36	16	3.72
	GASTROINTESTINAL DISORDER	1	0.46	1	0.46	13	1.53	5	1.16
	FLATULENCE	4	1.85	1	0.46	8	0.94	6	1.40
ENDOCRINE	HYPOTHYROIDISM	0	0.00	0	0.00	1	0.12	0	0.00
HEMIC / LYMPHATIC	ECCHYMOSIS	1	0.46	1	0.46	9	1.06	1	0.23
METABOLIC / NUTRITION	WEIGHT LOSS	0	0.00	2	0.92	20	2.36	1	0.23
	PERIPHERAL EDEMA	1	0.46	2	0.92	13	1.53	4	0.93
	EDEMA	1	0.46	2	0.92	10	1.18	4	0.93
	HYPERGLYCEMIA	0	0.00	0	0.00	9	1.06	2	0.47
MUSCULOSKELETAL	ARTHRALGIA	5	2.31	8	3.69	48	5.65	15	3.49
	MYALGIA	4	1.85	2	0.92	16	1.88	8	1.86
	ARTHROSIS	3	1.39	2	0.92	5	0.59	1	0.23
NERVOUS	SOMNOLENCE	35	16.20	30	13.82	145	17.08	20	4.65
	DIZZINESS	19	8.80	30	13.82	122	14.37	26	6.05
	INSOMNIA	3	1.39	4	1.84	48	5.65	8	1.86
	NERVOUSNESS	0	0.00	3	1.38	42	4.95	4	0.93
	ANXIETY	2	0.93	3	1.38	30	3.53	5	1.16
	WITHDRAWAL SYNDROME	0	0.00	0	0.00	23	2.71	3	0.70
	DEPRESSION	4	1.85	3	1.38	22	2.59	2	0.47

	APATHY	0	0.00	0	0.00	17	2.00	1	0.23
	PARESTHESIA	3	1.39	2	0.92	15	1.77	6	1.40
	DEPERSONALIZATION	1	0.46	0	0.00	15	1.77	1	0.23
	AGITATION	0	0.00	0	0.00	15	1.77	0	0.00
	CONFUSION	0	0.00	2	0.92	13	1.53	2	0.47
	TREMOR	0	0.00	0	0.00	11	1.30	3	0.70
	EUPHORIA	1	0.46	3	1.38	8	0.94	1	0.23
	HYPERTONIA	3	1.39	0	0.00	3	0.35	2	0.47
RESPIRATORY	SINUSITIS	2	0.93	2	0.92	45	5.30	11	2.56
	RHINITIS	2	0.93	1	0.46	29	3.42	11	2.56
	BRONCHITIS	3	1.39	3	1.38	23	2.71	5	1.16
	COUGH INCREASED	3	1.39	1	0.46	14	1.65	9	2.09
	PHARYNGITIS	2	0.93	2	0.92	11	1.30	4	0.93
SKIN / APPENDAGES	PRURITUS	6	2.78	19	8.76	70	8.24	11	2.56
	SWEATING	10	4.63	7	3.23	64	7.54	4	0.93
	RASH	4	1.85	2	0.92	24	2.83	4	0.93
SPECIAL SENSES	AMBLYOPIA	2	0.93	0	0.00	3	0.35	2	0.47
UROGENITAL	URINARY TRACT INFECTION	5	2.31	3	1.38	30	3.53	8	1.86
	URINE ABNORMALITY	2	0.93	2	0.92	7	0.82	3	0.70

Table 7.1.5.4.B. Common AEs occurring with greatest frequency in the Tramadol ER 300 mg dose > 5% of patients – double blind trials

PREFERRED TERM	TRAMADOL						PBO N = 430	
	100 MG N = 216		200 MG N = 217		300 MG N = 849			
	N	%	N	%	N	%	N	%
NAUSEA	38	17.59	44	20.28	209	24.62	27	6.28
CONSTIPATION	21	9.72	31	14.29	184	21.67	20	4.65
SOMNOLENCE	35	16.20	30	13.82	145	17.08	20	4.65
HEADACHE	37	17.13	32	14.75	138	16.25	63	14.65
DRY MOUTH	12	5.56	18	8.29	125	14.72	15	3.49
DIZZINESS	19	8.80	30	13.82	122	14.37	26	6.05
VOMITING	17	7.87	25	11.52	84	9.89	8	1.86
ASTHENIA	8	3.70	16	7.37	80	9.42	10	2.33

PRURITUS	6	2.78	19	8.76	70	8.24	11	2.56
SWEATING	10	4.63	7	3.23	64	7.54	4	0.93
ANOREXIA	7	3.24	10	4.61	55	6.48	0	0.00
INFECTION	5	2.31	6	2.76	48	5.65	30	6.98
ARTHRALGIA	5	2.31	8	3.69	48	5.65	15	3.49
INSOMNIA	3	1.39	4	1.84	48	5.65	8	1.86
DYSPEPSIA	6	2.78	5	2.30	46	5.42	17	3.95
SINUSITIS	2	0.93	2	0.92	45	5.30	11	2.56
NERVOUSNESS	0	0.00	3	1.38	42	4.95	4	0.93

Table 7.1.5.4C. Common AEs occurring with greatest frequency in the Tramadol ER 300 mg dose > 5% of patients – open-label trial

BODY SYSTEM	**PREFERRED TERM**	**300 MG N = 244**	
		N	**%**
BODY AS A WHOLE	HEADACHE	60	24.6
	INFECTION	32	13.1
	ASTHENIA	28	11.5
	FLU SYNDROME	22	9.0
	ACCIDENTAL INJURY	21	8.6
	PAIN	18	7.4
DIGESTIVE	NAUSEA	61	25.0
	DRY MOUTH	45	18.4
	CONSTIPATION	36	14.8
	VOMITING	30	12.3
	DIARRHEA	18	7.4
MUSCULOSKELETAL	ARTHRALGIA	17	7.0
NERVOUS	SOMNOLENCE	50	20.5
	DIZZINESS	41	16.8
	INSOMNIA	32	13.1
	NERVOUSNESS	20	8.2
	ANXIETY	13	5.3
	EUPHORIA	13	5.3
RESPIRATORY	RHINITIS	22	9.0

SKIN / APPENDAGES	SWEATING	45	18.4
	PRURITUS	23	9.4

7.1.5.5 Identifying common and drug-related adverse events

Refer to Section 7.1.5.4.

7.1.5.6 Additional analyses and explorations

Refer to Section 7.1.5.4.

7.1.6 Less Common Adverse Events

Exploration for less common adverse events was not done. There are 11 years of market experience with tramadol Ultram and the less frequent effects of treatment have already been characterized.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing was performed at baseline and then at the end of study. A short term laboratory database contained subjects who terminated early or completed the three months for the Trials 01 and 02. A long-term database comprised subjects who continued into an open label trial, TRAMCT02.03, from the two 3 month trials and then also subjects in the TRAMCT02.04 twelve month double-blind trial. The laboratory assessments included hematology, clinical chemistry, and urine. The specific hematologic measurements were RBC count, hemoglobin, hematocrit, WBC count with a differential, and platelets. Serum chemistry included glucose, BUN, SGOT (AST), SGPT (ALT), alkaline phosphatase, GGT, total bilirubin, sodium, potassium, chloride and calcium. Urinalysis included pH, specific gravity, glucose, ketones, bilirubin, protein, occult blood and microscopy. In addition a pregnancy test was performed at every study visit.

In the short-term database 1697 subjects had baseline and follow-up testing completed. This included 217, 220, 839, and 421 subjects in the 100 mg, 200 mg, 300 mg, and placebo doses, respectively. In the long-term database, 606 subjects had 52 week data.

Table 7.1.7.1 Summary of Exposed Subjects with follow-up laboratory assessments at 12 and 52 weeks.

Time	Tramadol 100 mg	Tramadol 200 mg	Tramadol 300 mg	Placebo
12 weeks	217	220	839	421
52 weeks	60	61	317	168

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The three double-blind and the one open-label trial were evaluated for effects of Cip-Tramadol ER on laboratory parameters.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The mean laboratory values at the beginning and end of study where compared as well as the change from baseline. No clinically significant differences were seen in either the means or the mean change.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.7.3.2.1 Serum Electrolyte Outliers

Significant changes in electrolytes were not reported by the Applicant.

Since one of the common adverse reactions that subjects developed was nausea and vomiting, dehydration was a potential consequence. Hypernatremia and renal insufficiency can be manifestations of significant dehydration.

The short-term double-blind database contained three (3/1697, 0.2%) subjects who developed an abnormal serum sodium level over 148 meq/L. All three serum sodiums were 149 meq/L; two of these occurring in placebo subjects. The long-term database contained only one subject (1/606, 0.2%) who developed an abnormal serum sodium level (>148 meq/L). The Tramadol ER subject's serum sodium was 150 meq/L; an increase of 6 meq/L from baseline.

Hyponatremia might have been a theoretical concern for Tramadol ER (Table 7.1.7.3.2.1). The Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) has occurred with some drugs that block the reuptake of serotonin. However, there was no evidence for Tramadol ER to induce hyponatremia. Eleven (11/606, 1.8%) subjects had hyponatremia at the end of 52 weeks. Of these 6 (6/168, 3.6%) were placebo subjects. No subject had a serum sodium less than 130 meq/L.

Table 7.1.7.3.2.1. Subjects who developed hyponatremia at the end of the long-term studies.

Serum Sodium	Baseline	Change	Tramadol 200 mg	Tramadol 300 mg	Placebo
131	136	-5	0	0	1
132	140	-8	0	0	1
132	142	-10	0	1	0
132	145	-13	0	1	0
133	135	-2	1	0	0
133	138	-5	0	1	0
133	142	-9	0	0	1
133	143	-10	0	0	1
134	139	-5	0	1	1
134	142	-8	0	0	1

The safety database does not contain evidence for tramadol-induced abnormalities of the serum sodium.

7.1.7.3.2.2 Renal Function Test Outliers

Theoretically, subjects taking Tramadol ER might be at some risk for developing renal insufficiency. Vomiting was a common adverse effect. Moderate to severe vomiting may cause dehydration where renal insufficiency might develop. Subjects who have underlying renal insufficiency might have an additional risk. One SAE was related to a BUN increase.

In the short-term trials, 9 (9/1697, 0.5%) subjects [Tramadol ER 100 mg (1/217, 0.5%), Tramadol ER 200 mg (1/220, 0.5%), Tramadol ER 300 mg (5/839, 0.6%) and placebo 2/421, 0.5%)] had a serum BUN increase by at least 8 mg/dL and rise over 30 mg/dL. Therefore, this was not disproportionate to the 3:1 active drug to placebo ratio. Five long-term subjects developed a serum BUN greater than 30 mg/dL. All five subjects were on active drug. Two subjects who had serum BUNs greater than 30 mg/dL at baseline developed a serum BUN of 52 mg/dL and did not complete the study. Thirteen subjects (10 study drug and 3 placebo) in the short-term database had abnormal serum BUNs greater than 30 mg/dL. These subjects did not develop significant changes in their serum BUN.

Table 7.1.7.3.2.2A. Subjects who had a serum BUN increase over 7 mg/dL and level greater than 30 mg/dL at the three month end of study – short-term database.

End BUN	Baseline	Change	100 mg	200 mg	300 mg	Placebo
31	22	9	0	0	1	0
32	22	10	0	0	1	0
32	24	8	0	0	1	0
33	25	8	0	0	0	1
33	20	13	0	1	0	0
34	24	10	0	0	1	0

34	24	10	0	0	0	1
34	25	9	0	0	1	0
37	15	22	1	0	0	0

Table 7.1.7.3.2.2B. Subjects who developed a serum Blood Urea Nitrogen (BUN) greater than 30 mg/dL at the end of the study - long-term database.

BUN	Baseline	Change	200 mg	300 mg	Placebo
31	27	4	1	0	0
32	20	12	0	1	0
38	19	19	0	1	0
52	36	16	0	1	0
52	39	13	0	1	0

Table 7.1.7.3.2.2C. Subjects with baseline abnormal serums BUNs compared to the end of study BUN - short-term trials.

BUN	Baseline	Change	100 mg	200 mg	300 mg	Placebo
32	34	-2	1	0	0	0
33	35	-2	0	1	0	0
33	38	-5	0	0	0	1
34	39	-5	0	0	1	0
35	32	3	0	0	1	0
35	38	-3	0	0	1	0
36	34	2	0	0	0	1
37	39	-2	0	0	1	0
38	32	6	0	0	1	0
39	41	-2	0	0	0	1
41	42	-1	1	0	0	0
43	37	6	0	0	1	0
56	51	5	1	0	0	0

In the short-term database there were five Tramadol ER subjects who had their serum creatinines increase by 0.5 mg/dL or more and develop abnormal serum creatinines above 1.6 mg/dL. In one subject taking Tramadol ER 300 this increase was from 0.9 mg/dL to 2.6 mg/dL. In the long-term database three subjects developed serum creatinine levels greater than 1.7 mg/dL. Two of these three were the same subjects that developed the serum BUN level of 52 mg/dL. The baseline creatinines were 1.3 and 1.7 mg/dL. The third subject was administered Tramadol ER 200 mg and had a baseline creatinine of 1.1 mg/dL.

Table 7.1.7.3.2.2D. Subjects whose developed an abnormal serum creatinine having increased by 0.5 mg/dL – short-term database.

Creatinine	Baseline	Change	100 mg	200 mg	300 mg	Placebo
1.6	1.1	0.5	0	1	0	0
1.8	1.1	0.7	1	0	0	0

1.9	1.2	0.7	0	0	1	0
1.9	1.3	0.6	0	0	1	0
2.6	0.9	1.7	0	0	1	0

The renal function tests do not contain evidence that Tramadol ER causes nephrotoxicity or renal insufficiency. None the less, it would be prudent for a clinician treating a patient administered Tramadol ER to monitor renal function tests should vomiting develop.

7.1.7.3.2.3 Hepatic Function Outliers

During part of this review, I was assigned to receive safety reports for the referenced drug Ultram. I have received spontaneous safety reports from AERS (Adverse Event Reporting System) describing cases of hepatic transaminase elevations that the author of the report considered related to tramadol. In the short-term database one subject on Tramadol ER 300 mg developed an AST greater than 100 IU/L. This result was an increase from 54 IU/L. Five subjects developed an ALT greater than 100 IU/L, maximum 159 IU/L. One subject was on placebo, while three were taking 300 mg and one was administered 200 mg (Table 1). In the long term database of 606 patients no subject had a measured AST or ALT level greater than 80 IU/L.

Table 7.1.7.3.2.3A. Subjects developing serum alanine transferase levels greater than 100 IU/L – short-term database.

ALT	Baseline	Change	200 mg	300 mg	Placebo
104	31	73	0	0	1
106	42	64	0	1	0
129	19	110	1	0	0
135	27	108	0	1	0
159	24	135	0	1	0

Changes in serum gamma glutamyl transpeptidase (GGT) elevations did not show evidence for a difference between study drug and placebo (Table 7.1.7.3.2.3B). Of the 17 patients detailed, four were placebo including the subject with the highest serum GGT level.

In the long-term database the two subjects that had an increase of over 100 IU/L from baseline were placebo subjects. Only one subject had a serum GGT level over 200 IU/L. This Tramadol ER 300 subject's GGT rose from 448 to 469 IU/L.

Table 7.1.7.3.2.3B. Subjects who had a serum GGT increase of at least 40 IU/L to over 100 IU/L – short-term database.

GGT	Baseline	Change	100 mg	200 mg	300 mg	Placebo
101	44	57	0	0	1	0
102	45	57	0	0	1	0

111	50	61	0	0	1	0
112	53	59	0	0	1	0
125	72	53	0	0	1	0
130	49	81	0	0	0	1
137	78	59	0	0	1	0
139	96	43	0	0	0	1
145	70	75	0	0	1	0
148	50	98	0	0	0	1
157	105	52	1	0	0	0
166	111	55	0	1	0	0
170	48	122	0	0	1	0
171	97	74	0	0	1	0
228	30	198	0	1	0	0
282	153	129	0	0	1	0
337	223	114	0	0	0	1

In conclusion, in the Cip-Tramadol ER trials, there was no pattern of serum transaminases changes suggestive of differential hepatotoxicity between active drug and placebo.

7.1.7.3.2.4 Serum Glucose Outliers

The analysis of outliers for serum glucose levels notes one trend. There appears to be a disproportionate number of study subjects who developed serum glucose levels less than 60 mg/dL. In the short term database, seven of eight subjects were on study drug. Of note is the one placebo subject's level was 57 mg/dL (Table 7.1.7.3.2.4A), while five study drug subjects had serum glucose levels less than 50 mg/dL. In the long-term database, there were only three subjects with serum glucose levels less than 60 mg/dL (Table 7.1.7.3.2.4b). All three subjects were taking Tramadol ER 300 mg.

Table 7.1.7.3.2.4A. Subjects with serum glucose less than 60 mg/dL at end of study – short-term database

Glucose	Baseline	Change	100 mg	200 mg	300 mg	Placebo
33	93	-60	0	0	1	0
38	113	-75	1	0	0	0
41	77	-36	0	1	0	0
41	107	-66	1	0	0	0
48	174	-126	1	0	0	0
53	76	-23	0	1	0	0
53	96	-43	1	0	0	0
57	99	-42	0	0	0	1

Table 7.1.7.3.2.4B. Subjects with serum glucose less than 60 mg/dL at end of study – long-term database. (All subjects were taking Tramadol ER 300 mg).

Glucose	Baseline	Change

46	84	-38
50	126	-76
54	84	-30

Hypoglycemia was listed as a treatment emergent adverse event for one subject. Catecholamines are important to the regulation of glucose. Tramadol does block the reuptake of norepinephrine. Tramadol subjects do develop altered levels of consciousness as a result of the opioid agonism, hypoglycemia is always considered part of the differential for altered levels of consciousness. Surveillance of tramadol products, however, has not uncovered episodes of hypoglycemia. At this time, these episodes of hypoglycemia predominantly seen in the tramadol subjects represent an observation.

No other laboratory outlier analyses found clinically significant abnormalities.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

The two discontinuations for a laboratory abnormality were increased BUN and hypercalcemia. The subject with the elevated BUN was suffering from prostatic cancer. One subject developed hypercalcemia, serum calcium 13.5 mg/dL. This developed four days after tramadol administration and persisted for one week without an etiology determined. A search of the dataset however found one other tramadol subject who developed a serum calcium level greater than 11.0 mg/dL. These two dropouts for laboratory abnormalities do not appear related to tramadol, but rather underlying medical conditions.

7.1.7.4 Additional analyses and explorations

Not further analyses were performed.

7.1.7.5 Special assessments

Not applicable.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The safety assessments focused upon two vital signs, pulse rate and blood pressure. Measurements were taken at all study visits. Individual studies did contain an analysis of the means at each study visit. The Applicant reported no significant changes in these vital signs between the study groups and placebo. The Applicant presented tables of these results that support their conclusion. The Integrated Summary of Safety (ISS) that the Applicant provided contains two databases of these vital sign measurements. One subset was for short-term, 3

months of exposure, and a second long-term 12 months of exposure. The databases, however, contained only the baseline and the end of study visits.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The three double-blind studies were selected for the vital sign analyses. TRAMCT02.01, TRAMCT02.02 and the first three months of TRAMCT02.04 comprise the short-term, 3 month, database. The ISS was used for the following analyses. A subset of completers was made. From this subset the mean pulse rates were compared between baseline and the end of study by treatment group. The mean change from baseline was also compared. The same analysis was performed for blood pressure as well. A long-term, 12 month, database was created in a similar manner as described above for the laboratory parameters. Subjects in TRAMCT02.03 and TRAMCT02.04 comprised the long-term database.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The mean vital sign data are found in the tables below.

Table 7.1.8.3.1A. Mean change from baseline pulse rate at end of study – short-term database.

Pulse (Short) bpm	100 mg	200 mg	300 mg	Placebo
Baseline	72 +/- 9	72 +/- 9	73 +/- 10	73 +/- 9
End of study	71 +/- 9	72 +/- 9	71 +/- 9	71 +/- 8
Mean Change	-1.6 +/- 9	-0.1 +/- 8	-1.5 +/- 11	-1.8 +/-10

Table 7.1.8.3.1B. Mean change from baseline pulse rate at end of study – long-term database.

Pulse (Long)	300 mg	Placebo
Baseline	73 +/- 10	75 +/- 11
End of study	72 +/- 10	72 +/- 12
Mean Change	-1.0 +/- 11	-2.1 +/- 10

Table 7.1.8.3.1C Mean change for systolic blood pressure at end of study – short-term database.

Systolic Blood Pressure (Short)	100 mg	200 mg	300 mg	Placebo
Baseline	131 +/- 16	131 +/- 15	130 +/- 14	130 +/- 15
End of study	130 +/- 15	130 +/- 14	129 +/- 16	130 +/- 15
Mean Change	-1.6 +/- 16	0.3 +/- 14	-0.7 +/- 18	-0.7 +/- 16

Table 7.1.8.3.1D Mean change for systolic blood pressure at end of study – long-term database.

Diastolic Blood Pressure (Short)	100 mg	200 mg	300 mg	Placebo
Baseline	78 +/- 9	78 +/- 8	80 +/- 7	78 +/- 8
End of study	77 +/- 8	77 +/- 8	78 +/- 9	79 +/- 9
Mean Change	-1.0 +/- 10	-0.3 +/- 8	-1.7 +/- 9	1.0 +/- 10

Table 7.1.8.3.1E Mean change for diastolic blood pressure at end of study – short-term database.

Systolic Blood Pressure (Long)	300 mg	Placebo
Baseline	129 +/- 14	131 +/-17
End of study	131 +/- 16	131 +/- 17
Mean Change	1.5 +/-16	0.8 +/-17

Table 7.1.8.3.1F Mean change for diastolic blood pressure at end of study – long-term database.

Diastolic Blood Pressure (Long)	300 mg	Placebo
Baseline	78 +/- 8	79 +/- 8
End of study	78 +/- 9	77 +/- 8
Mean Change	0 +/- 89	-1.2 +/- 10

The mean VS values were similar at baseline and at study end. The mean changes from baseline were not clinically significant. There was no pattern of differences between any tramadol group and placebo.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

In the short-term vital sign dataset there were few vital sign outliers. No subject had a heart rate greater than 105 bpm. No subject developed a diastolic blood pressure above 104mm Hg. In the long-term dataset again no tramadol subject developed a heart rate greater than 104 bpm. Only two subjects in the open label trial developed diastolic blood pressures greater than 100 mm Hg. One subject was taking Tramadol ER 100 mg and another was taking Tramadol ER 200 mg.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were two discontinuations for abnormal vital signs, one case of hypertension and one case of hypotension. The hypotension case was in a placebo subject. The hypertension case was a subject who stopped taking her blood pressure medications.

A theoretical concern exists that tramadol could cause some vital sign changes in some patients. Opioids in supratherapeutic doses or in combination with other drugs may lower blood pressure, while agents that impact norepinephrine and serotonin neurotransmission may possibly elevate blood pressure. In this safety database there was no evidence for tramadol inducing significant vital sign derangements.

7.1.8.4 Additional analyses and explorations

None.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiograms were obtained at baseline and end of study. The interpretation was recorded by the study investigator as normal or abnormal and if abnormal the reason and if the abnormality was considered clinically significant or not.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The three double-blind and the open-label trial trials were analyzed. Similar to the laboratory and vital sign data, the analyses were divided into a short-term, 3 months, database and a long-term database, 12 months.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Central tendency analyses were not performed because the structure of the data was categorical, normal and abnormal, and clinically significant or not clinically significant.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 9.1.9.3.2. Subjects who had ECGs considered abnormal clinically significant as a change from baseline at study end – short-term database.

	100 mg	200 mg	300 mg	Placebo

	N = 101 N - %	N = 77 N - %	N = 55 N - %	N = 80 N - %
ECG Abnormal Clinically significant Change from Baseline	1 (1.0%)	1 (1.3%)	4 (7.3%)	0

Subjects who enrolled in long-term studies also had 12 month ECGs. This subset only contained 2 (2/1021, 0.02%) subjects who developed abnormal clinically significant ECGs. One (1/61, 1.6%) subject was taking the 200 mg dose and the other was in the placebo group (1/261, 0.4%). No (0/639) Tramadol ER 300 mg subjects were in this category.

There is no evidence in the safety database that tramadol produces electrocardiographic changes.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

One discontinuation for an electrocardiogram abnormality, atrial fibrillation, occurred in a placebo subject.

7.1.9.4 Additional analyses and explorations

None

7.1.10 Immunogenicity

Not applicable

7.1.11 Human Carcinogenicity

No carcinogenic effect of tramadol has been observed. The Applicant did not perform carcinogenicity studies.

7.1.12 Special Safety Studies

No special safety studies were done or were required.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The active ingredient in Cip-Tramadol ER, tramadol, is an opioid. This product is, therefore, known to have a risk for both withdrawal phenomenon and abuse potential. Tramadol products (in any dose form) have not been scheduled by the DEA. In the initial Pre-IND meeting with the Agency the Applicant was informed that they were to address abuse dependence and potential.

The Applicant tested for abuse potential by the use of its' own scale, the (b) (4)
(b) (4)
(b) (4)
The Applicant interpreted these results, as indicating a low potential for drug abuse for Cip-Tramadol ER 300 mg that did not trend higher with longer duration. The use of an un-validated instrument makes interpretation of these results speculative.

Tramadol discontinuation has been associated with classical opioid withdrawal effects. Characteristic symptoms may include any of the following; anxiety, sweating, insomnia, rigors/tremors, nausea, diarrhea, rhinorrhea, piloerection, yawning, and hallucinations. These classic symptoms were reported as an SAE for one subject who discontinued Tramadol ER 300 mg after one year. The Applicant did test for opiate withdrawal at the end of the study. A validated instrument was used. The Clinical Opiate Withdrawal Scale (COWS) was administered at the final study visit, two weeks after drug discontinuation. The COWS is an 11-item tool to assess levels of opiate withdrawal and physical dependency. Total scores for 11 questions are grouped and give a withdrawal score of None (0-4), Mild (5-12), Moderate (13-24), Moderately Severe (25-36) and Severe (> 36) points. 696/873 Tramadol ER 300 mg subjects had this post-treatment assessment; the Mean+/-SD score was 1.1+/-2.3. 29/695 (4.2%) had mild withdrawal. 4/696 (0.6%) had moderate withdrawal. One subject (0.1%) had moderately severe withdrawal. 158/213 placebo subjects had the COWS administered. The placebo Mean+/-SD score was 0.76 +/-1.6. 6/158; 6/158 (3.8%) had scores consistent with mild withdrawal.

This reviewer's main criticism of this withdrawal assessment was the administration of the COWS a full two weeks after drug discontinuation. Since the half-life of Cip-Tramadol is about 8-9 hours, withdrawal signs and symptoms would be expected as early as 2-3 days after stopping the drug. The COWS should have been administered during this timeframe with a phone follow-up a few days later.

Both drug abuse potential and withdrawal are addressed in the reference labeled drug, Ultram. The Applicant's proposed label does not adequately address these concerns. Another question to be answered is whether subjects taking doses above 100 mg per day should be tapered down before discontinuation.

7.1.14 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data were collected during any clinical trials. Pregnancy tests were conducted at every visit. No pregnancies occurred is this population over the age of 40.

7.1.15 Assessment of Effect on Growth

The study population consisted of adults aged ≥ 40 years. Therefore, the effect of Cip-Tramadol ER on growth in this study population was not a concern and was not assessed.

7.1.16 Overdose Experience

There were no cases of overdose in this trial. Overdose for tramadol is well described and addressed in the tramadol label.

7.1.17 Postmarketing Experience

There is no post-marketing data for this reformulated tramadol product.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Safety datasets were submitted with the original NDA received 7/03/2006. An Integrated Summary of Safety (ISS) dataset was included. It included SAS Transport files (.xpt) for Adverse events in three datasets. There was an ADVERSE1.xpt file for the per Protocol subjects, an ADVERSE2.xpt for the 300 mg patients. There was then an ADVERSE3.xpt for all studies. This review focused on the Adverse1.xpt database to focus on the double-blind pivotal (b) (4) trials. For laboratory data the Applicant separated the results into two files, BIOCHEM1.xpt and BIOCHEM2.xpt. The BIOCHEM1 was for shorter-term exposure at 3 months or early termination, while the BIOCHEM2 was for longer term exposure of 12 months or early termination. Hematology (HAEM1.xpt and HAEM2.xpt) and Urinalysis tests (URINE1.xpt and URINE2.xpt) were likewise separated into short and long-term files. Electrocardiogram data was contained in one file, ECG.xpt. The vital sign data similar to laboratory was in short and long-term datasets, VITALS1.xpt and VITALS2.xpt. OPWTHDR.xpt contained files to assess for opiate withdrawal two weeks after the 12 month trials ended. The (b) (4) .xpt file contained data to evaluate for drug abuse potential.

7.2.1.1 Study type and design/patient enumeration

The total number of exposed subjects for all trials is 1474 subjects. Refer to Table 4.2A for details of the 6 Phase 1 and single Phase 2 study. In summary, the phase 1 bioavailability and

pharmacokinetic/pharmacodynamic trials had 130 healthy volunteers. The dental pain phase 2 trial had 62 post-dental procedure subjects. The three phase 3 double-blind trials had 1282 subjects exposed to study drug plus 430 placebo subjects.

Table 7.2.1.1A Exposure from Phase 3 Trials

Study ID	Objective	Study Design	Subject #	Dosage
TRAMCT.02.01	Safety (b) (4) @12 weeks osteoarthritis of knee or hip	Randomized, PBO-controlled, parallel group	433	Tramadol ER 100, 200 or 300 mg QD vs Placebo
TRAMCT.02.02	Safety (b) (4) @12 weeks osteoarthritis of knee or hip	Randomized, PBO-controlled, parallel group	450	Tramadol ER 100, 200 or 300 mg QD vs Placebo
TRAMCT.02.03	Safety for 12 months	Open label	260	Tramadol ER 300 mg QD
TRAMCT.02.04	Safety (b) (4) @12 weeks	Randomized, PBO-controlled, parallel group	855	Tramadol ER 300 mg QD vs Placebo

7.2.1.2 Demographics

Refer to Table 4.2A for details of the 6 Phase 1 and single Phase 2 study for the Applicant provided demographics. Table 7.2.1.2 is the demographic for subjects in the three phase 3 pivotal studies. The study population is predominantly Caucasian and female. The population included close to half of the subjects being elderly > 65 years of age.

Table 7.2.1.2 Demographics of the Combined Phase 3 Protocols

Table 2.7.3.3.1.2: Demographics and Baseline Characteristics in the Pooled Pivotal Studies

	Tramadol ER 100 mg N=216	Tramadol ER 200 mg N=217	Tramadol ER 300 mg N=653	Placebo N=360
Gender				
Male	70 (32.4%)	66 (30.4%)	246 (37.7%)	146 (40.6%)
Female	146 (67.6%)	151 (69.6%)	407 (62.3%)	214 (59.4%)
Ethnic Group				
Caucasian	181 (83.8%)	176 (81.1%)	512 (78.4%)	291 (80.8%)
Oriental	0 (0.0%)	0 (0.0%)	5 (0.8%)	0 (0.0%)
Hispanic	27 (12.5%)	31 (14.3%)	55 (8.4%)	35 (9.7%)
African	6 (2.8%)	7 (3.2%)	65 (10.0%)	30 (8.3%)
Asian	2 (0.9%)	1 (0.5%)	5 (0.8%)	1 (0.3%)
Other	0 (0.0%)	2 (0.9%)	11 (1.7%)	3 (0.8%)
Age (Years)				
Mean ± SD	64.1 ± 9.97	64.3 ± 9.92	63.2 ± 9.59	63.6 ± 9.97
Range	45.0 – 88.0	42.0 – 87.0	41.0 – 86.0	44.0 – 90.0
Age Group				
45-64 years old	104 (48.1%)	103 (47.5%)	365 (55.9%)	202 (56.1%)
≥65 years old	112 (51.9%)	114 (52.5%)	288 (44.1%)	158 (43.9%)
Weight (kg)				
Mean ± SD	85.10 ± 20.255	84.52 ± 19.724	89.81 ± 20.947	86.65± 21.757
Range	49.9 – 181.4	51.0 – 165.6	47.0 – 170.1	42.6 – 181.9
Height (cm)				
Mean ± SD	163.90 ± 10.278	164.18 ± 10.359	166.70 ± 10.675	166.31 ± 11.092
Range	142.0 – 191.8	139.7 – 195.6	129.5 – 198.1	137.0 – 193.0
BMI (kg/m^2)				
Mean ± SD	31.63 ± 6.697	31.38 ± 6.975	32.31 ± 7.027	31.25 ± 6.819
Range	18.2 – 57.4	20.6 – 63.7	20.0 – 66.4	13.0 – 56.7
BMI Group				
<25	28 (13.0%)	32 (14.7%)	67 (10.3%)	49 (13.6%)
25-35	137 (63.4%)	132 (60.8%)	415 (63.6%)	230 (63.9%)
>35	50 (23.1%)	53 (24.4%)	170 (26.0%)	79 (21.9%)
Missing	1 (0.5%)	0 (0.0%)	1 (0.2%)	2 (0.6%)
Study Joint				
Hip	70 (32.4%)	61 (28.1%)	167 (25.6%)	107 (29.7%)
Knee	146 (67.6%)	156 (71.9%)	486 (74.4%)	253 (70.3%)

†Patients who have received at least one dose of study medication; Percentages are rounded, and may not equal 100%;
SD: Standard deviation.

7.2.1.3 Extent of exposure (dose/duration)

Adequate exposure data is shown based on the number of patients treated in the combined pivotal (b) (4) open-label trials. Table 7.2.1.3 provides the overall exposure data pooled for all the double-blind trials and the one open-label trial. Over 300 patients were on study drug greater than 6 months. 144 subjects remained on Cip-Tramadol ER 300 mg for a year or more.

Table 7.2.1.3 Duration of Exposure by Dose.

Duration	**100 mg**	**200 mg**	**DB 300 mg**	**Total**	**OL 300 mg**	**Overall Total**
	N = 216	**N = 217**	**N = 849**	**N = 1282**	**N = 244**	**N =**

0 - 2 wks	43	45	244	322	64	396
> 2 wk - 1 mo	28	40	110	178	11	189
> 1 mo - 2 mo	10	16	66	92	12	104
> 2 mo - 3 mo	78	63	95	236	18	254
> 3 mo - 4 mo	57	53	60	170	14	184
> 4 mo - 5 mo	0	0	13	13	5	18
> 5 mo - 6 mo	0	0	22	22	7	29
> 6 mo - 9 mo	0	0	89	89	19	108
> 9 mo - 12 mo	0	0	61	61	39	100
> 12 mo - 15 mo	0	0	89	89	55	144

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There were no secondary clinical data sources used to evaluate safety for this NDA.

7.2.2.1 Other studies

There were no additional studies that provided data for this NDA.

7.2.2.2 Postmarketing experience

There is no post-marketing data available for Cip-Tramadol ER.

7.2.2.3 Literature

No studies from the literature were used in the clinical evaluation of safety for this NDA.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience with the study drug was adequate in terms of the numbers of exposed and demographic subsets. Although it may have been desirable to achieve greater ethnic diversity, this is a problem endemic to clinical trials, and not specific to this development program. The doses and durations of exposure were also adequate, as they reflected the intended use of the product in an appropriate pain population.

The study design was adequate and well-controlled. The dropout rate, however, for tramadol trials and other opioids is high. (b) (4)
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7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There were no special pharmacology/toxicology studies submitted in this NDA.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing of the study population in this NDA, including monitoring of vital signs, physical examination, clinical laboratory testing, and eliciting AE data appear adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Comparative PK studies (using Ultram as a reference) and drug-food interaction studies were conducted during the Phase 1 trials. See Section 5, the Pharmacology review for details.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The serious risks of tramadol-associated opioid and non-opioid effects are well known, including respiratory depression, interaction with other CNS depressants, withdrawal symptoms/physical dependence, seizure, serotonin syndrome and increased suicide risk. The applicant made appropriate efforts, as based on the study design and conduct, to avoid or detect expected adverse events associated with tramadol. For example, studies excluded many subjects with potential for a drug-drug interaction that may potentially induce a seizure and the serotonin syndrome. No new safety signals or AEs with higher severity were observed during the clinical development of Tramadol ER as compared to the approved tramadol products.

7.2.8 Assessment of Quality and Completeness of Data

As a 505(b)(2) application, the safety data provided in the four Phase 3 trials were generally acceptable in quality to conduct the safety review. However, the following issues in the submission impacted analyses of the safety data:

- Although the study designs were similar Trial 04 had one less study visit, this made for some difficulty for pooling of the safety datasets for laboratory assessments.
- Not all CRFs were available to evaluate some significant treatment emergent adverse effects.
- The Safety Update arrived less than two weeks before this primary review was due.
- There was some evidence for miscoding when comparing the narratives to the safety databases.
- Two patients had laboratory assessments that were obviously aberrant, lab quality issues, these were not addressed in the report; an information request is pending.

7.2.9 Additional Submissions, Including Safety Update

The Applicant was late in sending the 120-day safety update which did not include data from TRAMCT.02.05 (Trial 05). Trial 05 was ongoing at the time of the NDA submission and a safety report for this trial should have been sent. (b) (4) . On the January 18 teleconference to request the safety update, the Division learned that the trial had been completed. The Applicant sent the report February 9, 2007. Therefore, the updated safety update are only addressed in this section and not incorporated into the rest of this review.

Trial 05 was similar in design to Trials 01 and 02. The one significant difference was that subjects were on study medication for an additional two weeks. Therefore, subjects taking Cip-Tramadol ER 300 mg, after the 2-week titration, were at their dose for 12 weeks.
The safety population (851 subjects) comprised another 635 subjects who received any dose of tramadol and 216 placebo subjects.

There were two deaths reported in the trial. One subject was a passenger in a fatal motor vehicle accident. It was uncertain, if she had started her study medication, Cip-Tramadol ER 300 mg. The second death was in a subject assigned to the 200 mg group. This subject died secondary to a carcinoma after 1.5 months.

In addition to the two deaths there were 21 subjects who developed SAEs. A total of 4/216 (1.9%) placebo patients, 9/213 (4.2%) of the Tramadol ER 100 mg patients, 5/217 (2.3%) of the Tramadol ER 200 mg patients, and 3/205 (1.5%) of the Tramadol ER 300 mg patients developed one or more SAEs. Of these SAEs one was considered study drug related. This was a patient who developed a gastrointestinal hemorrhage, but this subject was on placebo. Two cases were considered undetermined. One patient developed leucopenia, while suffering from a flu-like syndrome. Another subject developed abdominal pain.

Leucopenia can be a complication from flu-like illnesses and is most likely not related to study drug. The case of abdominal pain, however, may be study drug related. This case was a 74-year old female who developed abdominal pain and diarrhea. She did have a past history of multiple abdominal surgeries, cholecystectomy and hysterectomy, and also a diagnosis of colon cancer. Her hospital work-up found an ileus. She was treated with intravenous fluids and antibiotics and recovered. Opioids can slow gut activity and therefore it is possible that her study drug, Tramadol ER 300 mg may have contributed.

Table 7.2.9 summarizes the SAEs by COSTART body system and preferred terms. The review of the safety update does not alter the preceding conclusions.

Table 7.2.9 SAEs in Trial 05 by body system and preferred term by study group – Applicant's submission

Text Table 43: Summary of Treatment-Emergent Serious Adverse Events – Population: Safety

	Tram ER 100 mg (N=213)	Tram ER 200 mg (N=217)	Tram ER 300 mg (N=205)	Placebo (N=216)
COSTART BODY SYSTEM COSTART TERM				
TOTAL	9 (4.23%)	5 (2.30%)	3 (1.46%)	4 (1.85%)
BODY AS A WHOLE	6 (2.82%)		1 (0.49%)	2 (0.93%)
ABDOMINAL PAIN			1 (0.49%)	
ACCIDENTAL INJURY	1 (0.47%)		1 (0.49%)	1 (0.46%)
CARCINOMA	2 (0.94%)			
CHEST PAIN	2 (0.94%)			
FLU SYNDROME	1 (0.47%)			
HERNIA				1 (0.46%)
CARDIOVASCULAR	2 (0.94%)	3 (1.38%)		
ARRHYTHMIA	1 (0.47%)			
ATRIAL FIBRILLATION		1 (0.46%)		
AV BLOCK		1 (0.46%)		
CONGESTIVE HEART FAILURE		1 (0.46%)		
DEEP THROMBOPHLEBITIS	1 (0.47%)			
DIGESTIVE	1 (0.47%)			3 (1.39%)
ESOPHAGEAL ULCER	1 (0.47%)			
GASTRITIS				1 (0.46%)
GASTROINTESTINAL HEMORRHAGE				2 (0.93%)
PANCREATITIS		1 (0.46%)		
HEMIC / LYMPHATIC	1 (0.47%)			
LEUKOPENIA	1 (0.47%)			
NERVOUS	1 (0.47%)	1 (0.46%)		
CEREBROVASCULAR ACCIDENT	1 (0.47%)			
PARESTHESIA		1 (0.46%)		
RESPIRATORY	1 (0.47%)			
DYSPNEA	1 (0.47%)			
PNEUMONIA	1 (0.47%)			
UROGENITAL			1 (0.49%)	1 (0.46%)
KIDNEY FAILURE				1 (0.46%)
URINARY TRACT INFECTION			1 (0.49%)	

Note: This table summarizes the number of patients. % of patients is calculated based on the number of patients within a treatment group.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The majority of common AEs experienced by ≥5% of patients were related to Tramadol ER treatment. These AEs demonstrated a temporal relationship with the treatment. The drug-related AEs were expected based upon the pharmacology of tramadol and from the safety profile of approved tramadol products.

No new safety signals associated with Tramadol ER were identified during the clinical development.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The Applicant provided an Integrated Summary of Safety that pooled data from the three double-blind and one open-label trial. Patients receiving at least one dose of drug comprised the database. For this reviewer's analyses, data were pooled from the double-blind, 3-month trials. Long-term double-blind and open-label safety data were analyzed separately.

7.4.1.2 Combining data

See Section 7.4.11

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The common AEs in the trials tested with different dose levels of Tramadol ER showed dose-dependent increases in incidence for patients from 100 mg to 300 mg Tramadol ER. This was consistent with findings from the approved Tramadol products. Refer also to Section 7.1

7.4.2.2 Explorations for time dependency for adverse findings

The majority of AEs seem to appear at drug initiation or during the first 2-4 weeks of therapy.

7.4.2.3 Explorations for drug-demographic interactions

The Applicant did subset analyses of the AEs that did not demonstrate differences in safety by age or gender. There have been no reported demographic differences with other tramadol products.

7.4.2.4 Explorations for drug-disease interactions

Not applicable.

7.4.2.5 Explorations for drug-drug interactions

No apparent drug-drug interactions were associated with the common AEs observed during the trials. However, therapeutic agents that may potentially interact with Tramadol ER were not permitted.

7.4.3 Causality Determination

The causality of any AEs associated with the study medication was determined by temporal relationship, underlying medical conditions and medications, and previous experience with approved tramadol products.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

(b) (4)

. A dose titration was used in all Phase 3 trials with the following titration regimen: 100 mg once daily for one week, then 200 mg once daily for one week and then 300 mg once daily. The dosing regimen tested in the pivotal trials is consistent with the dosing instruction in the proposed labeling. The titration phase is slower compared to the approved product, Ultram ER.

8.2 Drug-Drug Interactions

Drug interactions with Tramadol ER were not specifically studied in this NDA. Tramadol is known to metabolically interact with many other drugs through CYP2D6 and CYP3A4 pathways. Pharmacodynamic interactions are likely. Opioids may induce respiratory depression. The concomitant use of another CNS depressant may further depress respiration to the point of a respiratory arrest. In addition the concomitant use of another drug with serotonergic or norepinephrine activity may result in seizures and the serotonin syndrome. For this 505(b)(2) application, the Applicant references the information on Drug Interactions (both PK- and PD-related) described in the labeling of Ultram ER into the proposed labeling for Cip-Tramadol ER.

8.3 Special Populations

Cip-Tramadol ER will reference Ultram. The Ultram label addresses many Special Populations.

8.4 Pediatrics

(b) (4)

8.5 Advisory Committee Meeting

A specific advisory meeting regarding this NDA was not held.

8.6 Literature Review

No separate literature review was performed in the clinical review of this NDA.

8.7 Postmarketing Risk Management Plan

The applicant did not submit a postmarketing risk management plan.

Tramadol products have been marketed for approximately 11 years. There has been no required risk management tool beyond standard product labeling and routine post-marketing safety surveillance.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

(b) (4)

The Agency informed the Applicant that they would need to provide substantial evidence of efficacy from one adequate and well-controlled trial. The

(b) (4)

(b) (4)

The Applicant claimed that there were no new safety signals for Cip-Tramadol ER compared to Ultram, the referenced drug. This reviewer agrees with this conclusion.

9.2 Recommendation on Regulatory Action

I recommend non-approval of the Cip-Tramadol ER application.

(b) (4)

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No post-marketing risk management activities would be required. There is over 11 years of experience with tramadol products.

9.3.2 Required Phase 4 Commitments

Because moderate to moderately severe pain occurs in children studies of Cip-Tramadol would be required.

9.3.3 Other Phase 4 Requests

Not applicable

9.4 Labeling Review

Because of the recommendation for non-approval a complete labeling review has not been done at this time.

9.5 Comments to Applicant

(b) (4)

3. Further safety assessments are recommended:
    a. Future trials should evaluate withdrawal symptoms in patients titrated off of Cip-Tramadol ER.
    b. Assess daily medication compliance to determine if some of the CNS and GI adverse effects are actually withdrawal symptoms related to non-compliance.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Title: A double-blind, randomized, placebo-controlled, multi-dose, phase 3, parallel group study of Tramadol ER in the relief of signs and symptoms of osteoarthritis of the hip and knee.

Protocol: TRAMCT.02.01

This protocol had treatment duration of 12 weeks. The study included 20 sites in the United States and Mexico.

Objectives:
The primary objective was to determine the analgesic, functional and global efficacy of treatment with Tramadol ER capsules 100 mg, 200 mg, and 300 mg once daily for 12-weeks. The secondary objectives were to determine the safety and tolerability of 12 weeks of continuous once-daily treatment, as measured by treatment emergent signs and symptoms and measurement of clinical and laboratory parameters during the study period.

(b) (4)

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(b) (4)

Safety Results:

No deaths were seen during the study.

Serious AEs were reported in three patients and included intestinal obstruction, myocardial infarction, and deep thrombophlebitis. The applicant reported these as not being related to study drug. *This reviewer agrees with this conclusion.*

Adverse event rates did increase with increasing dose strength, placebo (64/108, 59.3%), 100 mg (70/106, 66.0%), 200 mg (73/104, 70.2%), and 300 mg (90/112, 80.4%). The common AEs, seen in > 5%, were nausea, constipation, dry mouth, headache, dizziness, asthenia, insomnia, nervousness, pruritus, vomiting, abdominal pain, anxiety, arthralgia, and dyspepsia.

There were no treatment–emergent vital sign AEs in this study. Mean vital sign measurements at baseline and end of study are presented in Table 22. The results do not demonstrate clinically significant differences or changes.

Table 22. Mean Vital Signs at baseline and end of study

Vital Sign (Mean +/- SD)	Tramadol ER 100 mg	Tramadol ER 200 mg	Tramadol ER 300 mg	Placebo
Heart Rate (BPM)				
Baseline	73 +/- 8	72 +/- 8	74 +/- 10	73 +/- 9
End of Study	71 +/- 8	71 +/- 8	73 +/- 9	73 +/- 9
Systolic Blood Pressure (mmHg)				
Baseline	130 +/- 14	129 +/- 15	133 +/- 15	128 +/- 15
End of Study	129 +/- 15	129 +/- 15	131 +/- 20	130 +/- 15
Diastolic Blood				

Pressure				
Baseline	79 +/- 9	77 +/- 7	79 +/- 9	77 +/- 8
End of Study	77 +/- 8	77 +/- 7	76 +/- 10	79 +/- 9

Electrocardiograms: At the end of the study there were 5 subjects who had clinically significantly abnormal ECGs. One (1/106, 0.9%) Tramadol ER 300 mg subject developed marked sinus bradycardia. One (1/103, 1.0%) Tramadol ER 200 mg subject developed premature atrial contractions. Three (3/112, 2.7%) Tramadol ER 300 mg subjects developed abnormal ECGs, PVCs, sinus bradycardia, and left ventricular hypertrophy with systemic overload.

Summary and Conclusions:

(b) (4)

10.1.2

Title: A double-blind, randomized, placebo-controlled, multi-dose, phase 3, parallel group study of Tramadol ER in the relief of signs and symptoms of osteoarthritis of the hip and knee.

Protocol: TRAMCT.02.02

This protocol contained treatment duration of 12 weeks. The study included 15 sites in Canada and Argentina.

Objectives:
The primary objective was to determine the analgesic, functional and global efficacy of treatment with Tramadol ER capsules 100 mg, 200 mg, and 300 mg once daily for 12-weeks. The secondary objectives were to determine the safety and tolerability of 12 weeks of continuous once-daily treatment, as measured by treatment emergent signs and symptoms and measurement of clinical and laboratory parameters during the study period.

(b) (4)

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Safety Results:

No deaths were seen during the study. Adverse event rates did increase with increasing dose strength, placebo (53/112, 47.3%), 100 mg (58/110, 66.0%), 200 mg (67/113, 59.3%), and 300 mg (84/110), 76.4%. The common AEs, seen in > 5%, were nausea, constipation, dry mouth, headache, somnolence, dizziness, anorexia, asthenia, insomnia, nervousness, pruritus, abdominal pain, vomiting, arthralgia, and dyspepsia. A Serious AE was reported in one patient. This was a case of colitis that was considered unrelated. *This reviewer agrees with this conclusion.*

No clinically significant differences in mean vital sign measurements were seen between groups at baseline or the end of study Table 28.

Table 28. Mean Vital Signs at baseline and end of study

Vital Sign (Mean +/- SD)	Tramadol ER 100 mg	Tramadol ER 200 mg	Tramadol ER 300 mg	Placebo
Heart Rate (BPM)				
Baseline	73 +/- 9	73 +/- 10	74 +/- 10	73 +/- 9
End of Study	71 +/- 9	72 +/- 9	73 +/- 9	71 +/- 8
Systolic Blood Pressure (mmHg)				
Baseline	135 +/- 17	132 +/-15	133 +/- 15	132 +/- 16
End of Study	133 +/-17	133 +/- 17	131 +/- 20	130 +/- 16
Diastolic Blood Pressure				
Baseline	78 +/- 10	78 +/- 9	79 +/- 9	78 +/- 10
End of Study	78 +/- 9	79 +/- 11	76 +/- 10	78 +/- 9

No treatment-emergent vital sign abnormalities were reported.

Electrocardiograms: The sponsor reported one end of study clinically significant abnormal ECG for Tramadol ER 300 mg (1/110, 0.9%). This patient (#56049) had possible ischemia in the anterior leads.

Summary and Conclusions:

(b) (4)

10.1.3 **Title:** A double-blind, randomized, placebo-controlled, phase 3 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.

Protocol: TRAMCT.02.04

(b) (4)

Study Drugs:
Tramadol ER 100, 200 and 300 mg capsules and placebo identical in appearance.

(b) (4)

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Safety Results:

There was one death seen during the study. A patient taking Tramadol ER 300 mg went on a trip out of the country. While in the hotel he suddenly collapsed and died. The autopsy ruled the cause of death as a myocardial infarction. The clinical investigator considered it unrelated to study drug.

There were 29 subjects with SAEs in the first three months of the trial. Tramadol ER 300 mg subjects with SAEs were 17 (17/627, 2.7%), while there were 12 placebo SAE subjects (12/210, 5.7%). A summary is provided below in Table 25. Two of the SAEs were considered treatment –emergent in subjects taking Tramadol ER 300 mg. An 83 yo male developed a BUN of 44 mg/dL at the 3-month visit. A 71 year old female developed hypercalcemia at 11.0 mg/dL at the 3-month visit. Details of the cases are provided in Appendix 10.1.4.

Table 25. Serious Adverse Events in the Double-blind portion of the trial.

Text Table 41: Summary of Incidence of Treatment-Emergent Serious Adverse Events – Population Safety

Body System Preferred Term	Tramadol ER 300mg† (N=627)	Placebo (N=210)
All Systems		
Patients with Any Serious Adverse Event††	17 (2.71%)	12 (5.71%)
Body as a Whole		
Cellulitis	2 (0.32%)	0 (0.00%)
Chest Pain	2 (0.32%)	0 (0.00%)
Spondylolisthesis	1 (0.16%)	0 (0.00%)
Accidental Injury	0 (0.00%)	1 (0.48%)
Carcinoma	0 (0.00%)	1 (0.48%)
Cardiovascular		
Angina Pectoris	1 (0.16%)	0 (0.00%)
Hypertension	1 (0.16%)	0 (0.00%)
Atrial Fibrillation	0 (0.00%)	1 (0.48%)
Congestive Heart Failure	0 (0.00%)	1 (0.48%)
Coronary Artery Disorder	0 (0.00%)	1 (0.48%)
Hypotension	0 (0.00%)	1 (0.48%)
Myocardial Infarct	0 (0.00%)	3 (1.43%)
Digestive System		
Gastritis	1 (0.16%)	0 (0.00%)
Gastrointestinal Carcinoma	1 (0.16%)	0 (0.00%)
GI Perforation	1 (0.16%)	0 (0.00%)
Metabolic / Nutrition		
BUN Increased	1 (0.16%)	0 (0.00%)
Hypercalcemia	1 (0.16%)	0 (0.00%)
Nervous System		
Cerebral Ischemia	1 (0.16%)	0 (0.00%)
Convulsion	1 (0.16%)	0 (0.00%)
Paralysis	1 (0.16%)	0 (0.00%)
Vertigo	1 (0.16%)	0 (0.00%)
Respiratory		
Pneumonia	2 (0.32%)	2 (0.95%)
Asthma	1 (0.16%)	1 (0.48%)
Lung Disorder	0 (0.00%)	1 (0.48%)
Urogenital		
Cervix Neoplasm	1 (0.16%)	0 (0.00%)
Kidney Calculus	0 (0.00%)	1 (0.48%)
Pyelonephritis	0 (0.00%)	1 (0.48%)

Patient population base: Safety: all patients randomized into the study who received at least one dose of study drug.

The adverse event rates for Tramadol ER 300 mg was 438/627 (69.9%) compared to 80/210 (38.1%) for placebo subjects. The common AE rates for subjects at >5% are detailed in Tables 26. Tables 27 and 28 provide a depiction over time. The high rates occur during the first three months. Afterwards the rates seem to remain consistent across the time intervals.

Table 26. Common adverse events at >5%.

Text Table 37: Summary of Incidence of Common Treatment-Emergent Adverse Events – Population Safety

Body System Preferred Term	Tramadol ER 300mg† (N=627)	Placebo (N=210)
All Systems		
Patients with any Common Event††	438 (69.86%)	80 (38.10%)
Body as a Whole		
Headache	109 (17.38%)	25 (11.90%)
Asthenia	60 (9.57%)	2 (0.95%)
Infection	41 (6.54%)	22 (10.48%)
Digestive System		
Nausea	148 (23.60%)	10 (4.76%)
Constipation	123 (19.62%)	8 (3.81%)
Dry Mouth	95 (15.15%)	11 (5.24%)
Vomiting	61 (9.73%)	3 (1.43%)
Anorexia	36 (5.74%)	0 (0.00%)
Diarrhea	33 (5.26%)	8 (3.81%)
Dyspepsia	33 (5.26%)	10 (4.76%)
Musculoskeletal System		
Arthralgia	38 (6.06%)	6 (2.86%)
Nervous System		
Somnolence	96 (15.31%)	8 (3.81%)
Dizziness	86 (13.72%)	12 (5.71%)
Insomnia	35 (5.58%)	3 (1.43%)
Nervousness	33 (5.26%)	3 (1.43%)
Respiratory		
Sinusitis	38 (6.06%)	9 (4.29%)
Skin		
Pruritus	56 (8.93%)	2 (0.95%)
Sweating	53 (8.45%)	1 (0.48%)

Patient population base: Safety: All patients randomized into the study who received at least one dose of study drug.
Common: Treatment-emergent adverse events experienced by ≥5% of patients in either treatment group.
† Within each body system, common treatment-emergent adverse events are listed in descending order by their incidence in the Tramadol ER 300 mg group.
†† The total number of patients who experienced any common treatment-emergent adverse event. Within a body system, a patient may have experienced more than one common treatment-emergent adverse event. The sum of terms by body system may have exceeded 100%.
Source: Table 14.3.1.2.2.

Table 27. Common AEs >5% in the Tramadol ER 300 mg subjects over time

Text Table 38: Summary of Incidence of Common Treatment-Emergent Adverse Events by Time on Treatment – Population Safety – Tramadol ER 300 mg Group

	Tramadol ER 300mg				
Body System Preferred Term†	**≤3 Months n=627§**	**>3 to ≤6 Months n=292§**	**>6 to ≤9 Months n=240§**	**>9 to ≤12 Months n=154§**	**>12 Months n=111§**
All Systems					
Patients with any Common Event††	453 (72.25%)	135 (46.23%)	100 (41.67%)	59 (38.31%)	33 (29.73%)
Body as a Whole					
Headache	88 (14.04%)	9 (3.08%)	13 (5.42%)	7 (4.55%)	5 (4.50%)
Asthenia	49 (7.81%)	2 (0.68%)	3 (1.25%)	2 (1.30%)	1 (0.90%)
Infection	16 (2.55%)	12 (4.11%)	10 (4.17%)	4 (2.60%)	3 (2.70%)
Digestive System					
Nausea	136 (21.69%)	8 (2.74%)	8 (3.33%)	1 (0.65%)	1 (0.90%)
Constipation	110 (17.54%)	8 (2.74%)	5 (2.08%)	2 (1.30%)	0 (0.00%)
Dry Mouth	92 (14.67%)	4 (1.37%)	2 (0.83%)	1 (0.65%)	0 (0.00%)
Vomiting	48 (7.66%)	5 (1.71%)	9 (3.75%)	3 (1.95%)	1 (0.90%)
Anorexia	34 (5.42%)	0 (0.00%)	1 (0.42%)	1 (0.65%)	0 (0.00%)
Diarrhea	18 (2.87%)	4 (1.37%)	3 (1.25%)	2 (1.30%)	6 (5.41%)
Dyspepsia	27 (4.31%)	4 (1.37%)	1 (0.42%)	1 (0.65%)	2 (1.80%)
Musculoskeletal System					
Arthralgia	16 (2.55%)	11 (3.77%)	9 (3.75%)	2 (1.30%)	1 (0.90%)
Nervous System					
Somnolence	92 (14.67%)	0 (0.00%)	0 (0.00%)	2 (1.30%)	1 (0.90%)
Dizziness	78 (12.44%)	3 (1.03%)	2 (0.83%)	1 (0.65%)	0 (0.00%)
Insomnia	16 (2.55%)	3 (1.03%)	1 (0.42%)	5 (3.25%)	7 (1.12%)
Nervousness	24 (3.83%)	3 (1.03%)	1 (0.42%)	2 (1.30%)	0 (0.00%)
Respiratory					
Sinusitis	13 (2.07%)	14 (4.79%)	10 (4.17%)	3 (1.95%)	1 (0.90%)
Skin					
Pruritus	53 (8.45%)	3 (1.03%)	1 (0.42%)	1 (0.65%)	0 (0.00%)
Sweating	45 (7.18%)	5 (1.71%)	0 (0.00%)	2 (1.30%)	0 (0.00%)

Patient population base: Safety Population Subset: All patients randomized to the Tramadol ER 300 mg group who received at least one dose of study drug.
Common: Treatment-emergent adverse events experienced by ≥5% of patients in either treatment group.
The reporting periods are determined by days following the first dose date: a month is defined as 30 days.
The data reflect the time to first occurrence of the adverse event, determined by days between the date of the first dose and the date of first onset of the adverse event.
§ The number of patients remaining on treatment at the beginning of each reporting period.
† Within each body system, the common treatment-emergent adverse events are listed in descending order by their incidence in the Tramadol ER 300 mg group during any time in the study (See Text Table 37 and Table 14.3.1.2.2).

Table 28. Common AEs >5% for the Placebo group over time.

Text Table 39: Summary of Incidence of Common Treatment-Emergent Adverse Events by Time on Treatment – Population Safety – Placebo Group

	Placebo (N = 210)				
Body System Preferred Term†	**≤3 Months n=210§**	**>3 to ≤6 Months n=107§**	**>6 to ≤9 Months n=84§**	**>9 to ≤12 Months n=62§**	**>12 Months n=39§**
All Systems					
Patients with any Common Event††	98 (46.67%)	40 (37.38%)	33 (39.29%)	13 (20.97%)	10 (25.64%)
Body as a Whole					
Headache	19 (9.05%)	3 (2.80%)	6 (7.14%)	1 (1.61%)	1 (2.56%)
Asthenia	2 (0.95%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infection	10 (4.76%)	6 (5.61%)	5 (5.95%)	2 (3.23%)	1 (2.56%)
Digestive System					
Nausea	7 (3.33%)	1 (0.93%)	1 (1.19%)	0 (0.00%)	0 (0.00%)
Constipation	7 (3.33%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	0 (0.00%)
Dry Mouth	10 (4.76%)	1 (0.93%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vomiting	2 (0.95%)	0 (0.00%)	1 (1.19%)	0 (0.00%)	0 (0.00%)
Anorexia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diarrhea	7 (3.33%)	2 (1.87%)	1 (1.19%)	0 (0.00%)	0 (0.00%)
Dyspepsia	8 (3.81%)	1 (0.93%)	1 (1.19%)	0 (0.00%)	0 (0.00%)
Musculoskeletal System					
Arthralgia	2 (0.95%)	2 (1.87%)	1 (1.19%)	0 (0.00%)	1 (2.56%)
Nervous System					
Somnolence	5 (2.38%)	3 (2.80%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dizziness	8 (3.81%)	2 (1.87%)	2 (2.38%)	0 (0.00%)	0 (0.00%)
Insomnia	2 (0.95%)	1 (0.93%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervousness	2 (0.95%)	0 (0.00%)	1 (0.48%)	0 (0.00%)	0 (0.00%)
Respiratory					
Sinusitis	6 (2.86%)	0 (0.00%)	2 (2.38%)	1 (1.61%)	1 (2.56%)
Skin					
Pruritus	2 (0.95%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sweating	0 (0.00%)	0 (0.00%)	1 (1.19%)	0 (0.00%)	0 (0.00%)

Patient population base: Safety Population Subset: All patients randomized to the Placebo group who received at least one dose of study drug.
Common: Treatment-emergent adverse events experienced by ≥5% of patients in either treatment group.
The reporting periods are determined by days following the first dose date: a month is defined as 30 days.
The data reflect the time to first occurrence of the adverse event, determined by days between the date of the first dose and the date of first onset of the adverse event.
§ The number of patients remaining on treatment at the beginning of each reporting period.
† Within each body system, the common treatment-emergent adverse events are listed in descending order by their incidence in the Tramadol ER 300 mg group during any time in the study (See Text Table 37 and Table 14.3.1.2.2).

No differences in mean vital sign measurements were seen between placebo and Tramadol at baseline or the end of study (Table 29).

Table 29. Vital Sign Means for Baseline and End of Study

Vital Sign (Mean +/- SD)	Tramadol ER 300 mg	Placebo
Heart Rate (BPM)		
Baseline	73 +/- 10	72 +/- 10
End of Study	72 +/- 10	72 +/- 10
Systolic Blood Pressure (mmHg)		
Baseline	130 +/- 15	130 +/- 14

End of Study	130 +/- 15	129 +/- 15
Diastolic Blood Pressure		
Baseline	79 +/- 9	79 +/- 8
End of Study	78 +/- 9	77 +/- 9

Hypertension was reported as a treatment emergent AE in 24/627 (3.8%) of the Tramadol ER 300 mg subjects compared to 3/210 (1.4%) of the placebo patients. Hypotension was an AE for 1/627 (0.2%) of the Tramadol ER 300 mg subjects and one (1/210, 0.5%) of the placebo subjects. Two subjects with abnormal vital signs were considered Serious AEs. One of the Tramadol ER 300 mg had hypertension and a placebo subject had hypotension. Appendix 10.1.4 describes these later cases.

Electrocardiograms: Eight patients on Tramadol ER 300 mg had a change in their ECG to clinically significant.

Drug Abuse Potential Assessment: The mean (b) (4) agonist scores at the end of the study (b) (4).

The Clinical Opiate Withdrawal Score (COWS) was administered two weeks after the discontinuation of study drug. 96.2% of the placebo group and 95.4% of the Tramadol ER 300 mg group had no withdrawal symptoms. Mild symptoms were reported by 3.8% of the placebo and 3.6% of the Tramadol group.

Summary and Conclusions

The Applicant concluded that the results of the trial indicate that Tramadol ER 300 mg is an (b) (4) safe treatment for moderate to moderately severe chronic pain in patients with osteoarthritis.

10.1.4 Summaries of Serious Adverse Events

10.1.4.1 SAEs in TRAMCT02.01

In TRAMCT02.01 there were three serious AEs reported. A 63 yo female developed a bowel obstruction after 49 doses of placebo. A 72 year old female developed a deep venous thrombophlebitis five weeks after she was started into the Tramadol ER 300 mg arm. The patient also had elevations of her ALT, AST and BUN. The patient was not taking any concomitant medications. The patient did have preexisting ankle edema. Her PMH was significant for diabetes mellitus, PUD, PVD, and hypercholesterolemia. She recovered following anticoagulant therapy.

A 60 year old female developed an acute myocardial infarction 68 days after initiating Tramadol ER 100 mg. The event was complicated by ventricular tachycardia. She was successfully treated with a stent in her left circumflex artery. Concomitant medications included Synthroid, hydrochlorthiazide, and Toprol-XL. The patient had a history of hypertension, but this was the only reported cardiac risk factor. The patient recovered after a three day hospital stay.

10.1.4.2: SAEs in TRAMCT02.02

In TRAMCT.02.02 one patient was reported to have had an SAE. A 74 yo male developed diverticulitis after receiving 10 doses of study medication in the Tramadol ER 300 mg arm. His concomitant medication was enalapril maleate. He did have a prior history of diverticular disease in addition to hypertension and gallbladder surgery. He fully recovered after antimicrobial therapy.

10.1.4.3: SAEs in TRAMCT02.04

In TRAMCT.02.04 many patients developed SAEs. A 74 yo male (PID #02437) was hospitalized for chest pain. This occurred after (b) (4) of study medication within the Tramadol ER 300 mg limb. Concomitant medications included lisinopril, hydrochlorthiazide, omeprazole, and calcium. PMH was significant for hypertension, heart murmur, gastroesophageal reflux disease, myelodysplasia, and prostatitis. The day prior to hospitalization the patient was diagnosed with bronchitis. The admission diagnosis was anginal pain with diaphoresis. An extensive cardiac work-up was done, although the Report only notes echocardiograms. Discharge diagnosis was chest pain of non-cardiac origin.

An 83 yo male (PID #02439) was hospitalized for congestive heart failure and pneumonia (b) (4) after starting study medication, Tramadol ER 300 mg limb. His concomitant medications were Lipitor, Prilosec, Ocuvite, Norvasc, furosemide, hydralazine, aspirin, lorazepam and Toprol-XL. PMH was significant for coronary artery disease with CABPG, hypertension, dyslipidemia, GERD, and testicular cancer. This 5-day hospitalization was 23 days after the patient had discontinued study medication. A cardiac catheritization revealed developing occlusion in his previous grafts. His hospitalization included placement of a pacemaker, antibiotic therapy and other medication adjustments.

An 82 yo male (PID #02449) discontinued study medication after two doses because of nausea, vomiting and dizziness. Concomitant medications included acetaminophen and propoxyphene. PMH was positive for BPH. The patient was in the Tramadol ER 300 mg limb. Three weeks later the patient was admitted to the hospital for pneumonia and gastroenteritis with vomiting and diarrhea. An additional discharge diagnosis included sepsis. The patient recovered after three weeks of antibiotic and antiemetic therapy.

A 66 yo male (PID #19416) after 7.5 months of therapy, Tramadol ER 300 mg, was diagnosed with metastatic adenocarcinoma. He underwent surgery and no additional information became available.

A 48 yo female (PID # 23430) was hospitalized for an asthma exacerbation. She had a PMH of COPD. Her concomitant medications included an albuterol inhaler and verapamil. Two months after initiating therapy, Tramadol ER 300 mg, while jogging on (b) (6) patient developed the severe asthma attack. The patient reported that her albuterol inhaler was empty when she tried to use it. The patient continued on study drug for a few months after this event, but was eventually terminated for non-compliance with study procedures after 144 doses of medication.

A 71 yo female (PID #34402) had two hospital admissions for hypercalcemia. The first admission occurred after four doses of study medication, Tramadol ER 300 mg. Study medication was not continued. The patient had emesis, confusion, shortness of breath, and inappropriate behavior. Her serum calcium was 13.5 mg/dL. Her diagnosis was acute renal failure but renal function tests were not provided. During her second admission seven days after the first her serum calcium was again 13.6 mg/dL. Her BUN was 44 mg/dL and her serum creatinine was 2.3 mg/dL. Her symptoms on this admission were weakness, confusion, dry mouth, lightheadedness, orthostasis and one episode of vomiting.

A 76 yo female (PID #38405) was admitted for leg cellulitis after one month of study medication. Her concomitant medications were Zocor, Glucophage, lisinopril, and aspirin. PMH included hypertension, diabetes mellitus, PVD, and hyperlipidemia. Reportedly she only took 14 doses. She was successfully treated with IV antibiotics, but then never returned for follow-up.

A 69 yo female (PID #43405) developed chest pressure, generalized itching, dry mouth, dizziness, dypsnea and weakness after 11 doses of placebo. PMH was significant for diabetes mellitus, hypertension, hypercholesterolemia, emphysema, and obesity. Concomitant medications included Lipitor, Accupril, Fosamax, glipizide, Toprol and metformin. The patient ruled out for an MI. Her discharge diagnosis was angina pectoris. Study medication was discontinued.

A 58 yo female (PID #45414) had a history of a benign tremor and was on no concomitant medications. After 10 months of therapy, Tramadol ER 300, the patient fell down steps and had LOC. Medics reported the patient to be diaphoretic and nauseated. The patient was hospitalized

for three days. Details of the evaluation were not provided. The patient did continue on study medication and completed the one year study.

A 48 yo female (PID #50407) developed nephrolithiasis complicated by pyelonephritis and urosepsis. The patient had taken 128 doses of study medication prior to termination. The patient's PMH included asthma, diabetes mellitus, hypertension, tachycardia, hyperlipidemia and proteinuria. Her concomitant medications included Crestor, Micardis, Metaglip and Avandamet. She was successfully treated with IV Zosyn.

A 71 yo female (PID #50419) developed a myocardial infarction and underwent CABPG. PMH was significant for a previous MI, DM, CHF, HTN, hypothyroidism, hypercholesterolemia, cardiac murmur, gastric bypass, and peripheral neuropathy. Concomitant medications were Glucophage, Actos, Glynase, Zestril, Toprol XL, Synthroid, Lipitor, Protonix and Tylox. The patient had taken 239 doses of placebo before discontinuing for treatment failure. This discontinuation was ten days before the MI.

An 83 yo male (PID #58403) was noted to have an elevated serum blood urea nitrogen of 44 mg/dL. PMH was only significant for prostatic CA, age-related deafness and a UTI. He was not taking any concomitant medications. This BUN elevation was recognized at an early termination visit for treatment failure after taking 98 doses of study medication, Tramadol ER 300 mg. The follow-up result one week later was 32 mg/dL. The investigator believed this to be study drug related.

A 60 yo male (PID #60413) on placebo, 264 doses, developed pneumonia. He had a PMH that included chronic bronchitis, GERD and hyperlipidemia. He was successfully treated with antibiotics. He was discontinued from the study secondary to a protocol violation.

A 54 yo female on placebo for 34 doses was admitted for an asthma exacerbation. Her PMH included asthma and hypertension. Her medications included Accupril, Bricanyl, Symbicort, Singulair, Xalatan and Biaxin. After failing outpatient therapy with prednisone for two days she was admitted for a prolonged hospitalization of 29 days and then discontinued from the study for a protocol violation.

A 61 yo male (PID #67401) developed ACE-inhibitor induced angioneurotic edema before initiating therapy with placebo. Patient was still started on placebo, but discontinued after 34 days secondary to nausea and dizziness.

A 65 yo female (PID # 68415) was hospitalized for pneumonia and bronchitis after receiving 4 doses of Tramadol ER 300 mg. PMH did not include preexisting pulmonary disease, but was positive for hypothyroidism, glaucoma and migraines. Her concomitant medications were Synthroid, Fosamax, Timoptol and aspirin.

A 63 yo male (PID # 69441) on placebo was admitted for atrial fibrillation and myocardial infarction after 10 months on the placebo. His PMH was significant for hypertension,

hypercholesterolemia, and heart murmur; and he was taking Toprol, Vytorin, Hyzaar, and acetaminophen.

A 66 yo male (PID #69455) on placebo, 37 doses, had a syncope with hypotension. It was precipitated by nausea and sweating. In the hospital he was noted to be febrile, 101 degrees. He was discharged after two days and discontinued from the study. PMH was hypercholesterolemia and he was taking Zocor and aspirin.

A 74 yo male (PID #92404) undergoing a routine colonoscopy was diagnosed with colon cancer and underwent surgery and was discontinued from the study after 71 doses of Tramadol ER 300mg.

A 75 yo female (PID #93403) was admitted to the hospital for vertigo, seizures and a transient ischemic attack. She had received 79 doses of placebo. PMH was significant for cerebro- and cardiovascular disease.

A 70 yo female (PID #94404) on placebo, 97 doses, was admitted for an evaluation of chest pain. Her PMH was significant for MI, HTN, DM and hyperlipidemia. Her cardiac catheterization, however, did not reveal any cardiac disease.

A 59 yo female (PID #95425) on placebo stopped all medications after being diagnosed with bleeding cervical uterine polyps.

A 55 yo female (PID #95431) who completed the study in the placebo arm was hospitalized for an episode of leg cellulitis.

A 67 yo male (PID #95445) on placebo was admitted for decompression surgery for spondylolisthesis.

A 58 yo male (PID #96414) on Tramadol ER 300 mg underwent was admitted for kidney stone extraction after three months of therapy. PMH did not list a prior history of kidney stones, but included overactive bladder, bladder neck obstruction, and pneumonia. His only concomitant medication was Requip.

A 48 yo male (PID #97408) on placebo was admitted for a lung mass that after bronchoscopy was determined to be a mycobacterium avium infection.

A 73 yo male (PID #97410) on placebo underwent emergency laporotomy for a perforated sigmoid colon secondary to diverticulitis.

A 49 yo male (PID #97411) who had received 94 doses of Tramadol ER 300 mg developed leg numbness and weakness. His hospitalization did not determine the etiology. He did have preexisting neurological disease, migraines and strokes. His concomitant medications were metoprolol, enalapril and Plavix. He discontinued from the study and returned one month later

for his early termination visit. He was also admitted one month prior to this admission for chest pain.

A 68 yo female (PID #99433) on Tramadol ER 300 mg was admitted from the study site clinic for hypertensive urgency with a blood pressure of 200/110mm Hg. She reportedly was feeling well and stopped her blood pressure medication. The summary, however, does not list hypertension in her PMH and her only concomitant medication was Micardis. The patient subsequently discontinued from the study secondary to this AE.

10.1.4.4: SAEs in TRAMCT.02.03 (Open-Label trial)

A 71 yo male (PID #02030) after 4 months of therapy was admitted for a right lower lobe pneumonia in (b) (6) of (b) (6). PMH was significant for HTN, hyperlipidemia and GERD. His concomitant medications included atorvastatin, Nexium, Captopril, Labetolol, clonidine, Lasix and penicillin. He subsequently discontinued therapy.

A 62 yo male (PID #05002) developed episodic chest pain requiring admission. His PMH was positive for hyperlipidemia, GERD, BPH and allergic rhinitis. Concomitant medications included Zestril, Prilosec and Prozac. His cardiac evaluation including an angiogram did not show coronary artery disease, but there was mild left ventricular dysfunction.

A 70 yo female (PID #06013) was admitted for chest pain and a gastrointestinal bleed. PMH was significant for PUD, gastric and colonic polyps, PVD and diabetes mellitus. Her concomitant medications were Pletal and Atacand. She had received 30 doses of Tramadol ER 300 mg. She ruled in for an MI and had a stent placed during cardiac catheterization.

A 45 yo male (PID #09097) underwent a lumbar fusion and laminectomy for disc disease.

After 7.5 months of therapy, a 74 yo male (PID # 16014) developed a pounding sensation in both ears. During his work-up he was found to have carotid stenosis and underwent a carotid endarterectomy. His PMH was positive for HTN. His medications were magnesium maleate and aspirin. Measurement of a salicylate level was not reported.

A 69 yo male (PID #31003) was involved in a motor vehicle accident in his twelfth month of therapy. His PMH was reportedly negative and his only medication was calcium.

A 65 yo male (PID #31014) was diagnosed with prostatic adenocarcinoma after 2.5 months of therapy. His PMH was negative and he took no other medications.

A 55 yo male (PID #33015) had two SAEs. During his first SAE he was hospitalized for renal colic. The stone passed into the bladder spontaneously with hydration. His PMH was only significant for BPH. He took no other medications. His second SAE was a withdrawal reaction when he discontinued the medication after a full year of therapy. He was admitted eight days after the study medication was stopped. He was anxious, agitated, and nervous. He suffered from insomnia for 4 nights and had negative thoughts with visual hallucinations. He also had chest

pain and tachycardia. He was treated with benzodiazepines and anxiolytics not defined and was discharged after three days in good condition.

A 50 yo female (PID #52003) after 7.5 months of therapy was diagnosed with breast cancer and had a mastectomy.

An 88 yo female (PID #56032) suffered a fall and fractured her left wrist and injured her left hip/leg. She was hospitalized for over one month before she was discharged in a stable condition to care for herself.

A 70 yo female (PID #56033) developed cholelithiasis while on study medication and underwent a cholecystectomy. She had received 45 doses of Tramadol ER.

A 46 yo male (PID #57017) developed typical ischemic chest pain. He underwent angioplasty and stent placement for LAD stenosis with spasm. The patient had a significant family history of early onset ischemic heart disease. He was taking aldronate at the time. These events occurred six days after starting Tramadol ER. Study medication was discontinued.

A 70 yo female (PID #58024) developed constipation requiring hospitalization and medical work-up. Study medication was discontinued after 203 doses and she recovered uneventfully. Her PMH was significant for hypothyroidism and HTN. She was taking Synthroid in addition to Detrol, Aggrenox, hydrochlorthiazide and Vasotec. The relationship of the constipation to the study medication was listed as undetermined.

A 74 yo female (PID #59014) after 8.5 months of therapy was diagnosed with colon cancer and underwent surgery.

10.2Line-by-Line Labeling Review

Not done, because of the recommendation for non-approval.

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

/s/

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3/13/2007 01:48:13 PM
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