CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-745

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	21-745
Submission Dates	7/2/2008 (Complete response to approvable letters dated September 28, 2006 and May 30, 2007)
Brand Name	RYZOLT™
Generic Name	Tramadol Hydrochloride
Reviewers	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Applicant	Labopharm
Relevant IND	IND 64,317
Type of Submission; Code	505 (b)(2); 5S
Reference Listed Drug	Ultram (Immediate Release), Ortho McNeil Pharmaceuticals, Inc. (NDA 20-281)
Formulation; Strength(s)	Extended-Release Tablets; 100, 200, and 300 mg
Proposed Indication	Management of moderate to moderately severe pain

Review of Complete Response

NDA 21-745 is a 505 (b)(2) application for a new extended-release formulation of tramadol hydrochloride tablets, tramadol ER. The reference product is Ultram®(tramadol hydrochloride tablets), which is currently marketed under approved NDA 20-281. Currently, there is one approved once-a-day extended-release formulation of tramadol HCl (Ultram ER, NDA 21-692, approved in September 2005).

The original NDA 21-745 was submitted on November 25, 2005 and the Sponsor received approvable letters on September 28, 2006 and May 30, 2007, respectively during the previous 2 review cycles. The main concerns were failure to demonstrate efficacy.

In this Complete Response submission, the Sponsor performed a reanalysis of the data using a modified version of the method put forth by Dr. Jenkins during the process of formal dispute resolution. Refer to Dr. Permutt's biostatistics review for a thorough assessment and acceptability of these data.

From a Clinical Pharmacology perspective, no new data was submitted and the recommendation of acceptability of the application pending agreement on the labeling language stands. This review contains assessment of Clinical Pharmacology related labeling changes. Refer to Appendix 1 for the labeling recommendations that are related to Clinical Pharmacology. Refer to the approval letter for the final labeling.

Recommendation

From a Clinical Pharmacology Perspective, because there is no new information to review in this submission, the recommendation made in the review of original NDA submission that "NDA 21-745 is acceptable provided that a satisfactory agreement can be reached between the Sponsor and the Agency" still stands.

11 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Lei K Zhang
12/10/2008 10:34:58 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
12/10/2008 10:40:30 AM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	21-745
Submission Dates	12/18/2006 (Complete response to approvable letter dated September 28, 2006)
Brand Name	Tramadol Contramid® OAD
Generic Name	Tramadol Hydrochloride
Reviewers	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Applicant	Labopharm
Relevant IND	IND 64,317
Type of Submission; Code	505 (b)(2); 5S
Reference Listed Drug	Ultram (Immediate Release), Ortho McNeil Pharmaceuticals, Inc. (NDA 20-281)
Formulation; Strength(s)	Extended Release Tablets; 100, 200, and 300 mg
Proposed Indication	Management of moderate to moderately severe pain

Review of Complete Response

NDA 21-745 is a 505 (b)(2) application for a new extended-release formulation of tramadol hydrochloride tablets, tramadol ER. The reference product is Ultram®(tramadol hydrochloride tablets), which is currently marketed under approved NDA 20-281. Currently, there is one approved once-a-day extended-release formulation of tramadol HCl (Ultram ER, NDA 21-692, approved in September 2005).

The original NDA 21-745 was submitted on November 25, 2005 and the Sponsor received an approvable letter on September 28, 2006. Review dated August 24, 2006 contains the Clinical Pharmacology assessment of the original NDA submission. The major deficiency cited in the approvable letter was a lack of efficacy of the proposed doses to support the proposed indication. In this Complete Response submission, the Sponsor provided additional statistical analysis based on the existing data and did not conduct new clinical studies.

The item listed in the approvable letter related to Clinical Pharmacology is:

> ***The pharmacokinetic profile of Ryzolt demonstrated low plasma levels of tramadol, compared to Ultram, for a significant portion of time during the proposed 24-hour dosing interval. This finding may be, at best, partially responsible for your inability***

to demonstrate efficacy in the clinical trials. Provide a discussion, and data as appropriate, to address this concern.

On November 27, 2006, a post-action meeting took place between the Agency and the Sponsor. With respect to Clinical Pharmacology, the Sponsor provided response to the above-mentioned deficiency in the meeting package which was followed by a discussion in the meeting. On December 18, 2006, the Sponsor submitted the complete response to the approvable letter. And the same argument was submitted again with regard to Clinical Pharmacology in this Complete Response submission.

Summary of Sponsor's Response from the November 27, 2006 Meeting Package:
The Sponsor argued that the PK data do not support the Division's assertion that plasma tramadol levels are below those of Ultram® for a "significant portion of time" because mean plasma tramadol concentrations following administration of Ryzolt were maintained above the lowest mean concentration attained for Ultram® **for 83% of the dosing interval** (from within 1 hour post-dose until at least 20 hours post-dose following once-daily administration of 200 mg) (Figure 1, Table 1). In comparison, mean steady-state plasma tramadol concentrations for the approved once daily formulation (Ultram ER®) were maintained above the lowest mean concentration attained for Ultram® for **only 70% of the dosing interval** (from approximately 5 hours post-dose until approximately 22 hours post-dose following once-daily administration of 200 mg) (Figure 2, Table 1).

In addition, the Sponsor cited the threshold value for analgesic efficacy for tramadol from one literature as 100 ng/mL[1] and stated that steady-state plasma tramadol concentrations following multiple-dose administration of Ryzolt were maintained above 100 ng/mL for the entire dosing interval.

---

1 Lintz W, Barth H, Osterloh G, Schmidt-Bothelt E. Bioavailability of enteral tramadol formulations. 1st communication: capsules. Arzneimittelforschung. 1986;36:1278-83.

Figure 1. Mean steady-state plasma tramadol concentrations over time following administration of Ryzolt 200 mg tablets once-daily and Ultram 50 mg tablets every 6 hours (n = 26)

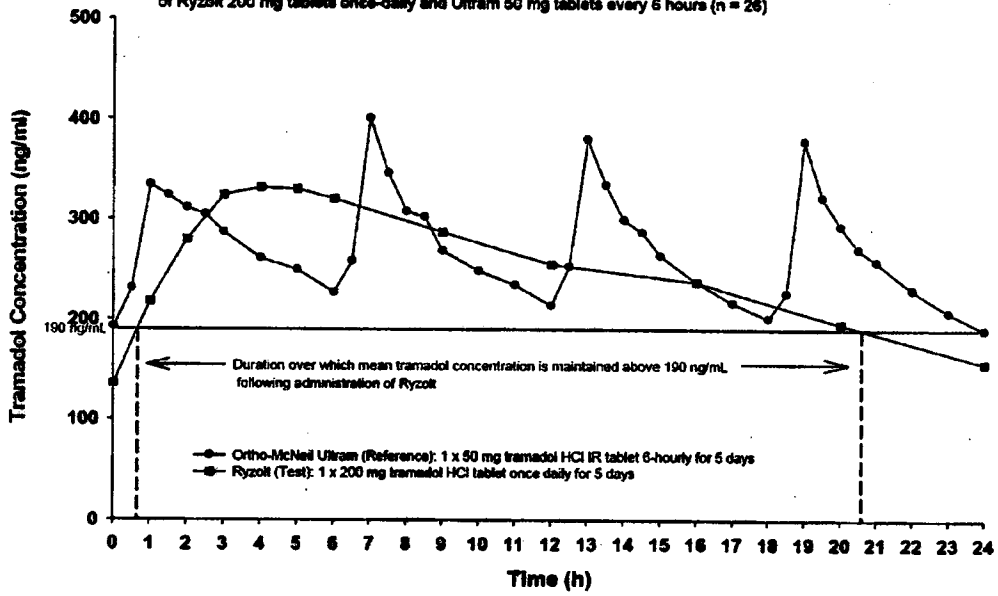
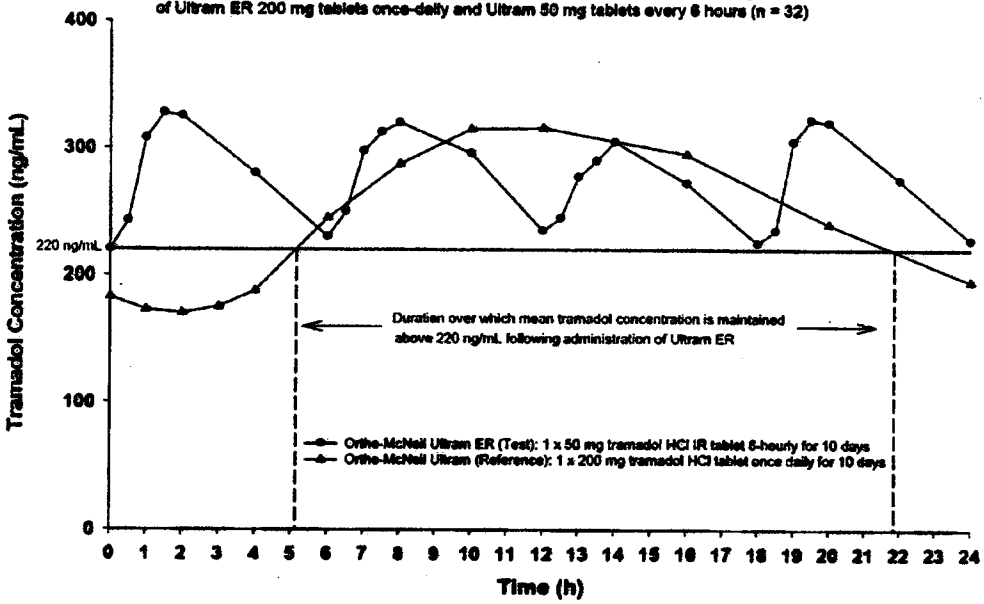


Figure 2. Mean steady-state plasma tramadol concentrations over time following administration of Ultram ER 200 mg tablets once-daily and Ultram 50 mg tablets every 6 hours (n = 32)



Adapted from NDA 21-692

Table 1. Mean steady-state plasma tramadol concentrations (ng/mL).

	MDT1-009 [a]		NDA 21-692 [b]	
Time (h)	Ultram®	Ryzolt	Ultram® [a]	Ultram ER® [a]
0	192.2	135.7	220.0	182.5
0.5	230.6	-	242.5	-
1	333.8	218.0	307.5	172.5
1.5	323.5	-	327.5	-
2	311.2	279.6	325.0	170.0
2.5	304.6	-	-	-
3	286.9	324.0	-	175.0
4	260.8	331.4	280.0	187.5
5	249.5	330.0	-	-
6	226.7	320.3	230.0	245.0
6.5	258.2	-	250.0	-
7	400.5	-	297.5	-
7.5	345.8	-	312.5	-
8	307.8	-	320.0	287.5
8.5	302.5	-	-	-
9	268.5	287.0	-	-
10	248.4	-	296.0	315.0
11	234.3	-	-	-
12	213.9	255.0	235.0	316.0
12.5	253.0	-	245.0	-
13	380.1	-	277.5	-
13.5	334.4	-	290.0	-
14	299.7	-	305.0	-
14.5	287.2	-	-	-
15	263.8	-	-	-
16	237.6	237.3	272.5	295.0
17	216.8	-	-	-
18	201.3	-	225.0	-
18.5	226.3	-	235.0	-
19	378.6	-	305.0	-
19.5	322.0	-	322.5	-
20	293.5	195.6	320.0	240.0
20.5	270.9	-	-	-
21	257.9	-	-	-
22	229.9	-	275.0	-
23	207.6	-	-	-
24	189.9	156.6	227.5	195.0

[a] *Mean concentration values estimated from NDA 21-692*

FDA's Response in the November 27, 2006 Meeting:

Reviewer's comments to the above mentioned argument by the Sponsor were documented in the post-action meeting minutes:

> ***To our knowledge, a pharmacokinetic/pharmacodynamic relationship supporting a minimum therapeutic level for tramadol is not well-established, and the 100 ng/mL value cited in the literature has not been validated.***

While your data suggest that Ultram ER had mean plasma tramadol concentrations above the lowest mean concentration attained for Ultram over a shorter period than Ryzolt, efficacy of Ultram ER was demonstrated in clinical trials. The clinical finding of efficacy supersedes any pharmacokinetic information regarding the percentage of time the mean plasma concentration of tramadol was below the C_{min}.

Discussion at the meeting:
The Division commented that the issue for this product is not whether tramadol is efficacious, but whether the Ryzolt formulation is suitable for once-daily chronic dosing. That is, does this new formulation of a known active moiety serve as an effective treatment for chronic pain.

Recommendation:
Because there is no new information to review in this submission, the recommendation made in the review of original NDA submission that "NDA 21-745 is acceptable provided that a satisfactory agreement can be reached between the Sponsor and the Agency" still stands.

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

/s/

Lei K Zhang
5/10/2007 03:45:47 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
5/10/2007 07:14:40 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Office of Clinical Pharmacology (Division of Clinical Pharmacology 2) Tracking/Action Sheet for Formal/Informal Consults**

From: Lei Zhang, Ph.D.			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 5/8/2007	IND No.: 64,317 Serial No.:	NDA No. 21-745	DATE OF DOCUMENT	11/7/2006
NAME OF DRUG [Tramadol Contramid® OAD (Tramadol HCl ER)]	PRIORITY CONSIDERATION **Standard**		Date of informal/Formal Consult:	
NAME OF THE SPONSOR: [Labopharm]				

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☒ MEETING PACKAGE (POST ACTION/END-OF-REVIEW MEETING)	☐ OTHER *(SPECIFY BELOW)*: [ ]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated) ☐ E-mail comments to: ☐Medical ☐Chemist ☐Pharm-Tox ☐Micro ☐Pharmacometrics ☐Others (Check as appropriate and attach e-mail)	☐ Oral communication with Name: [ ] ☒ Comments communicated in meeting/Telecon. see meeting minutes dated: [post-action meeting minutes in DFS on 12/26/2006]	☐ Formal Review/Memo (attached) ☐ ☐See comments below ☐ ☐See submission cover letter ☐ OTHER *(SPECIFY BELOW)*: [ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☒ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

NDA 21-745 is a 505 (b)(2) application for a new extended-release formulation of tramadol hydrochloride tablets, tramadol ER. The reference product is Ultram®(tramadol hydrochloride tablets), which is currently marketed under approved NDA 20-281. Currently, there is one approved once-a-day extended-release formulation of tramadol HCl (Ultram ER, NDA 21-692, approved in September 2005).

The original NDA 21-745 was submitted on November 25, 2005 and the Sponsor received an approvable letter on September 28, 2006. Review dated August 24, 2006 contains the Clinical Pharmacology assessment of the original NDA submission. The major deficiency cited in the approvable letter was a lack of efficacy of the proposed doses to support the proposed indication. The item listed in the approvable letter related to Clinical Pharmacology is:

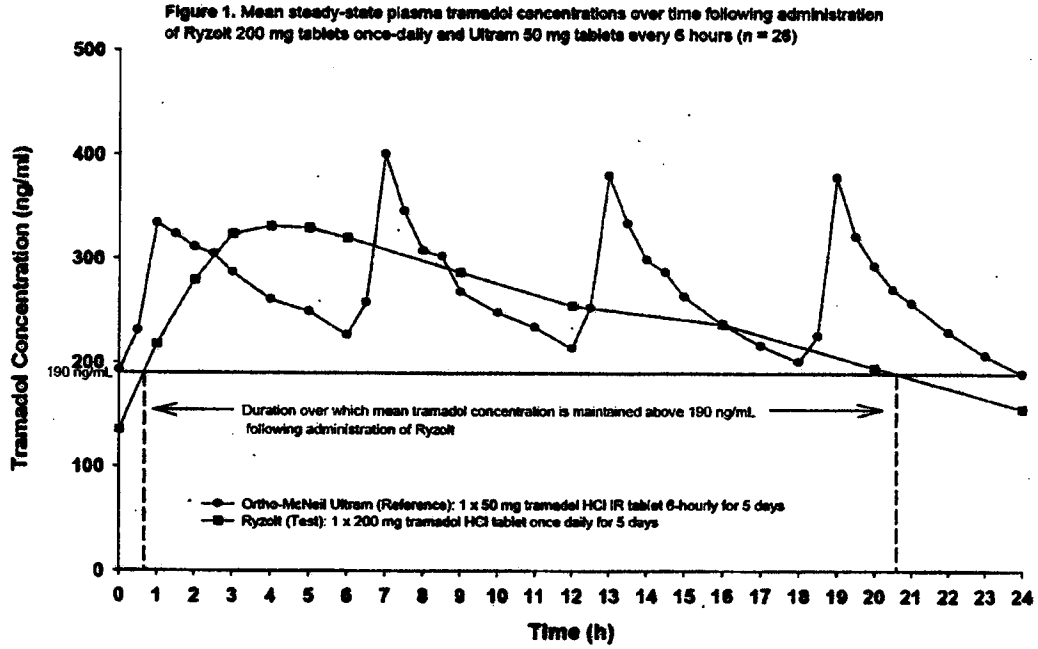
> *The pharmacokinetic profile of Ryzolt demonstrated low plasma levels of tramadol, compared to Ultram, for a significant portion of time during the proposed 24-hour dosing interval. This finding*

may be, at best, partially responsible for your inability to demonstrate efficacy in the clinical trials. Provide a discussion, and data as appropriate, to address this concern.

Summary of Sponsor's Response from the November 27, 2006 Meeting Package:

The Sponsor argued that the PK data do not support the Division's assertion that plasma tramadol levels are below those of Ultram® for a "significant portion of time" because mean plasma tramadol concentrations following administration of Ryzolt were maintained above the lowest mean concentration attained for Ultram® **for 83% of the dosing interval** (from within 1 hour post-dose until at least 20 hours post-dose following once-daily administration of 200 mg) (Figure 1, Table 1). In comparison, mean steady-state plasma tramadol concentrations for the approved once daily formulation (Ultram ER®) were maintained above the lowest mean concentration attained for Ultram® for **only 70% of the dosing interval** (from approximately 5 hours post-dose until approximately 22 hours post-dose following once-daily administration of 200 mg) (Figure 2, Table 1).

In addition, the Sponsor cited the threshold value for analgesic efficacy for tramadol from one literature as 100 ng/mL[1] and stated that steady-state plasma tramadol concentrations following multiple-dose administration of Ryzolt were maintained above 100 ng/mL for the entire dosing interval.



[1] Lintz W, Barth H, Osterloh G, Schmidt-Bothelt E. Bioavailability of enteral tramadol formulations. 1st communication: capsules. Arzneimittelforschung. 1986;36:1278-83.

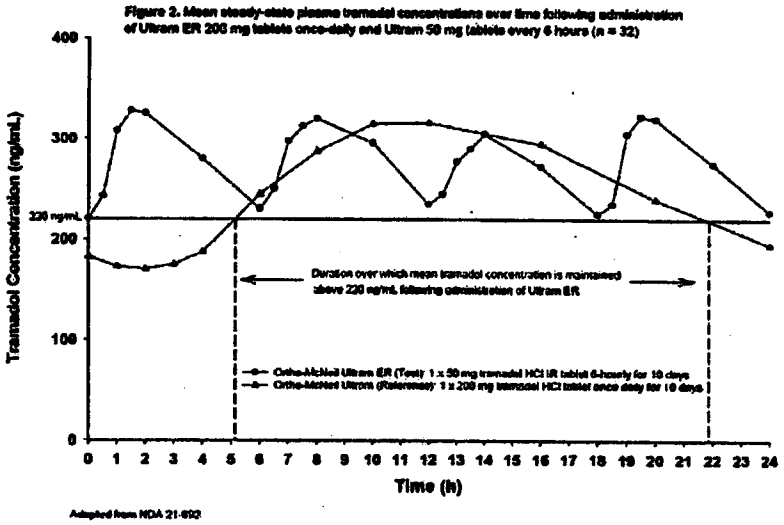


Table 1. Mean steady-state plasma tramadol concentrations (ng/mL).

	MDT1-009 [a]		NDA 21-692 [a]	
Time (h)	Ultram®	Ryzolt	Ultram® [a]	Ultram ER® [a]
0	192.2	135.7	220.0	182.5
0.5	230.6	-	242.5	-
1	333.8	218.0	307.5	172.5
1.5	323.5	-	327.5	-
2	311.2	279.6	325.0	170.0
2.5	304.6	-	-	-
3	286.9	324.0	-	175.0
4	260.8	331.4	280.0	187.5
5	249.5	330.0	-	-
6	226.7	320.3	230.0	245.0
6.5	258.2	-	250.0	-
7	400.5	-	297.5	-
7.5	345.8	-	312.5	-
8	307.8	-	320.0	287.5
8.5	302.5	-	-	-
9	268.5	287.0	-	-
10	248.4	-	296.0	315.0
11	234.3	-	-	-
12	213.9	255.0	235.0	316.0
12.5	253.0	-	245.0	-
13	380.1	-	277.5	-
13.5	334.4	-	290.0	-
14	299.7	-	305.0	-
14.5	287.2	-	-	-
15	263.8	-	-	-
16	237.6	237.3	272.5	295.0
17	216.8	-	-	-
18	201.3	-	225.0	-
18.5	226.3	-	235.0	-
19	378.6	-	305.0	-
19.5	322.0	-	322.5	-
20	293.5	195.6	320.0	240.0
20.5	270.9	-	-	-
21	257.9	-	-	-
22	229.9	-	275.0	-
23	207.6	-	-	-
24	189.9	156.6	227.5	195.0

[a] *Mean concentration values estimated from NDA 21-692*

FDA's Response in the November 27, 2006 Meeting:

Reviewer's comments to the above mentioned argument by the Sponsor were documented in the post-action meeting minutes:

> ***To our knowledge, a pharmacokinetic/pharmacodynamic relationship supporting a minimum therapeutic level for tramadol is not well-established, and the 100 ng/mL value cited in the literature has not been validated.***
>
> ***While your data suggest that Ultram ER had mean plasma tramadol concentrations above the lowest mean concentration attained for Ultram over a shorter period than Ryzolt, efficacy of Ultram ER was demonstrated in clinical trials. The clinical finding of efficacy supersedes any pharmacokinetic information regarding the percentage of time the mean plasma concentration of tramadol was below the C_{min}.***
>
> *Discussion at the meeting:*
> *The Division commented that the issue for this product is not whether tramadol is efficacious, but whether the Ryzolt formulation is suitable for once-daily chronic dosing. That is, does this new formulation of a known active moiety serve as an effective treatment for chronic pain.*

SIGNATURE OF REVIEWER: Lei Zhang, Ph.D. **SIGNATURE OF TEAM LEADER: Suresh Doddapaneni, Ph.D.**	**Date** **Date**
CC.: HFD # [ ]; TL: [ ]	**Project Manager: Paul Balcer** **Date**

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

/s/

Lei K Zhang
5/11/2007 12:10:35 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
5/11/2007 12:37:18 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

NDA	21-745
Submission Dates	11/25/2005, 3/28/2006, 6/12/2006, 6/16/2006, and 6/27/2006
Brand Name	Tramadol Contramid® OAD
Generic Name	Tramadol Hydrochloride
Reviewers	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology 2
OND Division	Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Applicant	Labopharm
Relevant IND	IND 64,317
Type of Submission; Code	505 (b)(2); 5S
Reference Listed Drug	Ultram (Immediate Release), Ortho McNeil Pharmaceuticals, Inc. (NDA 20-281)
Formulation; Strength(s)	Extended Release Tablets; 100, 200, and 300 mg
Indication	Management of moderate to moderately severe pain in adults

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

This NDA is a 505 (b)(2) application for a new extended-release once-a-day product of tramadol hydrochloride tablets, Tramadol Contramid OAD. The reference product is Ultram® (tramadol hydrochloride tablets), an immediate release product that is currently marketed under approved NDA 20-281. Currently, there is one approved once-a-day extended-release formulation of tramadol HCl (Ultram ER, NDA 21-692, approved in September 2005). The Sponsor is seeking the same indication as Ultram®, i.e., for the management of moderate to moderately severe pain. There are three dosage strengths: 100, 200 and 300 mg tablets. The intended dosing regimen is 100 to 300 mg once daily.

During the development, the Sponsor undertook a site transfer to another contract manufacturer, Confab Laboratories, St. Hubert, Quebec, Canada, to increase total production capacity in February 2005. All the pivotal clinical and PK studies used tablets manufactured at the old site. At the filing review, it was found that there was inadequate data linking the product manufactured at old and new sites. Therefore, the Sponsor was asked to conduct a bioequivalence study to compare tablets manufactured at old and new sties. In addition, food effect was studied for 300 mg tablets manufactured at the new site. The study report (Study MDT1-016) was submitted during the review cycle and included for review.

This NDA submission is for a change in formulation from the currently marketed immediate release (IR) to extended release (ER) formulation, and consequently administration of dose from once every 4-6 hours (QID) to once-a-day (QD) regimen. The primary focus of the Clinical Pharmacology review was to determine whether the following aspects were studied:

(1) The drug product meets the extended release claims made for it.
(2) The bioavailability profile established for the drug product rules out the occurrence of any dose dumping with food and alcohol.
(3) Dose proportionality
(4) The drug product's steady-state performance relative to a currently marketed IR product
(5) PK parameters in special populations (for labeling purpose)

To support human PK and biopharmaceutics requirement, Tramadol Contrmid OAD was studied in a total of 11 *in vivo* PK studies. Among these studies, 4 studies were considered pivotal for this NDA and were reviewed in detail. Remaining studies appear to be either pilot or conducted for registration in Europe and these data are only peripherally relevant to the US product. The pivotal studies assessed bioequivalence of Tramadol Contramid OAD compared to Ultram IR after multiple doses, dose proportionality, food effect, and bioequivalence (comparing tablets manufactured at old and new sites) studies. No exposure response data was submitted in the NDA. The sponsor did not conduct PK studies in special populations (e.g., renal and hepatic impairment patients, elderly patients) and drug-drug interaction studies. Instead, sponsor is

relying on Agency's previous findings for Ultram to construct their labeling. Sponsor has not established *in vitro* and *in vivo* correlation prospectively for the formulation. Dissolution method and specification were proposed based on actual performance of tablet batches used in clinical and bioavailability studies. Interaction of the ER formulation with alcohol was investigated by the *in vitro* dissolution method.

To support clinical efficacy and safety for Tramadol Contramid OAD, three pivotal 12-week efficacy trials (Study MDT3-002, 003, and 005) were conducted in knee osteoarthritis (OA) patients. Study 002 and 003 randomized patients to fixed doses of 100, 200 or 300 mg (pre-assigned dose). Study 005 included an open-label treatment phase prior to randomization and a dose titration to the fixed doses of 200 or 300 mg (not a pre-assigned dose) during the double-blind phase. In addition, there was one supportive efficacy trial (active-controlled) conducted in Europe and two long-term open-label safety trials.

In terms of safety, no new safety signal was identified with Tramadol Contramid OAD.
In terms of efficacy, Study 002 failed to demonstrate efficacy at all dose levels. Study 003 showed a statistically significant difference on Western Ontario and McMaster Universities (WOMAC) Pain Subscale Score, percent change from baseline to Week 12, at a dose of 300 mg compared to placebo in the last observation carried forward (LOCF) analysis on the full analysis set (FAS). Study 005 showed a statistically significant difference on Pain Intensity Numerical Rating Scale at Week 12 at a dose of 200 mg or 300 mg compared to placebo in the LOCF analysis on the FAS. However, both trials (Study 003 and 005) failed in the primary analysis for a chronic pain claim when the missing data due to dropouts (25-45%) were handled by BOCF (baseline observation carried forward) and continuous responder analysis (defining the dropouts as non-responders). From an efficacy standpoint, additional efficacy studies will be required for this application to be approved. Please refer to Dr. Jin Chen (Medical Reviewer) and Dr. Yongman Kim (Statistical Reviewer)'s reviews for additional details on this.

From a Clinical Pharmacology perspective, the Sponsor has adequately characterized the pharmacokinetic performance of the new extended-release formulation. The data suggested that Tramadol Contramid OAD has 20% lower C_{max} compared to Ultram IR although AUC was equivalent at steady-state. In addition, T_{max} at steady state was longer for Contramid OAD than that for Ultram (Median T_{max} 4 hr vs. 1 hr). Low concentrations of tramadol and M1 were observed in absorption phase (0-3 hr) and terminal phase (18-24 hr) following Contramid OAD once a day dosing compared to Ultram every 6 hour dosing. Because pain is usually intensified in the morning for OA, the lack of coverage for the 9 hour window that covers late evening and early morning from Tramadol Contramid OAD may have contributed to the lack of efficacy observed in the clinical trials.

Data from the bioequivalence study (Study MDT1-016 that compared 300 mg tablets manufactured at old and new sites) suggested that tablets were not bioequivalent based on the 90% confidence intervals approach. AUC was equivalent but C_{max} was 13% higher for tablets manufactured at the new site (90% CI: 93.6, 137). However, available information suggests that the 13% higher Cmax may not lead to additional safety concerns;

- The design of the study to dose 300 mg to healthy subjects may have contributed to the variability. Nausea and vomiting are adverse events associated with tramadol. To build

tolerability, patients are normally titrated to their desired dose. In this case, subjects were administered the 300 mg dose directly. Several subjects reported incidences of nausea and vomiting.

- The C_{max} of Tramadol Contramid OAD manufactured at the old site is about 20% lower compared to a corresponding total daily dose of Ultram.
- Tablets manufactured at the old site at doses of 300 mg and 400 mg (2x200 mg) have been studied in patients for up to 12 weeks (700 patients with 300 mg dose and 24 patients with 400 mg dose). These studies were conducted without regard to food and food is known to increase Cmax by at least 50%.
- In addition, 400 mg (2x200 mg) dose have been studied in 48 healthy subjects after a single dose under fasting conditions.
- Overall adverse event profile for 400 mg was similar to those of 100 to 300mg but with higher intensity as expected.
- Ultram IR was approved for use up to 400 mg/day (100 mg QID).

Since new clinical studies will be requested of Sponsor before approval, tablets produced at the commercial manufacturing site can be used to gain further clinical experience.

1.1 Recommendations

From a Clinical Pharmacology perspective, the Sponsor has adequately characterized the pharmacokinetic performance of the new extended-release formulation. The labeling recommendation is deferred pending demonstration of acceptable efficacy of the product.

Sponsor should use the tablets produced at the commercial manufacturing site (Confab Laboratories) in future clinical trial(s).

1.2 Phase 4 Commitments

None. (Not Applicable.)

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics (CPB) Findings

This application consists of 11 *in vivo* PK studies. Among these studies, 4 studies were considered pivotal and were reviewed in detail (See Appendix 4.2 for individual study reviews).

Relative Bioavailability to Ultram (IR product) (Study MDT1-009)

Relative bioavailability to Ultram (tramadol IR formulation) was determined after multiple doses. As shown in Table 1, at steady state, the 90% CIs of the geometric mean ratio (GMR) (Tramadol Contramid OAD/Ultram) of AUC_{ss} for tramadol and 90% CIs of GMR of AUC_{ss} and $C_{max,ss}$ for tramadol's active metabolite, O-desmethyl tramadol (M1), were within the 80.00% to 125.00% boundary for equivalence. However, the lower limit of 90% CI of GMR of $C_{max,ss}$ for tramadol is slightly lower than 80% (77.5%). In addition, the lower limit of 90% CIs of GMR of $C_{min,ss}$ for both tramadol and M1 are slightly lower than 80% (78.7% and 75.9%, respectively). For all conditions, 100% was not included in 90% CI indicating that exposure of tramadol and

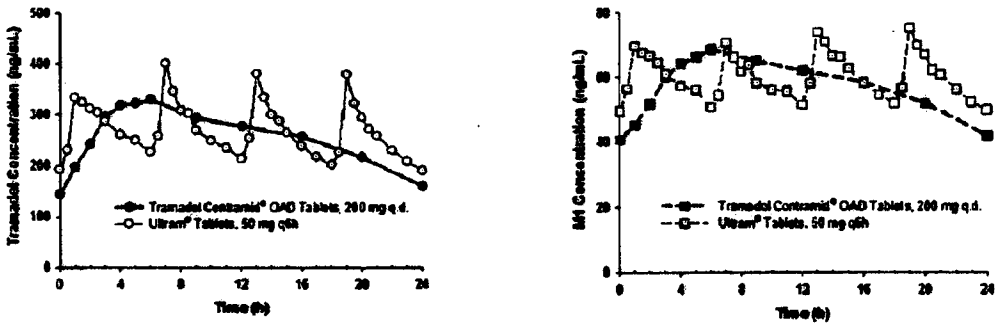
M1 after Tramadol Contramid OAD dosing is in general lower than that following Ultram Q6h dosing.

Table 1. Pharmacokinetic Parameter Values for Tramadol and its M1 Metabolite and the Comparison of Multiple Doses of 200-mg Tramadol Contramid OAD Tablets QD and 50-mg Ultram® Tablets Q6h.

PK Parameters	Contramid OAD	Ultram	Point Estimate (%)	90% Confidence Interval (%)
Tramadol				
Cmax (ng/mL)	345 ± 73	423 ± 97	81.8	77.5 - 86.3
Cmin (ng/mL)	157 ± 48	190 ± 64	83.4	78.7 – 88.4
AUC (ng·h/mL)	5991 ± 1330	6399 ± 1766	94.7	91.1 – 98.5
Tmax* (hr)	4 (3-9)	1.03 (1-3)		
M1				
Cmax (ng/mL)	71 ± 19	79 ± 17	88.5	84.1 – 93.2
Cmin (ng/mL)	41 ± 12	50 ± 15	80.7	75.9 – 85.8
AUC (ng·h/mL)	1361 ± 365	1438 ± 329	93.6	89.2 – 98.2
Tmax* (hr)	5 (3-20)	1.5 (1-3)		

* Medians (range)

Consistent with the design of the new extended release formulation, T_{max} at steady state is longer for Tramadol Contramid OAD than for Ultram (Median T_{max} 4 hr vs. 1 hr) (Figure 1). Low concentrations of tramadol and M1 were observed in absorption phase (0-3 hr) and terminal phase (18-24 hr) following Tramadol Contramid OAD once a day dosing compared to Ultram once every 6 hour dosing. Because pain is usually intensified in the morning for OA, the lack of coverage for the 9 hour window that covers late evening and early morning from Tramadol Contrmid OAD may have contributed to the lack of efficacy observed in the clinical trials.



(a) Tramadol (b) M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations on Day 5 for 200-mg Tramadol Contramid OAD Tablets QD and 50-mg Ultram® Tablets Q6h.

Dose Proportionality (Study MDT1-011)

Tramadol Contramid OAD is intended to be administered at doses ranging from 100 mg to 300 mg per day. Dose proportionality was evaluated in a single-dose study in which 100-mg, 200-mg, and 300 mg tablets were administered under fasting conditions. Dose-proportionality was evaluated by comparison of the treatment groups after dose normalization of concentration-dependent parameters (Cmax, AUC0-t, AUCinf). The 90% confidence interval around the point estimate for each comparison was in the range [0.80-1.25] for log-transformed parameters indicated that exposure of tramadol and M1 increased proportionally with dose within the investigated dose range (100-300 mg).

Food Effect (Study MDT1-006 and Study MDT1-016)

Food effect was studied in two studies: one is 200 mg single dose (Study MDT1-006) and the other is 300 mg single dose (Study MDT1-016). MDT1-016 was conducted during the review cycle and used the 300 mg tablets that were manufactured at the new site for commercial production.

Results from Study MDT1-006 suggested that food (a high fat breakfast) increased C_{max} but did not change AUC of tramadol after a single dose of 200 mg Tramadol Contramid OAD. The C_{max} of tramadol increased 54% in the presence of food (based on geometric mean ratio of fed vs. fasting). Besides AUC, mean T_{max} did not change much either in the presence of food. Similar results were observed for M1.

Results from Study MDT1-016 also showed a similar trend, i.e., food (a high fat breakfast) increases C_{max} but does not change AUC of tramadol after a single dose of 300 mg Tramadol Contramid OAD. The C_{max} of tramadol increased 67% in the presence of food (based on geometric mean ratio of fed vs. fasting). Besides AUC, mean T_{max} did not change much either in the presence of food. Similar results were observed for M1.

Therefore, there was a food-effect on C_{max} of tramadol from this extended release product.

Bioequivalence (Study MDT1-016)

During the filing review, it was found that product used in pivotal clinical trials and product proposed to be commercially marketed were manufactured at two completely different manufacturing sites. There is inadequate data linking the product manufactured at these two sites. Therefore, Study MDT1-016 was conducted during the review cycle to compare bioavailability of 300 mg tablets manufactured at the new commercial site (Confab Laboratories) to those used in pivotal clinical studies which were manufactured in the old site [redacted] b(4)

Results from Study MDT1-016 suggested that 300 mg tablets manufactured at the new site was equivalent to the tablets manufactured at the old site in terms of AUC. However, C_{max} for the new tablets was approximately 15% higher than old ones. The upper limit of 90% CIs of GMR of C_{max} for both tramadol and M1 are higher than 125% (137% and 130%, respectively).

Dissolution

The proposed dissolution method and acceptance criteria seemed adequate.

Effect of Alcohol

The effect of alcohol concentration on tablet dissolution performance was determined to evaluate the potential for dose dumping in the presence of alcohol. The rate of tramadol release decreased in proportion to the alcohol concentration (0-25% alcohol) so that when 25% alcohol was used, the amount of tramodol released was decreased by approximately 35% over the first 12hrs of dissolution. The effect of alcohol on the release of tramadol is similar for each strength of tablet. Based on these data, no *in vivo* evaluation was undertaken.

Lei Zhang, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 2

Concurrence:

Suresh Doddapaneni, Ph.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology 2

An OCP briefing (Required Inter-Divisional Level) was held on August 23, 2006.

2 QUESTION BASED REVIEW

Reviewer's Note: Because this is not a new molecular entity, question-based review will focus on the aspects specific for the new formulation.

Tramadol HCl OAD and Tramadol Contramid OAD were used interchangeably in the review.

2.1 General Attributes

2.1.1 What are the highlights of the formulation of the drug product?

TRAMADOL CONTRAMID® OAD tablets are comprised of a dual-matrix delivery system with an outer compression coat (containing tramadol hydrochloride and [redacted] and a controlled-release core containing tramadol hydrochloride and Contramid®, which provides the controlled-release characteristics (Figure 2.1.1.1). b(4)

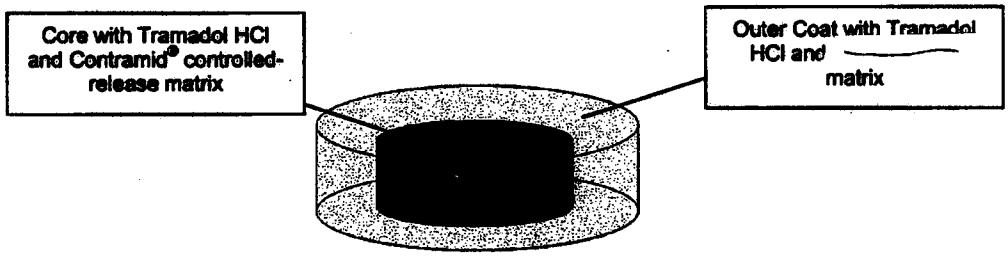


Figure 2.1.1.1. Tablet Showing the "Immediate Release" Matrix (lighter outer part) and the Controlled Release Matrix (dark inner part).

The tablet outer coat layer is not completely immediate-release. The coat is predominantly a mixture of tramadol, [redacted] that is designed to release drug in a controlled manner but more rapidly than the core, particularly over the 0-2 hour period. The tablet core is predominantly a mixture of Contramid® and tramadol is designed to release drug in a quasi-zero order manner over 24 hrs. b(4)

Dose strengths are 100, 200 and 300 mg (tramadol hydrochloride). The ratio of the amount of tramadol HCl in the coat and the core are [redacted] for 100 and 200 mg tablets, and [redacted] for 300 mg tablet. The inactive components for the tablet are not proportional for 100, 200 and 300 mg tablets (See Section 2.5.1). b(4)

2.1.2 What is the proposed mechanism of drug action and therapeutic indication?

Tramadol HCl is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite (M1) to μ-opioid receptors. Tramadol-induced analgesia is only partially antagonized by the opiate

antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

In this application, the Sponsor is seeking the same indication as that of Ultram (tramadol IR product), i.e., management of moderate to moderately severe pain in adults.

2.1.3 What are the proposed dosage recommendations and route of administration of Tramadol Contramid OAD for the proposed indication?

Tramadol Contramid OAD is taken orally.

The following language is proposed by the sponsor regarding dosage and administration:

[redacted] b(4)

[redacted] b(4)

The above proposal will be reviewed pending the completion of a successful demonstration of efficacy.

2.2 General Clinical Pharmacology

2.2.1 What are the clinical pharmacology and clinical studies used to support dosing or claims?

To support human PK and biopharmaceutics requirement, Tramadol Contramid OAD was studied in a total of 11 *in vivo* PK studies. Among these studies, 4 studies were considered pivotal for this NDA and were reviewed in detail. These studies included the assessment of bioequivalence of Tramadol Contramid OAD compared to Ultram IR after multiple doses, dose proportionality, food effect, and bioequivalence (comparing tablets manufactured at old and new sites) studies.

To support clinical efficacy and safety for Tramadol Contramid OAD, three pivotal 12-week efficacy trials (Study MDT3-002, 003, and 005) were conducted in osteoarthritis (OA) patients. Study 002 and 003 randomized patients to fixed doses of 100, 200 or 300 mg (pre-assigned

dose). Study 005 included an open-label treatment phase prior to randomization and a dose titration to the fixed doses of 200 or 300 mg (not a pre-assigned dose) during the double-blind phase. In addition there was one supportive efficacy trial (active-controlled) conducted in Europe and two long-term open-label safety trials.

2.2.2 What were the clinical endpoints used to assess efficacy in the pivotal clinical efficacy studies? What was the clinical outcome?

Studies MDT3-002, MDT3-003 and MDT3-005 are pivotal trials.

Studies 002 and 003 are replicated trials. The following are the highlights of the studies:

- Double-blind, placebo-controlled study in knee OA patients
  - MDT3-002: n=565 (75 sites in US)
  - MDT3-003: n=554 (74 sites in US)
- Study population: patients with moderate to severe pain due to knee OA, age 40-75 yrs, 60% females
- Titration (after randomization) for 1 week to the fixed dose level: 100, 200 or 300 mg once a day Tramadol OAD or placebo
- 12-week Maintenance treatment at the fixed dose: Tramadol OAD 100, 200, 300 mg or placebo
- **3 co-primary endpoints:**
  change from baseline to week 12:
  - Patient Global Ratings of Pain relief
  - Western Ontario and McMaster Universities (WOMAC) Pain Score
  - WOMAC Physical Function Score
- VAS scores are the secondary endpoints.

Study MDT3-005 has different trial design compared to Studies 002 and 003. The following are the highlights of the trial design:

- Double-blind, placebo-controlled trial in knee OA patients in US (60%), Romania, Canada and France
  - Enrolled: n=1028
  - Randomized: n=646
- 4-week open-label treatment phase
  - 2-week Run-in (titration from 100 to 300 mg)
  - 1-week Taper down from 300 to 100 mg
  - 1-week Washout
- Eligibility for randomization at end of the washout:
  - PI-NRS (Pain Intensity on 11-point Numerical Rating Scale) ≥ 4
  - PI-NRS increase ≥ 2 vs. end of Run-In
- Randomization: eligible pts (n=646) were randomized to Tramadol OAD and placebo at ratio of 2:1
- Double-blind phase
  - 2-week Titration (from 100 to 300 mg) to an optimum dose 200 mg or 300 mg
  - 12-week Maintenance dosing: 200 or 300 mg
- **Primary endpoint**: pain intensity on 11-point NRS (PI-NRS) at week 12

- Main secondary endpoints:
  - WOMAC Pain and Function
  - Patient Global Impression
  - Time-course of PI-NRS

In terms of safety, no new safety signal was identified with Tramadol Contramid OAD.
In terms of efficacy, Study 002 failed to demonstrate efficacy at all dose levels. Study 003 showed a statistically significant difference on Western Ontario and McMaster Universities (WOMAC) Pain Subscale Score, percent change from baseline to Week 12, at dose of 300 mg compared to placebo in the last observation carried forward (LOCF) analysis on the full analysis set (FAS). Study 005 showed a statistically significant difference on Pain Intensity Numerical Rating Scale at Week 12 at dose of 200 mg or 300 mg of tramadol Contramid OAD compared to placebo in the LOCF analysis on the FAS. However, the statistically significant difference shown in the studies MDT3-003 and MDT3-005 was sensitive to dropout handling methods and to choice of analysis set. The statistically significant difference was not shown in the baseline observation carried forward (BOCF) analysis, in the continuous responder analysis, or in the ITT LOCF analysis in both studies.

Overall, although the evidence of efficacy was replicated in two well controlled studies MDT3-003 and MDT3-005, the submitted data of studies with high dropout rates failed to provide substantial evidence supporting pain indication of tramadol Contramid once a day formulation because the efficacy shown might be driven by imputation of missing data due to dropouts. From an efficacy standpoint, additional efficacy studies will be required for this application to be approved. Please refer to Dr. Jin Chen (Medical Reviewer) and Dr. Yongman Kim (Statistical Reviewer)'s reviews for details.

2.2.3 Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Tramadol and its active metabolite, M1 (O-desmethyltramadol), were measured in human plasma. Please refer to Section 2.6 Analysis for analytical details.

2.2.4 What is exposure-response relationship of Tramadol Contramid OAD in terms of efficacy and safety?

Exposure-response relationship of Tramadol Contramid OAD in terms of efficacy and safety has not been studied by the Sponsor.

2.2.5 What are the PK characteristics of Tramadol Contramid OAD?

2.2.5.1 What are single dose and multiple dose PK parameters of Tramadol Contramid OAD?

Single Dose (Study MDT1-011)

Table 2.2.5.1.1. Summary of PK Parameters (Mean ± SD) for Tramadol and M1 after Single Dose (Study MDT1-011).

N = 26	Tramadol			M1		
	100 mg	200 mg	300 mg	100 mg	200 mg	300 mg
Cmax (ng/mL)	91.0 ± 26.8	196.5 ± 58.3	290.1 ± 147.2	20.4 ± 6.7	43.1 ± 16.5	59.9 ± 19.2
AUC0-t (ng·h/mL)	2064 ± 707	4332 ±1149	6568 ± 2050	502 ± 165	1050 ± 322	1570 ± 498
AUCinf (ng·h/mL)	2108 ± 731	4416 ± 1192	6741 ± 2156	520 ± 170	1080 ± 328	1640 ± 538
Tmax (h) #	9.0	5.5	5.0	12	8	16
T1/2 (h)	6.1 ± 1.3	6.1 ± 1.3	6.3 ± 1.5	7.0 ± 1.9	6.7 ± 1.8	7.4 ± 2.2

median values presented

Multiple Doses (Study MDT1-009)

Table 2.2.5.1.2. Summary of PK Parameters (Mean ± SD) for Tramadol and M1 after Multiple Doses (200 mg QD) (Study MDT1-009).

N = 26	Tramadol	M1
Cmax (ng/mL)	345 ± 72.6	70.6 ± 18.7
Cmin (ng/mL)	157 ± 48.4	40.6 ± 12.3
Tmax # (h)	4.00 (3.00 - 9.00)	5 (3-20)
AUCss (ng.h/mL)	5991 ± 1330	1361 ±365

medians (ranges)

2.2.5.2 What are the ADME (absorption, distribution, metabolism and elimination) characteristics of Tramadol Contramid OAD?

Because Tramadol Contramid OAD contains the same active moiety as the currently marketed immediate release (IR) drug product, the drug substance itself has a similar distribution and metabolism profile as tramadol IR products. The ER formulation has the most impact on absorption and elimination profile of the drug product which is indicative of a rate controlled or extended release product.

Absorption

Consistent with extended release nature, T_{max} of tramadol is longer for Tramadol Contramid OAD than for Ultram (median T_{max} 4 hr vs. 1 hr) at steady state.

Distribution (Cited from Ultram Labeling)

The volume of distribution of tramadol was 2.6 and 2.9 liters/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Metablism
Tramadol is mainly metabolized by CYP2D6 and CYP3A4. The formation of the active metabolite, M1, is mediated by CYP2D6, thus susceptible to polymorphism and inhibition.

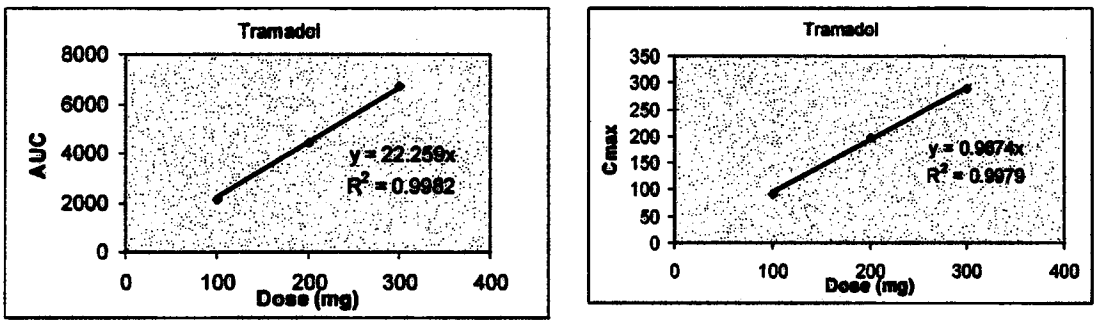
Elimination
The mean terminal plasma elimination half-lives of tramadol and M1 after administration of Tramadol Contromid OAD are approximately 6.5 and 7.5 hours, respectively, similar to that of Ultram.

2.2.5.3 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?
Tramadol Contramid OAD is intended to be administered at doses ranging from 100 mg to 300 mg per day. Dose proportionality was evaluated in a single-dose study (MDT1-011) in which 100-mg, 200-mg, and 300-mg tablets were administered under fasting conditions. PK parameters for tramadol and M1 at different doses are listed in Tables 2.2.5.1.1. Dose corrected pharmacokinetic data indicated that AUC_t and C_{max} of tramadol and M1 increased proportionally with dose within the investigated dose range (and Table 2.2.5.3.1, Figures 2.2.5.3.1 and 2.2.5.3.2).

Table 2.2.5.3.1. Mean (±SD) Pharmacokinetic Parameters of Tramadol and Statistical Analysis of Proportionality.

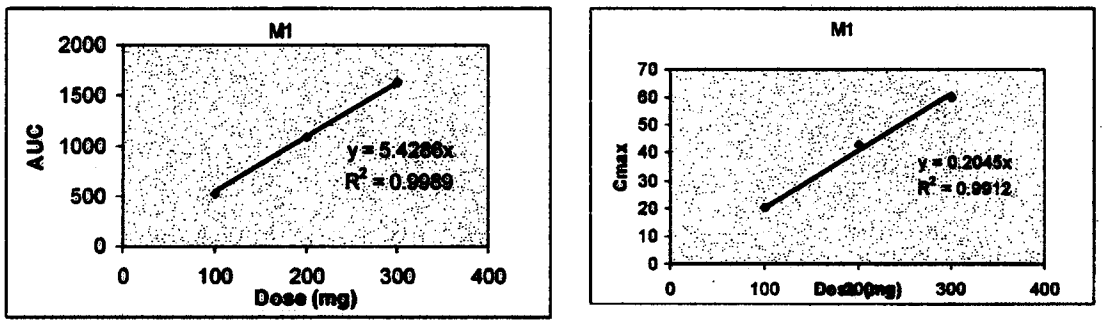
N = 26	Tramadol Contramid® OAD			Geometric Mean Ratio (90% CI) (normalised to 100 mg)		Schuirmann
	100 mg A	200 mg B	300 mg C			
C_{max} (ng/mL)	91.0 ± 26.8	196.5 ± 58.3	290.1 ± 147.2	A vs B	1.09 (1.00 – 1.19)	Excluded
				A vs C	1.02 (0.93 – 1.11)	Excluded
				B vs C	0.94 (0.86 – 1.02)	Excluded
AUC_{0-t} (ng·h/mL)	2064 ± 707	4332 ± 1149	6568 ± 2050	A vs B	1.08 (1.02 – 1.13)	Excluded
				A vs C	1.07 (1.02 – 1.12)	Excluded
				B vs C	0.99 (0.95 – 1.04)	Excluded
AUC_{inf} (ng·h/mL)	2108 ± 731	4416 ± 1192	6741 ± 2156	A vs B	1.07 (1.02 – 1.13)	Excluded
				A vs C	1.07 (1.02 – 1.12)	Excluded
				B vs C	1.00 (0.95 – 1.05)	Excluded
T_{max} (h) #	9.0	5.5	5.0	NS (nonparametric test on medians)		
$T_{1/2}$ (h)	6.1 ± 1.3	6.1 ± 1.3	6.3 ± 1.5	NS (ANOVA)*		

\# median values presented
* based on statistical assessment of treatment effect
NS Not statistically significant



a. AUC(0-∞) b. Cmax

Figure 2.2.5.3.1. Relationship between Tramdol AUC(0-inf) (a) and dose, and Cmax (b) and dose.



a. AUC(0-∞) b. Cmax

Figure 2.2.5.3.2. Relationship between M1 AUC(0-inf) (a) and dose, and Cmax (b) and dose.

2.2.6 What is the relative bioavailability of Tramadol Contramid OAD vs. Ultram following multiple doses?

At steady state, the 90% CIs of geometric mean ratio (GMR) (Tramadol Contramid OAD/Ultram) of AUC_τ for tramadol and 90% CIs of GMR of AUC_τ and C_{max} for M1 were within 80.00% to 125.00% boundary for equivalence. However, the lower limit of 90% CI of GMR of C_{max} for tramadol is slightly lower than 80% (77.5%) (Table 2.2.6.2).

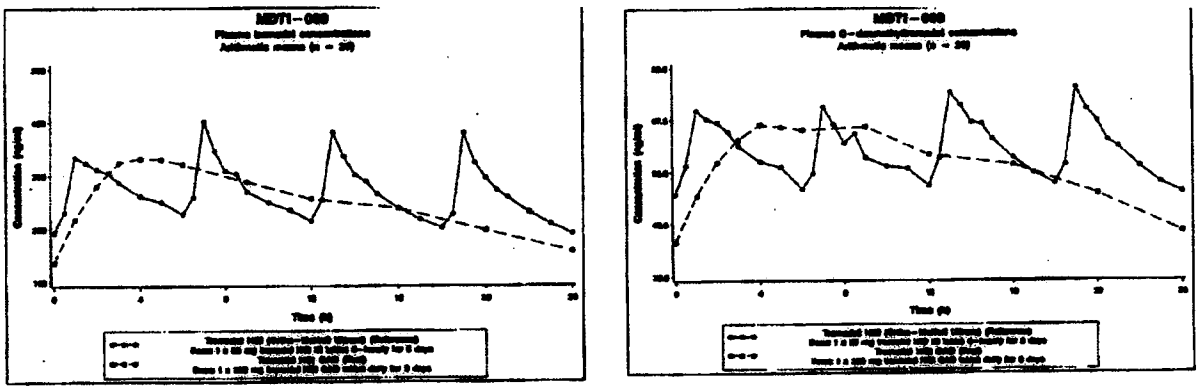
Table 2.2.6.2. Pharmacokinetic Parameter Values for Tramadol and its M1 Metabolite and the Comparison of Multiple Doses of 200-mg Tramadol Contramid OAD Tablets QD and 50-mg Ultram® Tablets Q6h.

PK Parameters	Contramid OAD	Ultram	Point Estimate (%)	90% Confidence Interval (%)
Tramadol				
Cmax (ng/mL)	345 ± 73	423 ± 97	81.8	77.5 - 86.3
Cmin (ng/mL)	157 ± 48	190 ± 64	83.4	78.7 – 88.4
AUC (ng·h/mL)	5991 ± 1330	6399 ± 1766	94.7	91.1 – 98.5
Tmax* (hr)	4 (3-9)	1.03 (1-3)		
M1				
Cmax (ng/mL)	71 ± 19	79 ± 17	88.5	84.1 – 93.2
Cmin (ng/mL)	41 ± 12	50 ± 15	80.7	75.9 – 85.8
AUC (ng·h/mL)	1361 ± 365	1438 ± 329	93.6	89.2 – 98.2
Tmax* (hr)	5 (3-20)	1.5 (1-3)		

* Medians (range)

The lower limit of 90% CI of test/reference ratio of Cmin,ss for tramadol and M1 are also slightly lower than 80% (78.7% and 75.9%, respectively). For all conditions, 100% was not included in 90% CI indicating that exposure of tramadol and M1 after Tramadol HCl OAD dosing is in general lower than that following Ultram (tramadol IR formulation) Q6h dosing.

PK profiles of tramadol following Tramadol Contramid OAD vs. Ultram dosing are different (Figure 2.2.6.1). Low concentrations of tramadol and M1 were observed in absorption phase (0-6 hr) and terminal phase (18-24 hr) following ER QD dosing compared to Ultram QID dosing.



a. Tramadol b. M1

Figure 2.2.6.1. Mean Plasma Tramadol (a) and M1 (b) Concentrations on Day 5 for 200-mg Tramadol HCl OAD Tablets QD and 50-mg Ultram® Tablets Q6h.

2.3 Intrinsic Factors

Not Applicable. The Sponsor did not conduct new studies.

Gender and Race: Most PK data for Tramadol Contramid OAD were obtained in male Caucasian subjects.

2.4 Extrinsic Factors

Not Applicable. The Sponsor did not conduct new studies.

2.5 General Biopharmaceutics

2.5.1 What is formulation (quantitative composition) of Tramadol Contramid OAD 100, 200 and 300 mg tablets?

TRAMADOL CONTRAMID® OAD controlled-release tablets contain 100 mg, 200 mg or 300 mg of tramadol hydrochloride. The tablets are white in color. The inactive ingredients in the tablet are colloidal silicon dioxide, Contramid® (modified starch), hydrogenated vegetable oil, magnesium stearate, polyvinyl acetate, povidone, sodium lauryl sulfate, xanthan gum and [redacted] The ratio of the amount of tramadol HCl in the coat and the core are [redacted] for 100 and 200 mg tablets, and [redacted] for 300 mg tablet [redacted] (Tables 2.5.1.1 and 2.5.1.2). b(4)

Table 2.5.1.1. Quantitative Composition of 100, 200 and 300 mg Tramadol Contramid OAD Tablets.

Component and Quality Standard	Function	100 mg Tablet (mg)	Percent Formula (%)	200 mg Tablet (mg)	Percent Formula (%)	300 mg Tablet (mg)	Percent Formula (%)
Active substance							
Tramadol hydrochloride, In-house	Active substance	100.00		200.00		300.00	
Excipients							
Contramid®[1] ——— in-house							
——— in-house							
Xanthan Gum, NF							
Hydrogenated Vegetable Oil ———, NF							
Magnesium Stearate, NF ———							
Colloidal Silicon Dioxide, NF ———							
In-house							
Tablet Total							

[1] Contramid® is a pre-gelatinized modified starch that meets specifications of NF

[2] The quantitative and qualitative composition of the ink (in-house quality standard) is provided in ——— DMF No.——See letter of authorization from ——— in Module 1.

b(4)

Table 2.5.1.2. Quantitative Composition of Tablet Core and Coat.

Component	Reference to Quality Standard	Function	100 mg Tablet (mg)	200 mg Tablet (mg)	300 mg Tablet (mg)
	In-house				

b(4)

b(4)

b(4)

2.5.2 Which batches were used in the pivotal clinical and bioavailability studies?

Table 2.5.2.1 listed the pivotal clinical batches manufactured — and Confab. During the product development, the Sponsor undertook a site transfer to another contract manufacturer, Confab Laboratories, St. Hubert, Quebec, Canada, to increase total production capacity. The process transferred generated batch sizes of — tablets/batch (for 100 mg and 300 mg strength tablets) and of — tablets/batch (for 200 mg strength tablets).

The Sponsor was asked to conduct a bioequivalence study (Study MDT1-016) to provide linkage between the tablets manufactured at Confab and — Sections 2.5.4 and 4.2.4).

Table 2.5.2.1. Pivotal clinical batches manufactured at Trillium and Confab.

Strength and Batch Number	Batch Size	Date and Site of Production	Use
100 mg, RX-52844		09/02, [redacted]	Clinical study MDT1-011
100 mg, RX-52845		09/02, [redacted]	Clinical studies MDT3-002, MDT3-003
100 mg, RX-55221		11/02, [redacted]	Clinical studies MDT3-002, MDT3-003
100 mg, 3J0598		11/03, Confab Laboratories, Inc.	Stability study
100 mg, 100843		09/04, Confab Laboratories, Inc.	Stability study
100 mg, 100844		09/04, Confab Laboratories, Inc.	Stability study
200 mg, RX-52751		09/02, [redacted]	Clinical studies MDT3-002, MDT3-003
200 mg, RX-50245		09/02, [redacted]	Clinical studies MDT3-002, MDT3-003, MDT1-011
200 mg, 3J0322		11/03, Confab Laboratories, Inc.	Stability study
200 mg, 100823		09/04, Confab Laboratories, Inc.	Stability study
200 mg, 100824		09/04, Confab Laboratories, Inc.	Stability study
300 mg, RX-52187		10/02, [redacted]	Clinical study MDT1-011, Stability Study
300 mg, 3J0320		11/03, Confab Laboratories, Inc.	Stability study
300 mg, 100841		09/04, Confab Laboratories, Inc.	Stability study
300 mg, 100842		09/04, Confab Laboratories, Inc.	Stability study

b(4)

2.5.3 Dose three dose strength tablets demonstrate dosage form equivalence?

No study has been conducted.

2.5.4 Are the tablets manufactured at Confab Laboratories (commercial site) bioequivalent to the tablets manufactured at [redacted] the previous site?

b(4)

Bioequivalence study (Study MDT1-016) was conducted to determine whether 300 mg tablets manufactured at Confab (new site) and [redacted] (old site) were bioequivalent. Tablets were equivalent in terms of AUC and but not equivalent in terms of Cmax. 300 mg tablets manufactured at the new site had slightly higher Cmax than tablets manufactured at old site (90% CI: 93.6%-137% for tramadol and 81.5-130% for M1) (Tables 2.5.4.1).

Table 2.5.4.1. Pharmacokinetic Parameters for Tramadol and M1 (Confab vs. [redacted])

b(4)

PK Parameters	Confab (new)	[redacted] (old)	Point Estimate (%)	90% Confidence Interval (%)
Tramadol				
Cmax (ng/mL)	454 ± 210	400 ± 206	113	93.6 - 137
AUCt (ng·h/mL)	10315 ± 3445	9854 ± 3193	105	92.6 – 119
AUC(0-inf) (ng·h/mL)	10488 ± 3468	10603 ± 4179	101	88.5 – 116
Tmax* (hr)	8 (3-24)	12 (3.02-24)		
M1				
Cmax (ng/mL)	85.7 ± 47.9	83.0 ± 53.0	103	81.5 – 130
AUCt (ng·h/mL)	2136 ± 847	2095 ± 872	99.3	84.6 – 117
AUC(0-inf) (ng·h/mL)	2318 ± 886	2247 ± 867	99.3	85.5 – 115
Tmax* (hr)	12 (4-24)	16 (4-24)		

* Medians (range)

2.5.5 What is the effect of food on the bioavailability of the drug from the dosage form?

Food effect was evaluated in Study MDT1-006 with 200 mg tablets and Study MDT1-016 with 300 mg tablets. Food (high fat breakfast) increased Cmax of tramadol by 54 and 67%, respectively, based on geometric mean ratio of fed vs. fasting in these two studies. AUC and T_{max} did not change.

Table 2.5.5.1. Study MDT1-006 (200 mg Tablet).

SUMMARY OF PHARMACOKINETIC DATA FOR TRAMADOL

[n = 27; Test 1 dose: 1 x 200 mg tramadol-HCl OAD tablet
Test 2 dose: 1 x 200 mg tramadol-HCl OAD tablet]

		Tramadol-HCl/Contramid® (Test 1)			Tramadol-HCl/Contramid® (Test 2)					
VARIABLE	UNIT	ARITHMETIC			ARITHMETIC			MEAN RATIO	90% CONFIDENCE INTERVAL	INTRA INDIVIDUAL
		Mean	SD	Range	Mean	SD	Range	(%)*	(%)**	CV (%)
C_{max}	(ng/ml)	241	61.5	168 - 419	381	136	198 - 687	154	136 ; 173	26
T_{max}#	(h)	6.00		3.00 - 16.0	6.00		2.00 - 12.0	0.00	-1.50 ; 1.00	
AUC(0 - t_{last})	(ng·h/ml)	5198	1833	3340 - 10861	5115	1690	2601 - 9489	99.0	94.6 ; 104	10
AUC(0 - ∞)	(ng·h/ml)	5310	1908	3369 - 11284	5168	1749	2622 - 9621	98.0	93.7 ; 102	10
C_{max}/AUC(0 - ∞)	(1/h)	0.05	0.01	0.03 - 0.09	0.08	0.02	0.05 - 0.12	157	139 ; 176	25
$t_{1/2}$	(h)	6.83	1.51	4.61 - 11.5	5.76	1.05	4.54 - 9.21	88.9	86.2 ; 91.6	7
MRT	(h)	18.6	3.33	10.1 - 28.8	12.2	1.94	8.92 - 16.4			
MVD	(h)	20.0	3.39	9.10 - 23.2	12.9	4.64	4.90 - 20.6	57.7	48.8 ; 68.2	37

* : Point estimate of "test 2/test 1" mean ratio from analysis of log-transformed data.

** : 90% Conventional confidence interval for the "test 2/test 1" mean ratio from analysis of variance of log-transformed data.

: Medians, ranges, nonparametric point estimate of "test 2-test 1" median difference and corresponding confidence interval.

SUMMARY OF PHARMACOKINETIC DATA FOR O-DESMETHYLTRAMADOL

[n = 27; Test 1 dose: 1 x 200 mg tramadol-HCl OAD tablet
Test 2 dose: 1 x 200 mg tramadol-HCl OAD tablet]

		Tramadol-HCl/Contramid® (Test 1)			Tramadol-HCl/Contramid® (Test 2)					
VARIABLE	UNIT	ARITHMETIC			ARITHMETIC			MEAN RATIO	90% CONFIDENCE INTERVAL	INTRA INDIVIDUAL
		Mean	SD	Range	Mean	SD	Range	(%)*	(%)**	CV (%)
C_{max}	(ng/ml)	60.8	19.4	8.40 - 96.6	89.4	35.3	19.8 - 166	149	134 ; 167	24
T_{max}#	(h)	9.00		3.00 - 24.0	7.00		4.50 - 12.0	-3.00	-3.51 ; 0.00	
AUC(0 - t_{last})	(ng·h/ml)	1396	388	247 - 2111	1401	434	315 - 2230	100	97.0 ; 107	10
AUC(0 - ∞)	(ng·h/ml)	1430	389	288 - 2174	1445	434	325 - 2240	100	95.6 ; 105	10
C_{max}/AUC(0 - ∞)	(1/h)	0.04	0.01	0.03 - 0.07	0.06	0.02	0.04 - 0.10	149	135 ; 163	20
$t_{1/2}$	(h)	7.51	1.39	5.51 - 11.5	6.49	1.05	4.96 - 8.56	86.1	83.0 ; 89.4	8
MRT	(h)	17.7	3.91	11.6 - 30.6	14.3	2.05	10.4 - 18.8			
MVD	(h)	20.6	3.39	9.44 - 23.8	14.4	4.38	6.20 - 21.8	67.6	58.7 ; 77.8	31

* : Point estimate of "test 2/test 1" mean ratio from analysis of log-transformed data.

** : 90% Conventional confidence interval for the "test 2/test 1" mean ratio from analysis of variance of log-transformed data.

: Medians, ranges, nonparametric point estimate of "test 2-test 1" median difference and corresponding confidence interval.

Test 1: Fed; Test 2: Fasting

Table 2.5.5.2. Study MDT1-016 (300 mg Tablet).
Summary for Tramadol:

[N = 27 (*N = 26): Product A dose: 1 x 300 mg tramadol HCl controlled-release tablet (fasting)
N = 19: Product B dose: 1 x 300 mg tramadol HCl controlled-release tablet (fed)]

		Tramadol Contramid® OAD (Product A)			Tramadol Contramid® OAD (Product B)					
VARIABLE	UNIT	ARITHMETIC			ARITHMETIC			MEAN RATIO	90% CONFIDENCE INTERVAL	INTRA INDIVIDUAL
		Mean	SD	Range	Mean	SD	Range	(%)*	(%)**	CV (%)
C_{max}	(ng/ml)	454	210	237 - 1087	798	313	272 - 1345	167	130 ; 214	43
T_{max}#	(h)	8.00		3.00 - 24.0	10.0		3.00 - 20.0		p - 0.6056	
AUC(0 - t_{last})	(ng· h/ml)	10315	3445	6122 - 18081	10990	2779	6143 - 18068	108	99.1 , 124	28
AUC(0 - ∞)*	(ng· h/ml)	10488	3468	6417 - 19438	11268	3079	6227 - 19651	106	97.4 ; 124	30
$t_{1/2}$*	(h)	7.97	1.79	5.15 - 12.1	7.97	1.86	4.66 - 10.9	97.7	76.1 , 101	24
K_a*	(1/h)	0.89	0.02	0.06 - 0.14	0.10	0.02	0.06 - 0.15			

* : Point estimate of "test/reference" mean ratio from analysis of log-transformed data.

** : 90% Conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

. Medians, ranges, p-value for non-parametric Wilcoxon two-sample test.

Dataset No.1: Subjects who had no significant protocol deviations and did not vomit during the dosing interval

Summary for M1:

[N = 27 (*N = 26): Product A dose: 1 x 300 mg tramadol HCl controlled-release tablet (fasting)
N = 19: Product B dose: 1 x 300 mg tramadol HCl controlled-release tablet (fed)]

		Tramadol Contramid® OAD (Product A)			Tramadol Contramid® OAD (Product B)					
VARIABLE	UNIT	ARITHMETIC			ARITHMETIC			MEAN RATIO	90% CONFIDENCE INTERVAL	INTRA INDIVIDUAL
		Mean	SD	Range	Mean	SD	Range	(%)*	(%)**	CV (%)
C_{max}	(ng/ml)	85.7	47.9	19.7 - 203	131	75.4	24.8 - 262	151	112 ; 204	54
T_{max}#	(h)	12.0		4.08 - 24.0	10.0		5.00 - 20.0		p - 0.0318	
AUC(0 - t_{last})	(ng· h/ml)	2136	847	442 - 3757	2194	952	632 - 3441	106	85.8 ; 130	35
AUC(0 - ∞)*	(ng· h/ml)	2318	886	474 - 3939	2346	952	702 - 3473	109	92.9 ; 121	32
$t_{1/2}$*	(h)	9.57	2.28	5.86 - 13.3	7.74	1.85	5.57 - 12.5	78.8	66.3 ; 93.7	29
K_a*	(1/h)	0.88	0.02	0.06 - 0.12	0.89	0.02	0.06 - 0.12			

* . Point estimate of "test/reference" mean ratio from analysis of log-transformed data.

** . 90% Conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

: Medians, ranges, p-value for non-parametric Wilcoxon two-sample test.

Treatment A: Fed; Treatment B: Fasting

2.5.6 Has the Sponsor established in vitro-in vivo correlation (IVIVC) of Tramadol Contramid OAD?

The Sponsor did not establish IVIVC for the product.

2.5.7 Has the Sponsor developed an appropriate dissolution method and specifications that will ensure in vivo performance and quality of the product?

Dissolution Method

Table 2.5.7.1 lists the proposed dissolution method. It seems adequate.

Table 2.5.7.1. Dissolution Method.

Drug Release Parameters	Value
Apparatus	Automated USP Dissolution Apparatus #1 (Basket)
Dissolution medium	pH 6.8 buffer
Dissolution medium volume	900 mL
Dissolution medium temperature	37.0 ± 0.5°C
Rotation speed	100 rpm
Sampling Time	2, 7, 12, and 20 hours

The Sponsor used different dissolution methods during early development of the formulation. Two sets of *in vitro* dissolution test conditions (standard and robustness conditions) were used to evaluate the performance of the formulation in an attempt to mimic, *in vitro*, the potential gastrointestinal extremes to which the tablets might be exposed. These were:

Standard Conditions:

Apparatus :	USP Type III reciprocating cylinder
No. of Tablets/Test :	6
Reciprocation Rate :	15 dips/min.
Dissolution Medium/Duration:	Dilute HCl (pH 1.2; 0.5hr); Sodium phosphate buffer (pH 6.8 containing 4,500 IU/L alpha amylase; 0.5hr); Sodium phosphate buffer (pH 7.5; 23 hr).

Robustness Conditions:

Apparatus :	USP Type III reciprocating cylinder
No. of Tablets/Test :	6
Reciprocation Rate :	30 dips/min.
Dissolution Medium/Duration:	Dilute HCl (pH 1.2; 2.0hr); Sodium phosphate buffer (pH 6.8 containing 5000 IU/L alpha amylase; 22 hr);

The *in vitro* test conditions used for formulation development (standard Type III USP method as described above) were shown to be discriminatory since they allowed selection of formulations that met the target *in vitro* profile. The method also showed to identify tablets that had been damaged.

The methods used Type III apparatus were not considered practical for routine QC release of GMP lots for clinical, or subsequent commercial use. In addition, few QC laboratories possessed the Type III USP apparatus required to perform the test. Therefore, the Sponsor performed experiments to determine if tests under robustness condition were independent of *in vitro* conditions and whether they would result in similar release profiles as the proposed dissolution method that use USP Type I apparatus. The key tests were:

(i) Dissolution of tablets in sodium phosphate buffer pH 6.8 containing 4,500 IU/L alpha amylase for 24 hr at 30 dips per minute using USP Type III apparatus i.e. omitting the pH 1.2 and pH 7.5 incubations.

(ii) Dissolution of tablets in sodium phosphate buffer pH 6.8 for 24 hr using USP Type I apparatus and a rotation speed of 100 rpm.

The data showed that the removal of pH 1 and pH 7.5 incubations and an increase in the agitation rate had no effect on tablet performance. In addition, the dissolution profiles of numerous development batches are comparable using the different methods (Table 2.5.7.2).

Table 2.5.7.2. Similarity (f2) analyses, slope and correlation coefficients of mean dissolution results from complete dissolution profiles (0-24 hr) of tablets tested under development (Type III) and routine dissolution methods (Type I).

Tablet strength	Batch Number	Use	Slope	Correlation Coefficient (r^2)	F_2* QC Method vs. Development Method
100 mg	RX-40749	Phase I clinical studies	1.010	0.9998	97.2
	RX-52844	Phase I clinical studies	0.995	0.9987	77.3
	RX-71373	Validation Studies	0.984	0.9999	86.5
	RX-71374	Validation Studies	1.001	0.9998	87.1
		Slope/R^2/F_2 all lots	0.997	0.9998	87.7
200 mg	RX-40751	Phase I clinical studies	1.017	0.9994	92.6
	RX-40752	Phase I clinical studies	0.996	0.9997	93.4
	RX-47058	Phase I clinical studies	0.990	0.9987	82.1
	RX-50245	Phase I clinical studies	1.110	0.9996	68.8
	RX-71377	Validation Studies	0.972	0.9996	72.2
	RX-71378	Validation Studies	1.014	0.9997	91.7
		Slope/R^2/F_2 all lots	1.015	0.9995	92.0
300 mg	RX-52187	Phase I clinical studies	1.002	0.9997	95.6
	RX-71379	Validation Studies	0.995	0.9990	85.0
	RX-71380	Validation Studies	1.012	0.9991	87.8
		Slope/R^2/F_2 all lots	1.003	0.9993	89.6

* f2 values were generated for a total of 10 time points using 6 tablets per time point.

Therefore, the proposed dissolution method with Type 1 apparatus seems adequate.

Specifications:

In the absence of IVIVC data, following specifications were proposed for 100, 200 and 300 mg tablets based on numerical limits of +/-10 % around the mean value obtained (Tables 2.5.7.3 and 2.5.7.4). They seem acceptable.

Table 2.5.7.3. Summary of in vitro Dissolution Tests for Batches of Tramadol Contramid® OAD Tablets Used in Clinical Studies (Data Extracted From the Batch Analysis Certificates).

Study Ref. No.	Product ID / Batch No	Dosage form	Collection times Mean % dissolved (range)		
			2 h	6/7 h	20 h
MDT1-004	40749	100 mg	25 (24-27)	45 (44-48)	95 (93-95)
MDT1-011	52844	100 mg	26 (25-27)	51 (50-53)	97 (95-98)
MDT1-004 MDT1-007	40752	200 mg	27 (27-27)	52 (51-52)	94 (92-95)
MDT1-005	40751	200 mg	28 (27-30)	53 (51-58)	97 (95-99)
MDT1-006 MDT1-010	47058	200 mg	26 (25-27)	52 (51-54)	92 (90-94)
MDT1-011 MDT1-012	50245	200 mg	27 (26-28)	51 (50-54)	95 (94-97)
MDT1-009	52751	200 mg	28 (26-29)	52 (50-54)	95 (92-97)
MDT1-013	83537	200 mg	25 (24-25)	48 (47-51)	90 (89-91)
MDT1-013	83538	200 mg (film-coated)	24 (23-25)	48 (45-49)	89 (86-90)
MDT1-002	G-653	200 mg	29 (28-30)	51 (50-53)	94 (92-96)
MDT1-011	52187	300 mg	23 (22-24)	45 (44-46)	90 (88-91)

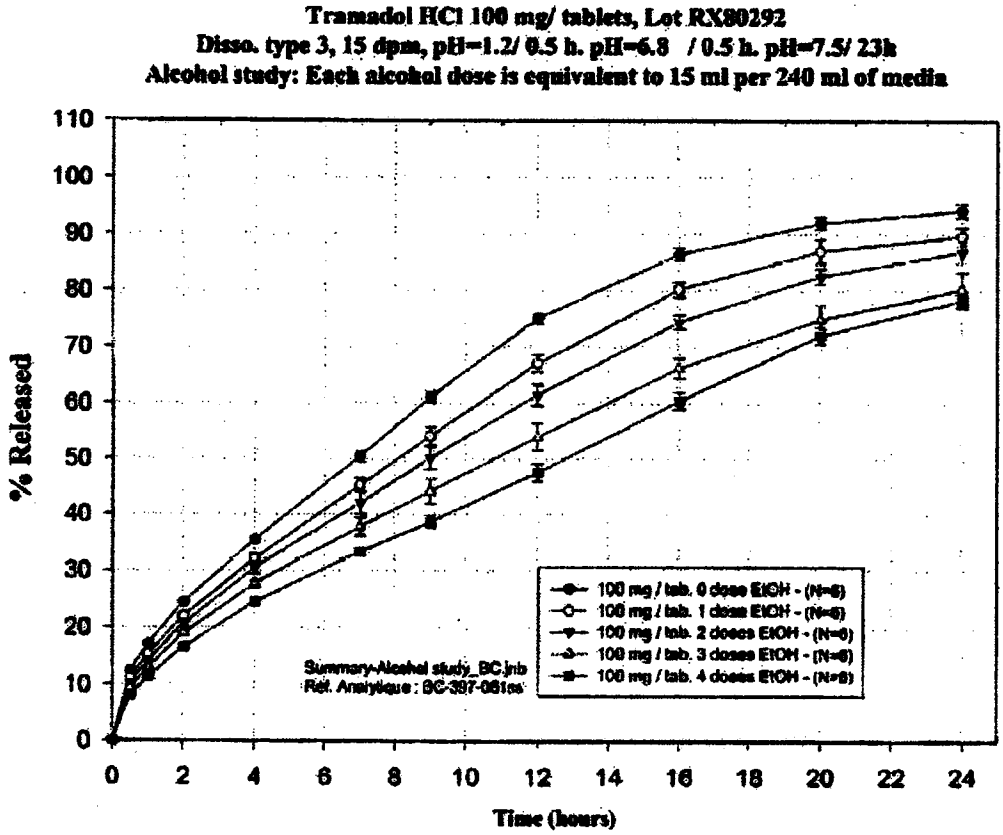


Figure 2.5.6.1. Effect of alcohol on the release of tramadol from Tramadol Contramid® OAD 100 mg strength tablets. (1 dose: 6.25% alcohol; 2 dose: 12.5% alcohol; 3 dose: 18.75% alcohol; 4 dose: 25% alcohol).

2.6 Analytical

2.6.1 Were the analytical methods used to determine Tramadol and M-1 in biological fluids adequately validated?

Yes, concentrations of tramadol and its metabolite, M1, were adequately measured in human plasma by validated LC/MS/MS assays and summarized in Table 2.6.1.1. The assays are sensitive and selective for the analytes.

Long-term stability of tramadol and M1 in frozen human plasma at -20°C was at least 2.5 months. The stability was long enough to cover the time span from sample collection to sample analysis.

Table 2.6.1.1. Analytical Methods used for the Determinations of Tramadol and M1 in Each Study.

Studies	Refer-ence Valida-tion Method	Analytes	Internal Standard	LOQ (ng/ml)	Linear Range (ng/ml)	Between Run Precision (%RSD)	Between Run Accuracy (% nominal values)	QC Samples (ng/mL)
MDT1-009	Validation No. 66/2000 (Applicable to Study 429/2002)	Tramadol M1		0.776 0.790	0.776-794 (r^2> 0.999) 0.790-880 (r^2 > 0.999)	< 7 < 7.4	95-104 95-107	0.922, 1.85, 3.72, 9.52, 24.7' 65.9, 170, 337, 667 0.939, 1.89, 3.79, 9.69, 25.2, 67.0, 173, 343, 678
MDT1-011	CeMAX No. 02.09.02	Tramadol M1	Propranolol	1 0.5	1-700 (r^2 0.999) 0.5-300 (r^2 0.999)	< 7.1 < 6.7	102 99-103	1, 3, 250, 600 0.5, 1.5, 100, 240
MDT1-006	Validation No. 66/2000 (Applicable to Study 172/2002)	Tramadol M1		0685 0.685	0.685-1403 (r^2> 0.999) 0.685-1403 (r^2 > 0.999)	< 11 < 6	99-103 96-104	0.889, 1.78, 3.55, 7.11, 19.5, 39.0, 78.0, 156, 312, 624 0.889, 1.78, 3.55, 7.11, 19.5, 39.0, 78.0, 156, 312, 624
MDT1-016	79081	Tramadol M1		3 0.792	3-775 (r^2> 0.999) 0.792-204 (r^2 > 0.999)	< 7 < 8	99-101 99-104	3.47, 6.94, 1.9, 31.5, 72.6, 166, 332, 667 0.881, 1.76, 3.52, 8, 18.4, 42.2, 84.4, 169

b(4)

3 DETAILED LABELING RECOMMENDATIONS

The labeling recommendation is deferred pending the completion of successful demonstration of efficacy.

Although labeling has not been reviewed in detail, among other things, the following items would need to be paid attention to during resubmission review:

- Food increases Cmax. Cmax at 300 dose is at the levels seen at the dose of 500 mg without food. Proper language is needed in the labeling with regard to food.
- [redacted] b(4)

Appears This Way
On Original

26 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Approvable Letter-_____

4.2 Individual Study Review

4.2.1 Study MDT1-009: A study to compare the bioavailability of two tramadol hydrochloride tablet products (50 mg and 200 mg, respectively) at steady-state under fasting conditions

---

Study Period: June 5, 2003 to August 8 2003
Sample Analysis Period: August 19 to August 28, 2003
Principle Investigator: Dr. J Terbalnché
Study Center: [redacted]

b(4)

Analytical Site: [redacted]

Objectives: To compare the pharmacokinetic profiles at steady-state of the test product, Tramadol HCl OAD 200 mg tablets and the reference product, Tramadol HCl 50 mg (IR) tablets (Ortho-McNeil Ultram®).

Study Design: The study was an open, multiple-dose, randomized, two-period crossover study in twenty-six (26) normal, healthy, non-smoking male and female subjects under fasting conditions. All subjects (22 males and 4 females) completed the study. 23 were Caucasians and 3 were black. Please refer to Table A1 in the Appendix for demographic information.

Subjects were randomized to Sequence 1 (AB) or Sequence 2 (BA). There was a 16-day washout period between Treatment A and B.

Treatment A:
Days 1-5: One Tramadol HCl OAD 200 mg tablet once daily
Treatment B:
Days 1-5: One Tramadol HCl 50 mg IR tablet (Ultram) every 6 hours

Test Articles:
Test:
Tramadol HCl 200 mg OAD Tablets
Manufacturer: Labopharm Inc., Canada
Batch #: RX 52751; Expiration Date: September 2004

Reference:
Ultram® 50 mg Tablets
Manufacturer: Ortho-McNeil Pharmaceutical, Inc. OMP Division
Batch #: 92P049 1E; Expiration Date: April 2004

Sample Collection:
Treatment A:
Days 1, 3 and 4: 0 (pre-dose)

Day 5: 0 (pre-dose), 1, 2, 3, 4, 5, 6, 9, 12, 16, 20 and 24 hours post-dose

Treatment B:
Days 1, 3 and 4: 0 (pre-dose)
Day 5: 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 12.5, 13, 13.5, 14, 14.5, 15, 16, 17, 18, 18.5, 19, 19.5, 20, 20.5, 21, 22, 23, and 24 hours post-dose

Sample Analysis: All plasma samples were delivered to the ——— for the analysis of tramadol and O-desmethyltramadol (M1) using a validated LC/MS/MS method (Validation No. 66/2000, August 2002). ——— was used as an internal standard. The LLOQ was 0.776 ng/mL for tramadol and 0.790 ng/mL for O-desmethyltramadol. b(4)

Pharmacokinetic and Statistical Analysis: All BLQ values were substituted by zero for calculation of the descriptive statistics of the concentrations.

The test product was compared to the reference product with respect to the pharmacokinetic variables Cmax,ss, Cmin,ss, Tmax, AUCss, %PTF, %SWING, HVD and T75%Cmax using an analysis of variance with sequence, subject(sequence), product and period effects after a logarithmic transformation of the data. Parametric point estimates and 90% confidence intervals for the "test/reference" mean ratios of those variables were calculated and presented graphically. In addition, a non-parametric point estimate and 90% confidence interval for the "test-reference" median difference of Tmax was calculated.

Pharmacokinetic Results:
Steady-State Assessment
Trough plasma tramadol levels were measured from Day 3 to Day 5 before the morning dose to verify that steady-state had been achieved (Tables 1 and 2).

Table 1. Trough Plasma Tramadol Levels in ng/mL (Mean ± SD).

	Tramadol Contramid® OAD tablets 200 mg	Ultram® tablets 50 mg QID
Day 3	137 ± 53	186 ± 59
Day 4	137 ± 64	192 ± 60
Day 5	136 ± 56	192 ± 61

Table 2. Trough Plasma O-Desmethyltramadol (M1) Levels in ng/mL (Mean ± SD).

	Tramadol OAD Tablets (200 mg QD)	Ultram Tablets (50 mg Q6hr)
Day 3	40 ± 13	51 ± 11
Day 4	37 ± 14	50 ± 11
Day 5	38 ± 17	50 ± 12

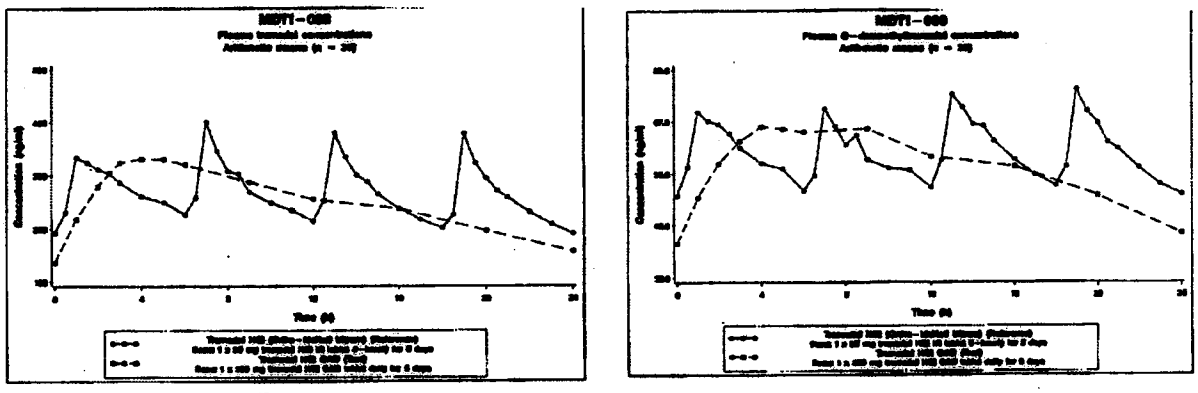
PK Profiles and Relative Bioavailability

The individual plasma concentration-time profiles for tramadol after multiple dosing of Ultram and Tramadol HCl OAD were shown in Figure 1 (a and b). The mean plasma concentration-time profiles of tramadol and M1 metabolite after multiple dosing are shown in Figure 2(a and b).

b(4)

a. Ultram b. Tramadol HCl OAD

Figure 1. Individual Plasma Tramadol Concentrations on Day 5 for 50-mg Ultram® Tablets Q6h (a) and 200-mg Tramadol HCl OAD Tablets QD (b) (Geometric mean is shown in dotted line).



a. Tramadol b. M1

Figure 2. Mean Plasma Tramadol (a) and M1 (b) Concentrations on Day 5 for 200-mg Tramadol HCl OAD Tablets QD and 50-mg Ultram® Tablets Q6h.

The mean pharmacokinetic parameters for tramadol and O-desmethyltramadol (M1) following multiple dose results are summarized in Tables 3 and 4. Graphical representation of the 90% confidence intervals for the mean ratios of tramadol and M1 pharmacokinetic variables are shown in Figures 3 and 4.

Reviewer's Note: When comparing the test and reference products, Cmax of the four dosing intervals (0-24 hr on Day 5) was Cmax,ss for Ultram. Cmin,ss was the concentration at the end of the dosing interval (24 hr on Day 5) for both Tramadol HCl OAD and Ultram. Tmax of the four dosing intervals was used for statistical analysis regardless whether it is associated with the Cmax,ss for Ultram. There would be small difference if using mean values for Cmax,ss, Tmax and Cmin,ss or observed Cmin and Tmax associated with Cmax,ss for Ultram. But overall trend would not change.

The 90% confidence intervals for the test/reference ratio of AUCss for tramadol and M1 are within the interval [80-125]% (Tables 3 and 4), indicating that in terms of extent of exposure, the test product is bioequivalent to the reference immediate-release formulation.

Table 3. Pharmacokinetic Parameters for Tramadol After Multiple-Dose Administration of Tramadol OAD (200 mg) and Ultram (50 mg Q6h).

SUMMARY OF PHARMACOKINETIC DATA FOR TRAMADOL

[n = 26; Reference dose: 1 x 50 mg tramadol HCl IR tablet 6-hourly for 5 days
Test dose: 1 x 200 mg tramadol HCl OAD tablet daily for 5 days]

		Tramadol HCl (Ortho-McNeil Ultram) (Reference)			Tramadol HCl OAD (Test)					
VARIABLE	UNIT	ARITHMETIC			ARITHMETIC			MEAN RATIO	90% CONFIDENCE INTERVAL	INTRA INDIVIDUAL
		Mean	SD	Range	Mean	SD	Range	(%)*	(%)**	CV (%)
$C_{max,ss}$	(ng/ml)	433	96.8	220 - 646	345	72.6	206 - 479	81.8	77.5 ; 86.3	11
$C_{min,ss}$	(ng/ml)	190	64.0	87.9 - 348	197	46.4	77.5 - 286	93.4	78.7 ; 82.4	12
T_{max}#	(h)	1.83		1.00 - 3.00	4.88		3.00 - 9.00	2.78	2.50 ; 3.24	
AUC_{ss}	(ng·h/ml)	6289	1766	3264 - 10801	5991	1330	3570 - 8227	94.7	91.1 ; 98.5	8
%PTF	(%)	91.1	20.9	53.5 - 130	76.9	20.0	27.6 - 110	83.1	75.2 ; 91.9	21
%SWING	(%)	133	39.5	64.6 - 222	131	52.2	31.3 - 247	94.4	82.1 ; 109	30
HVD	(h)	22.8	2.24	16.6 - 24.0	20.7	2.56	15.9 - 23.8	94.8	90.1 ; 98.0	9
$T_{75\%C_{max}}$	(h)	9.22	3.34	4.13 - 18.9	11.8	4.51	6.42 - 22.4	123	106 ; 144	34

* : Point estimate of "test/reference" mean ratio from analysis of log-transformed data.

** : 90% Conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

\# : Median, ranges, nonparametric point estimate of "test-reference" median difference and corresponding confidence interval.

Note: The observed Tmax (Tmax relating to the first dose at time 0) for tramadol following Ultram Q6h dosing was 10.5 ± 5.4 hr.

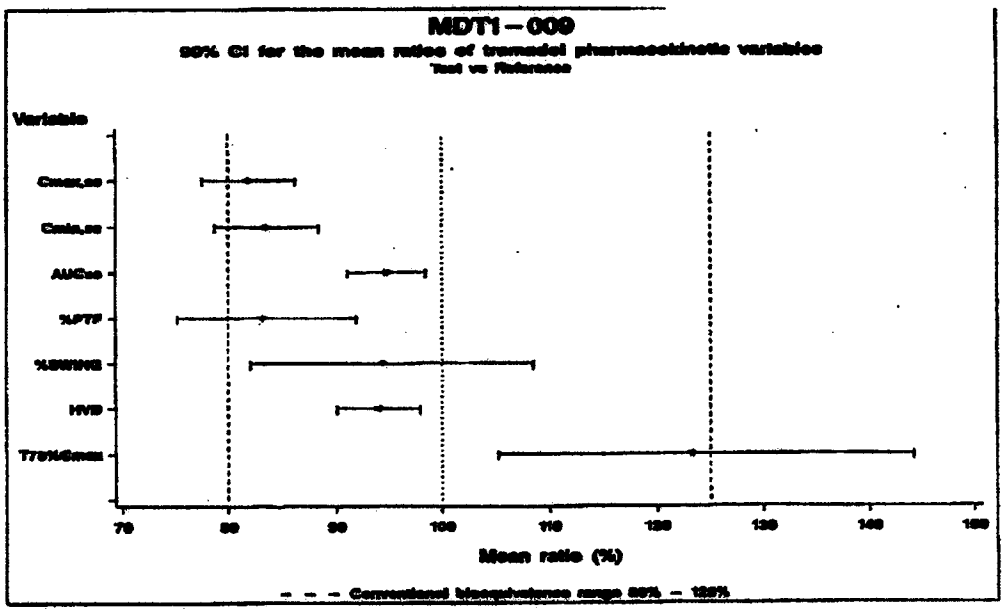


Figure 3. Graphical representation of the 90% confidence intervals for the mean ratios of tramadol pharmacokinetic variables.

Table 4. Pharmacokinetic Parameters for O-desmethyltramadol (M1) After Multiple-Dose Administration of Tramadol OAD (200 mg) and Ultram (50 mg Q6h).

SUMMARY OF PHARMACOKINETIC DATA FOR O-DESMETHYLTRAMADOL

[n = 26; Reference dose: 1 x 50 mg tramadol HCl IR tablet 6-hourly for 5 days
Test dose: 1 x 200 mg tramadol HCl OAD tablet daily for 5 days]

		Tramadol HCl (Ortho-McNeil Ultram) (Reference)			Tramadol HCl OAD (Test)				
VARIABLE	UNIT	ARITHMETIC			ARITHMETIC			MEAN RATIO	90% CONFIDENCE INTERVAL	INTRA INDIVIDUAL
		Mean	SD	Range	Mean	SD	Range	(%)*	(%)**	CV (%)
$C_{max,ss}$	(ng/ml)	78.7	17.3	58.9 - 115	78.6	18.7	27.7 - 114	88.5	84.1 ; 93.2	11
$C_{min,ss}$	(ng/ml)	58.0	14.4	29.5 - 82.2	48.6	12.3	22.4 - 78.1	80.7	75.9 ; 85.8	13
T_{max}#	(h)	1.50		1.00 - 3.00	5.00		3.00 - 20.0	5.25	4.00 ; 7.50	
AUC_{ss}	(ng/ml/h)	1438	329	965 - 2057	1361	368	586 - 2027	93.6	89.2 ; 98.2	10
%PTF	(%)	40.0	12.9	20.9 - 71.5	58.1	15.3	17.2 - 80.6	107	96.4 ; 120	23
%SWING	(%)	68.0	28.4	21.1 - 96.7	77.8	31.0	17.8 - 140	126	108 ; 144	31
HVB	(h)	22.0	0.56	21.2 - 24.0	22.5	0.80	20.2 - 24.0	98.1	96.5 ; 99.7	3
$T79\%C_{max}$	(h)	24.7	14.9	11.2 - 60.0	16.1	3.97	9.49 - 23.3	73.3	61.7 ; 86.7	37

* : Point estimate of "test/reference" mean ratio from analysis of log-transformed data.

** : 90% Conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

: Median, ranges, nonparametric point estimate of "test-reference" median difference and corresponding confidence interval.

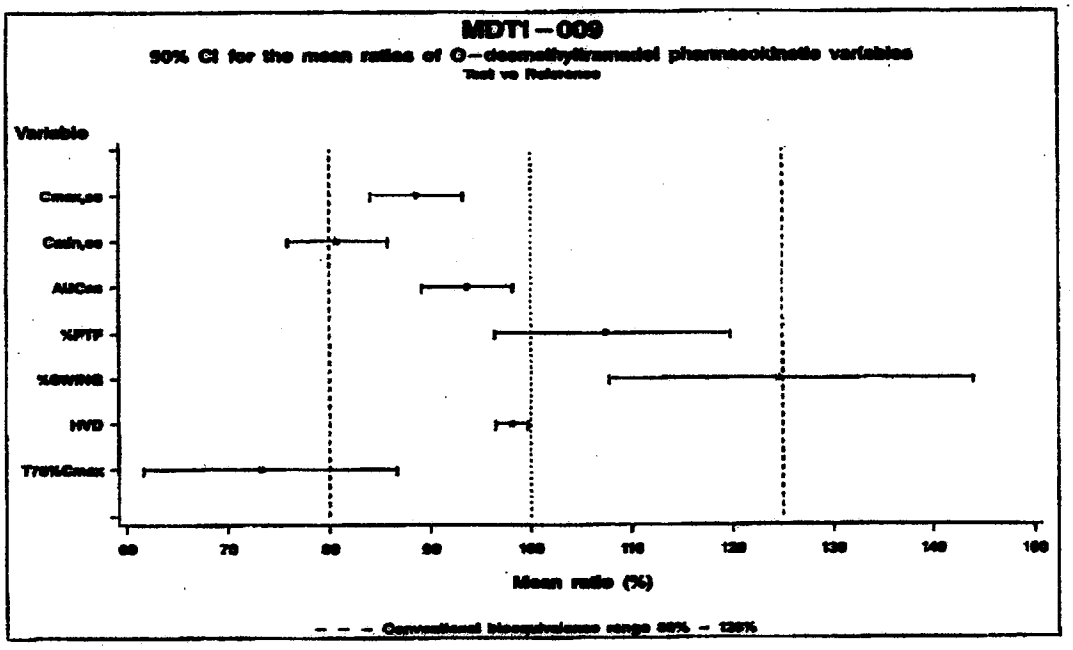


Figure 4. Graphical representation of the 90% confidence intervals for the mean ratios of M1 pharmacokinetic variables.

Conclusions: When Tramadol HCl OAD Tablets were compared to Ultram® 50 mg Tablets under the multiple dose regimen, at steady state, 90% confidence intervals (CIs) of test/reference ratio of AUCss for tramadol and 90% CIs of test/reference ratio of AUCss and Cmax,ss for M1 are within 80.00% to 125.00%. The lower limit of 90% CI of test/reference ratio of Cmax,ss for tramdol is slightly lower than 80% (77.5%) (Table 3). The lower limit of 90% CI of test/reference ratio of Cmin,ss for tramdol and M1 are also slightly lower than 80% (78.7% and 75.9%, respectively) (Tables 3 and 4). For all conditions, 100% was not included in 90% CI indicating that exposure of tramadol and M1 after Tramadol HCl OAD dosing is in general lower than that following Ultram (tramadol IR formulation) Q6h dosing.

Although in terms of extent of exposure, the test product is equivalent to the reference immediate-release formulation, noticeable difference in 24-hr PK profile between Ultram and Tramadol HCl OAD exists (Figure 2), e.g., C_{max} and C_{min} of tramadol and M1 are slightly lower with tramadol OAD administration and there is a lack of exposure for an approximately 9 hour window (0-3 hr and 18-24 hr) for a 24-hr dose interval.

Appendix for Study MDT-01-009. Demographic Information.

Table A1. Demographic Data for All Subjects.

Subject	Race	Age (years)	Height (cm)	Body mass (kg)	BMI (kg/m²)
1	Caucasian	47.000	173.000	74.300	24.826
2	Caucasian	46.000	175.000	68.700	29.657
3	Caucasian	25.000	182.000	68.200	20.722
4	Caucasian	31.000	164.000	70.300	26.138
5	Caucasian	44.000	172.000	81.300	27.481
6	Caucasian	55.000	172.000	72.000	24.337
7	Caucasian	27.000	188.000	95.000	26.788
8	Caucasian	21.000	177.000	70.900	22.631
9	Caucasian	23.000	176.000	70.000	22.598
10	Caucasian	36.000	176.000	87.400	28.538
11	Caucasian	19.000	186.000	77.700	22.460
12	Caucasian	37.000	171.000	73.000	24.966
13	Caucasian	22.000	176.000	77.600	25.404
14	Non-caucasian	22.000	176.000	70.000	23.118
15	Caucasian	19.000	173.000	72.000	24.057
16	Caucasian	19.000	176.000	70.900	22.877
17	Caucasian	24.000	171.000	73.400	25.102
18	Non-caucasian	20.000	176.000	74.000	24.785
19	Caucasian	28.000	180.000	82.400	25.432
20	Caucasian	19.000	180.000	71.500	22.068
21	Caucasian	22.000	184.000	76.700	22.655
22	Caucasian	21.000	185.000	87.200	25.478
23	Caucasian	23.000	180.000	73.600	22.716
24	Caucasian	19.000	185.000	76.900	23.063
25	Caucasian	23.000	180.000	82.500	25.086
26	Non-caucasian	24.000	180.000	76.300	20.986
Mean		27.538	177.192	77.442	24.894
SD		10.088	6.419	8.885	2.012
CV%		36.634	3.623	8.882	8.181
Geom Mean		26.111	177.081	77.162	24.887
GeoSD		1.386	1.038	1.848	1.088
Median		26.500	176.500	74.800	24.776
Min		19.000	164.000	70.000	22.059
Max		55.000	188.000	95.000	29.657
N	26	26	26	26	26

4.2.2 Study MDT1-011: A dose linearity study of the Labopharm formulation of tramadol HCl/Contramid®, 100 mg, 200 mg and 300 mg after a single oral administration in fasting condition in healthy human volunteers

---

Study Period:	November 5 2002 to December 16, 2002
Sample Analysis Period:	December 2002 to January 2003
Principle Investigators:	Drs. G. Paux, E. Guenole, J. Lefrancois
Study Center:	CeMAX, 3 rue Dufay, 76100 ROUEN, France
Analytical Site:	CeMAX, 3 rue Dufay, 76100 ROUEN, France

Objectives: To assess the pharmacokinetic profiles and dose-proportionality of tramadol and its major metabolite, M1, following single-dose administration of the 100 mg, 200 mg and 300 mg Tramadol Contramid® OAD tablets under fast conditions in healthy subjects.

Study Design: The study was performed as an open-label, single-dose, randomized, crossover study in 27 healthy male Caucasian subjects under fasting conditions receiving a single oral dose of 100, 200 or 300 mg Tramadol Contramid® OAD (Table 1). There were 7-day washout period between each administration. All 27 subjects completed the study. One subject (Subject No. 24) vomited during the 24-hour dosing interval following administration of the 300 mg dose. Therefore, his data for all dose levels were excluded from the statistical analysis in order to respect the Latin square design of the study. Please refer to Tables A1 in the Appendix for demographic information.

Table 1. Demographic Data.

Demographic characteristics	Age (years)	Weight (kg)	Height (cm)	B.M.I. (kg/m²)
Mean	28	78	177	24.7
S.D.	7	12	9	2.2
C.V. (%)	25	15	5	9
Min – Max	19 - 44	58 - 110	156 – 200	21.2 – 30.0

Test Articles:
Tramadol Contramid® OAD 100 mg tablet; Batch No. RX-52844
Tramadol Contramid® OAD 200 mg tablet; Batch No. RX-50245
Tramadol Contramid® OAD 300 mg tablet; Batch No. RX-52187

Sample Collection:
Predose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, and 48 hours post-dose

Sample Analysis: All plasma samples were analyzed to determine the concentrations of tramadol and O-desmethyltramadol (M1) by the analytical facility CeMAX using a validated

b(4)

LC/MS/MS method. Full validation of the method, including precision, accuracy and reproducibility is included in the final report (Report No. 02.09.02, September 2003). Propranolol was used as an internal standard. The quantitation range for tramadol was 1-700 ng/mL and for M1 was 0.5-300 ng/mL using a sample volume of 0.5 mL.

Pharmacokinetic and Statistical Analysis: Descriptive statistics were performed on the plasma concentrations of tramadol and O-desmethyltramadol (M1) for PK parameters. All the subjects were included in the pharmacokinetic evaluation but Subject 24 was excluded from the descriptive statistics of the pharmacokinetic parameters due to his adverse event (vomiting).

Linearity between 100 mg and 300 mg was determined using the following standards assessed from the plasma levels of tramadol and its metabolite (O-desmethyl tramadol): The 90% confidence interval of the relative mean Cmax, AUC0-t, AUC0-∞ of each pairwise treatment comparison following dose normalization had to be between 80 and 125%.

Pharmacokinetic Results:

PK Profiles

Individual tramadol plasma concentration-time profiles after single dose of Tramadol Contramid OAD 100, 200, and 300 mg were shown in Figure 1 (a, b, and c). The mean tramadol and M1 plasma concentration time-course were shown in Figure 2a and 2b.

b(4

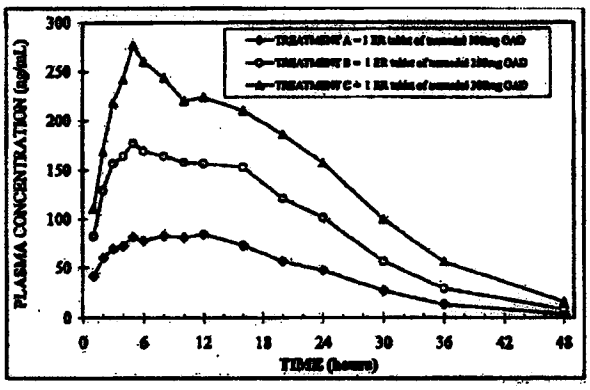
(a)

(b)

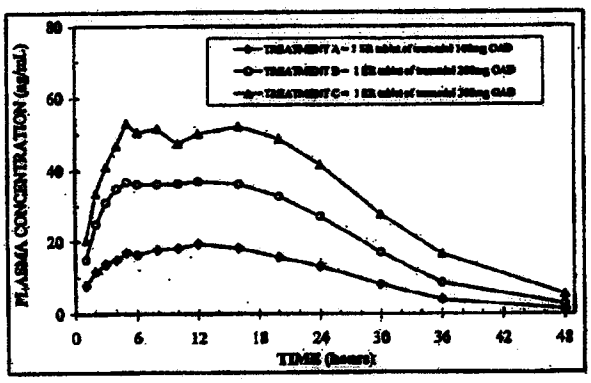
b(4)

Figure 1. Individual plasma concentration-time courses of tramadol, obtained in 27 healthy male Caucasian volunteers after the administration of 100 mg (a), 200 mg (b), and 300 mg (c) Tramadol Contramid OAD.

(c)



a. Tramadol



b. M1

Figure 2. Mean Steady-State Plasma Tramadol (a) and M1 (b) Concentrations for 100 mg, 200 mg, and 300 mg Tramadol Contramid OAD Tablets.

The mean pharmacokinetic parameters for tramadol and O-desmethyltramadol (M1) are summarized in Tables 2 and 3.

Table 2. Pharmacokinetic Parameters for Tramadol.

Tramadol	C_{max} (ng/mL)	$AUC_{0-t\ max}$ (ng.h/mL)	$C_{max}/AUC_{0-\infty}$ (h^{-1})	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	% of extrapol.
Treatment A : LABOPHARM extended release formulation prepared with Contramid® and dosed at 100 mg						
Mean[a] ± SD	91.0 ± 26.8	625 ± 277	0.0442 ± 0.0052	2064 ± 707	2108 ± 731	2.0 ± 1.4
min – max	48.3 – 141.3	166 – 1204	0.0357 – 0.0550	970 – 3171	995 – 3269	0.6 – 7.1
Treatment B : LABOPHARM extended release formulation prepared with Contramid® and dosed at 200 mg						
Mean[a] ± SD	196.5 ± 58.3	915 ± 567	0.0455 ± 0.0108	4332 ± 1149	4416 ± 1192	1.8 ± 1.3
min – max	114.1 – 360.3	265 – 2906	0.0334 – 0.0815	2316 – 6450	2330 – 6495	0.2 – 4.7
Treatment C : LABOPHARM extended release formulation prepared with Contramid® and dosed at 300 mg						
Mean[a] ± SD	290.1 ± 147.2	1575 ± 1338	0.0432 ± 0.0126	6568 ± 2050	6741 ± 2156	2.3 ± 1.9
min – max	151.4 – 807.1	378 – 4842	0.0295 – 0.0853	3177 – 9602	3202 – 10052	0.3 – 8.1

(a) arithmetic mean

Tramadol	Tmax (h)	$t_{1/2\beta}$ (h)	λ_z (h^{-1})	HVD (h)	MRT (h)
Treatment A : LABOPHARM extended release formulation prepared with Contramid® and dosed at 100 mg					
Mean[a] ± SD	9.0[b]	6.1 ± 1.3	0.118 ± 0.024	22.5 ± 3.4	16.1 ± 2.1
min – max	3.0 – 16.0	4.0 - 10.1	0.068 – 0.172	16.5 – 28.7	12.5 – 21.0
Treatment B : LABOPHARM extended release formulation prepared with Contramid® and dosed at 200 mg					
Mean[a] ± SD	5.5[b]	6.1 ± 1.3	0.118 ± 0.025	23.5 ± 4.5	16.5 ± 2.3
min – max	3.0 – 16.0	4.0 – 8.2	0.085 – 0.175	10.6 – 30.8	12.5 – 21.7
Treatment C : LABOPHARM extended release formulation prepared with Contramid® and dosed at 300 mg					
Mean[a] ± SD	5.0[b]	6.3 ± 1.5	0.115 ± 0.023	25.4 ± 6.6	17.6 ± 3.0
min – max	3.0 – 24.0	4.6 – 10.9	0.064 – 0.151	7.7 – 35.3	10.7 – 23.2

(a) arithmetic mean (b) median

Table 3. Pharmacokinetic Parameters for O-desmethyltramadol (M1).

O-desmethyl tramadol	Cmax (ng/mL)	$AUC_{0-t_{max}}$ (ng.h/mL)	$Cmax / AUC_{0-\infty}$ (h^{-1})	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	% of extrapol.
Treatment A : LABOPHARM extended release formulation prepared with Contramid® and dosed at 100 mg						
Mean[a] ± SD	20.4 ± 6.7	179 ± 92	0.039 ± 0.005	502 ± 165	520 ±170	3.5 ± 2.5
min – max	6.5 – 30.3	38 – 346	0.032 – 0.052	161 – 779	167 – 794	0.9 – 13.8
Treatment B : LABOPHARM extended release formulation prepared with Contramid® and dosed at 200 mg						
Mean[a] ± SD	43.1 ± 16.5	278 ± 185	0.039 ± 0.008	1050 ± 322	1080 ± 328	2.8 ± 2.4
min – max	12.8 – 76.8	48 – 783	0.031 – 0.058	388 – 1608	409 – 1629	0.3 – 8.7
Treatment C : LABOPHARM extended release formulation prepared with Contramid® and dosed at 300 mg						
Mean[a] ± SD	59.9 ± 19.2	587 ± 312	0.037 ± 0.009	1570 ± 498	1640 ± 538	4.0 ± 3.2
min – max	17.9 – 100.5	72 – 997	0.026 – 0.064	544 – 2509	554 – 2750	0.5 – 11.6

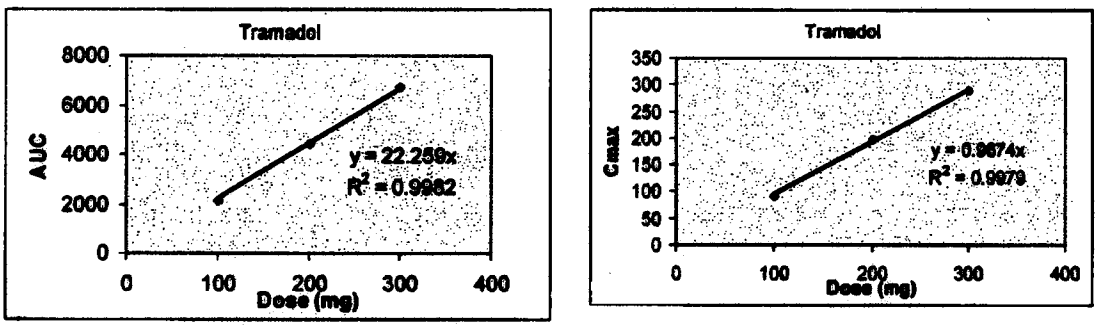
(a) arithmetic mean

O-desmethyl tramadol	Tmax (h)	$t_{1/2\lambda_z}$ (h)	λ_z (h^{-1})	HVD (h)	MRT (h)
Treatment A : LABOPHARM extended release formulation prepared with Contramid® and dosed at 100 mg					
Mean[a] ± SD	12.0 [b]	7.0 ± 1.9	0.106 ± 0.026	25.6 ± 2.9	18.3 ± 2.8
min – max	5.0 – 20.0	4.2 – 13.8	0.050 – 0.165	19.5 – 30.2	14.0 – 26.0
Treatment B : LABOPHARM extended release formulation prepared with Contramid® and dosed at 200 mg					
Mean[a] ± SD	8.0 [b]	6.7 ± 1.8	0.111 ± 0.029	26.3 ± 5.0	18.5 ± 2.8
min – max	4.0 – 24.0	3.8 – 11.1	0.062 – 0.183	16.9 – 33.1	13.7 – 24.9
Treatment C : LABOPHARM extended release formulation prepared with Contramid® and dosed at 300 mg					
Mean[a] ± SD	16.0 [b]	7.4 ± 2.2	0.102 ± 0.029	28.1 ± 6.6	19.9 ± 3.7
min – max	4.0 – 24.0	3.9 – 12.2	0.057 – 0.178	11.4 – 38.8	12.0 – 26.1

(a) arithmetic mean (b) median

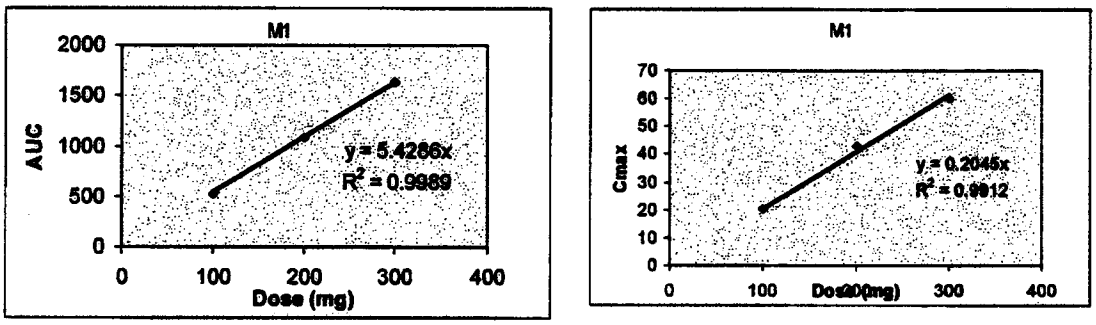
Dose Proportionality Analysis

Both AUC(0-∞) and Cmax of Tramdol and M1 exposure were dose-proportional to Tramadol Contramid OAD doses (100, 200 and 300 mg) after a single dose (Figures 3 and 4) as evidenced by the linear relationship between AUC(0-∞) and dose, and Cmax and dose.



a. AUC(0-∞) b. Cmax

Figure 3. Relationship between Tramdol AUC(0-inf) (a) and dose, and Cmax (b) and dose.



a. AUC(0-∞) b. Cmax

Figure 4. Relationship between M1 AUC(0-inf) (a) and dose, and Cmax (b) and dose.

Dose-proportionality was evaluated by comparison of the treatment groups after dose normalization of concentration-dependent parameters (Cmax, AUC0-t, AUC0-∞) for tramadol and M1. The 90% confidence interval around the point estimate for each comparison was in the range [0.80-1.25]% for log-transformed parameters indicated that exposure of tramadol and M1 increased proportionally with dose within the investigated dose range (100-300 mg) (Tables 4 and 5).

Table 4. Statistical Analysis of Proportionality for Tramadol.

Used test for the statistical comparison	Cmax	AUC_{0-t}	$AUC_{0-\infty}$	$AUC_{t_{last}-\infty}$	$Cmax/AUC_{0-\infty}$
Statistical analysis between the three treatments after normalization of the dose					
ANOVA					
Subject	S.($p<0.001$)	S.($p<0.001$)	S.($p<0.001$)	N.S.	N.S.
Treatment	N.S.	S.($p<0.05$)	S.($p<0.05$)	N.S.	N.S.
Period	N.S.	N.S.	N.S.	N.S.	N.S.
Sequence	N.S.	N.S.	N.S.	N.S.	N.S.
Power of the test	0.60	> 0.99	> 0.99	< 0.50	0.77
Statistical comparison between treatment Test A and treatment Test B Bioequivalence test (B/A) after dose normalization					
① 90% confidence interval	[1.00 – 1.19]	[1.02 – 1.13]	[1.02 – 1.13]	[0.55 – 0.93]	[0.93 – 1.13]
② Two one-sided T-tests (Schuirmann)	Excluded	Excluded	Excluded	Not excluded	-
③ Geometric mean ratio B/A	1.09	1.08	1.07	0.72	1.01
Statistical comparison between treatment Test A and treatment Test C Bioequivalence test (C/A) after dose normalization					
① 90% confidence interval	[0.93 – 1.11]	[1.02 – 1.12]	[1.02 – 1.12]	[0.55 – 0.93]	[0.88 – 1.06]
② Two one-sided T-tests (Schuirmann)	Excluded	Excluded	Excluded	Not excluded	-
③ Geometric mean ratio C/A	1.02	1.07	1.07	0.72	0.95
Statistical comparison between treatment Test B and treatment Test C Bioequivalence test (C/B) after dose normalization					
① 90% confidence interval	[0.86 – 1.02]	[0.95 – 1.04]	[0.95 – 1.05]	[0.77 – 1.20]	[0.85 – 1.03]
② Two one-sided T-tests (Schuirmann)	Excluded	Excluded	Excluded	Not excluded	-
③ Geometric mean ratio C/B	0.94	0.99	1.00	1.00	0.94

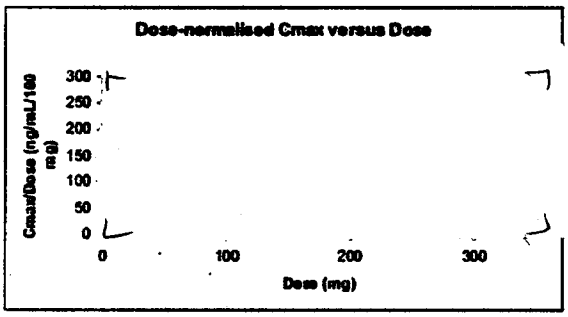
A: 100 mg; B: 200 mg; C: 300 mg

Table 4. Statistical Analysis of Proportionality for M1.

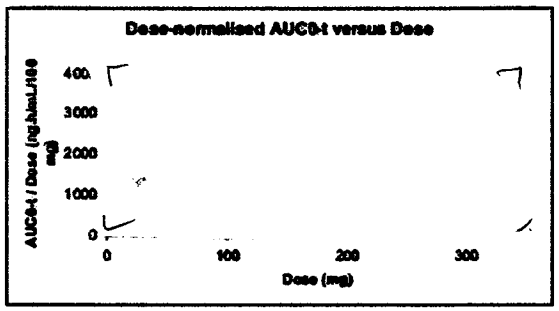
Used test for the statistical comparison	Cmax	AUC_{0-t}	$AUC_{0-\infty}$	AUC_{0-tmax}	$Cmax/AUC_{0-\infty}$
Statistical analysis between the three treatments after normalisation of the dose					
ANOVA					
Subject	S.($p<0.001$)	S.($p<0.001$)	S.($p<0.001$)	S.($p<0.001$)	S.($p<0.01$)
Treatment	N.S.	N.S.	N.S.	S.($p<0.05$)	N.S.
Period	N.S.	N.S.	N.S.	N.S.	N.S.
Sequence	N.S.	N.S.	N.S.	N.S.	N.S.
Power of the test	0.97	> 0.99	> 0.99	< 0.50	0.94
Statistical comparison between treatment Test A and treatment Test B Bioequivalence test (B/A) after dose normalisation					
① 90% confidence interval	[0.97 – 1.11]	[1.00 – 1.11]	[0.99 – 1.10]	[0.57 – 0.93]	[0.93 – 1.08]
② Two one-sided T-tests (Schuirmann)	Excluded	Excluded	Excluded	Not excluded	-
③ Geometric mean ratio B/A	1.04	1.05	1.05	0.73	0.99
Statistical comparison between treatment Test A and treatment Test C Bioequivalence test (C/A) after dose normalisation					
① 90% confidence interval	[0.91 – 1.05]	[0.99 – 1.09]	[0.99 – 1.10]	[0.82 – 1.33]	[0.87 – 1.03]
② Two one-sided T-tests (Schuirmann)	Excluded	Excluded	Excluded	Not excluded	-
③ Geometric mean ratio C/A	0.98	1.04	1.05	1.04	0.93
Statistical comparison between treatment Test B and treatment Test C Bioequivalence test (B/C) after dose normalisation					
① 90% confidence interval	[0.88 – 1.01]	[0.94 – 1.04]	[0.95 – 1.05]	[1.12 – 1.82]	[0.87 – 1.02]
② Two one-sided T-tests (Schuirmann)	Excluded	Excluded	Excluded	Not excluded	-
③ Geometric mean ratio C/B	0.94	0.99	0.99	1.43	0.94

A: 100 mg; B: 200 mg; C: 300 mg

The slope values from the plot of individual dose-normalized Cmax, AUC0-t and AUC0-∞ vs. dose were also close to 0 indicating the dose-linearity (Figure 5).

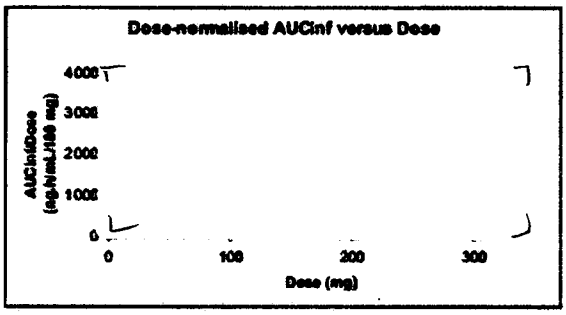


(a) Cmax



(b) AUC0-t

b(4)



(c) AUC0-∞

Figure 5. Plot of Individual Dose-normalised Cmax (a), AUC0-t (b), and AUC$_{0-\infty}$ versus Dose.

Conclusions: Results from this study suggest that the Cmax and AUC0-∞ of tramadol and M1 increased proportionally with dose in the range of 100 to 300 mg.

Appendix for Study MDT1-011. Demographic Information.

Table A1. Demographic Data for All Subjects.

Table 14.1.1. : Individual and mean demographic characteristics

Subject Number	Subject code	Date of birth	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m²)
001			29	110	200	27.5
002			29	80	177	25.5
003			23	62	165	22.8
004			33	80	181	24.4
005			24	90	192	24.4
006			19	76	182	22.9
007			19	90	185	26.3
008			40	69	170	23.9
009			44	88	180	27.2
010			23	80,5	188	22.8
011			26	90	183	26.9
012			21	74	181	22.6
013			29	92	175	30.0
014			39	81	180	25.0
015			22	70	172	23.7
016			20	63	169	22.1
017			38	70	176	22.6
018			31	80	179	25.0
019			35	65	162	24.8
020			38	76	171	26.0
021			26	80	188	22.6
022			25	89	182	26.9
023			24	77	168	27.3
024			27	85	179	26.5
025			24	63	170	21.8
026			19	65	175	21.2
027			27	58	156	23.8
Mean			28	78	177	24.7
Standard Deviation (SD)			7	12	9	2.2
Standard Error of the Mean (SEM)			1	2	2	0.4
Coefficient of variation (%)			25	15	5	9
Min. value			19	58	156	21.2
Max. value			44	110	200	30.0
Number of values			27	27	27	27

b(6)

4.2.3 Study MDT1-006: A food interaction study to compare the bioavailability of two tramadol·HCl products

---

Study Period: August 7, 2002 to October 15, 2002
Sample Analysis Period: September 26, 2002 to October 23, 2002
Principle Investigator: Dr. J Terbalnché
Study Center:

b(4)

Analytical Site:

Reviewer's Note: Food effect of two tramadol products (IR and Contromid® OAD) was studied in this study. Only Contromid® OAD is relevant to NDA 21-745 and food effect for Contromid® OAD 200 mg tablet was reviewed.

Objectives: To compare the pharmacokinetic profiles of 200 mg tramadol Contromid® OAD tablet under fasting and fed conditions after a single dose.

Study Design: The study was an open, single-dose, randomized, four-period crossover study in healthy, non-smoking Caucasian male subjects. The study consisted of 4 treatment phases which were separated by wash-out periods of 7 days between consecutive administrations of study medication on clinic days. Two of the treatment phases (one fasting and one fed) were related to Tramadal Contramid OAD 200 mg tablets. Twenty-eight eligible subjects entered the study. Subject 14 withdrew for personal reasons after his first treatment phase. Subject 4 was withdrawn prior to any dose administration due to conjunctivitis in both eyes and was replaced by Subject 29. Therefore, a total of twenty-seven subjects completed the study (Table 1). Please refer to Tables A1 in the Appendix for demographic information.

Table 1. Demographic Summary of Subjects who Completed the Study.

	Age (years)	Height (cm)	Body mass (kg)	BMI (kg/m²)
Mean	21	182	78.2	23.6
Range	18-28	166-194	70.2-94.9	19.6-27.3

During the fasting treatment phase, subjects received a 200 mg tramadol OAD tablet with 150 mL water after an overnight fast of at least 10 hours. During the fed treatment phase, subjects received a standardized high-fat, high kilojoule breakfast with 200 mL whole milk to be completed within 20 min after an overnight fast of at least 10 hours. Then subjects received a 200 mg tramadol OAD tablet with 150 mL of water within 5 min of completing the breakfast. Although the breakfast is different from the FDA breakfast as specified in the guidance, it is acceptable (~50% fat and total ~900 Calorie) (see Table 2).

Table 2. Breakfast Menu.

HIGH-FAT AND HIGH-KILOJOULE RECIPE CONSTITUENTS					
FOOD	AMOUNT (g)	ENERGY (kJ)	CHO (g)	PROTEIN (g)	FAT (g)
Bacon - fried	20.0	449.8	0.1	6.1	9.8
Eggs - fried	104.0	811.2	1.2	13.4	15.2
Potato chips - oven heated	120.0	1039.2	37.4	3.8	9.1
Bread/Rolls - brown	60.0	649.2	30.4	5.2	1.2
Butter	10.0	304.0	0.0	0.1	8.2
Milk - whole fresh	200.0	524.0	9.6	6.4	6.8
Tomato - raw	100.0	91.0	4.0	0.9	0.2
TOTAL % ENERGY		3868.4	82.9 35.6	35.9 15.4	50.5 49.0

[Grant *et al.*, 1995 (upgraded 2002)].

Test Articles:
Tramadol HC1 200 mg OAD Tablets
Manufacturer: Labopharm Inc., Canada
Lot #: 25184, Expiration Date: May 2003

Sample Collection and Handling:
Predose, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 9, 12, 16, 24, 36 and 48 hours post-dose

Sample Analysis: All plasma samples were delivered to the for the analysis of tramadol and O-desmethyltramadol (M1) using a validated LC/MS/MS method (Validation No. 66/2000, October 2002) was used as an internal standard. The LLOQ was 0.685 ng/mL for both tramadol and O-desmethyltramadol. b(4)

Pharmacokinetic and Statistical Analysis: All BLQ values were substituted by half the LLOQ values for calculation of the descriptive statistics of the concentrations.

The test product was compared under fasting and fed conditions with respect to the pharmacokinetic variables Cmax, Cmax/AUC(0-∞), t1/2,z, HVD, AUC(0-tlast) and AUC(0-∞) using an analysis of variance with sequence, subject(sequence), product and period effects after a logarithmic transformation of the data. Parametric point estimates and 90% confidence intervals for the "Fed/Fast" mean ratios of those variables were calculated and presented graphically. In addition, a non-parametric point estimate and 90% confidence interval for the "Fed/Fast" median difference of Tmax was calculated. Bioequivalence of the test and reference product was assessed on the basis of the confidence intervals for the primary variable AUC(0-∞) and Cmax in relation to the bioequivalence range of 80% to 125%.

Pharmacokinetic Results:

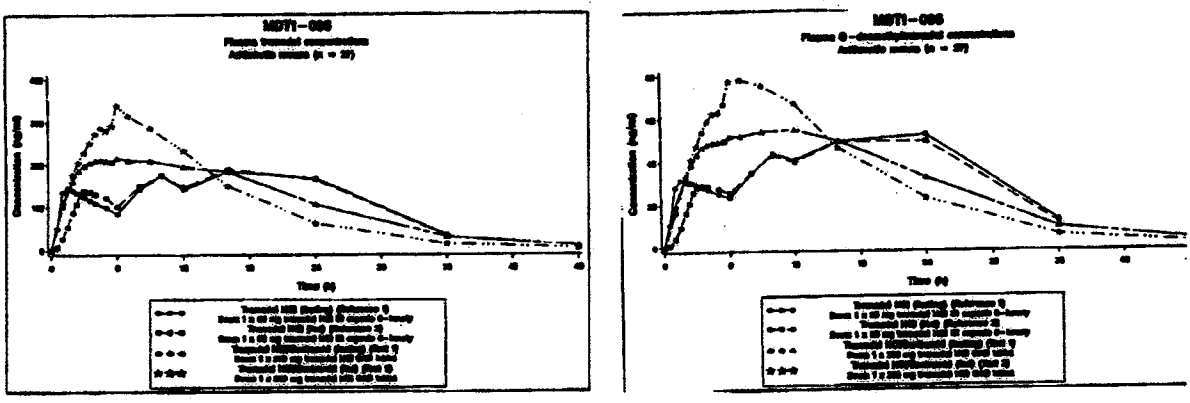
PK Profiles and Relative Bioavailability

The individual plasma concentration-time profiles for tramadol after a single 200 mg Tramadol HCl OAD dose under fasting and fed conditions were shown in Figure 1 (a and b). The mean plasma concentration-time profiles of the drug and M1 metabolite under fasting and fed conditions are shown in Figure 2 (a and b).

b(4

(a) Fasting (b) Fed

Figure 1. Individual Plasma Tramadol Concentrations after a Single 200-mg Tramadol HCl OAD Dose under Fasting (a) and Fed (b) Conditions.



a. Tramadol b. M1

Figure 2. Mean Plasma Tramadol (a) and M1 (b) Concentrations under Fasting (▲) and Fed (*) Conditions.

The mean pharmacokinetic parameters for tramadol and O-desmethyltramadol (M1) following multiple dose results are summarized in Tables 3 and 4.

Table 3.

SUMMARY OF PHARMACOKINETIC DATA FOR TRAMADOL

[n = 27; Test 1 dose: 1 x 200 mg tramadol-HCl OAD tablet
Test 2 dose: 1 x 200 mg tramadol-HCl OAD tablet]

		Tramadol-HCl/Contramid® (Test 1)			Tramadol-HCl/Contramid® (Test 2)					
VARIABLE	UNIT	ARITHMETIC			ARITHMETIC			MEAN RATIO	90% CONFIDENCE INTERVAL	INTRA INDIVIDUAL
		Mean	SD	Range	Mean	SD	Range	(%)*	(%)**	CV (%)
C_{max}	(ng/ml)	241	61.5	168 - 419	381	136	190 - 697	154	136; 173	26
T_{max}#	(h)	6.00		3.00 - 16.0	6.00		2.00 - 12.0	0.00	-1.50; 1.00	
AUC(0 - t_{last})	(ng·h/ml)	5152	1835	3340 - 10061	5115	1699	2681 - 9489	99.0	94.6; 104	10
AUC(0 - ∞)	(ng·h/ml)	5310	1963	3369 - 11284	5168	1749	2612 - 9821	98.0	93.7; 102	10
C_{max}/AUC(0 - ∞)	(1/h)	0.05	0.01	0.03 - 0.09	0.08	0.02	0.05 - 0.12	157	139; 176	25
$t_{1/2}$	(h)	6.00	1.51	4.61 - 11.5	5.75	1.05	4.54 - 9.21	88.9	86.2; 91.6	7
MRT	(h)	15.6	3.33	10.1 - 28.8	12.2	1.94	8.92 - 16.4			
BVD	(h)	28.0	3.39	9.10 - 23.2	12.3	4.64	4.90 - 28.6	57.7	48.8; 68.2	37

* : Point estimate of "test 2/test 1" mean ratio from analysis of log-transformed data.

** : 90% Conventional confidence interval for the "test 2/test 1" mean ratio from analysis of variance of log-transformed data.

: Medians, ranges, nonparametric point estimate of "test 2-test 1" median difference and corresponding confidence interval.

Table 4.

SUMMARY OF PHARMACOKINETIC DATA FOR O-DESMETHYLTRAMADOL

[n = 27; Test 1 dose: 1 x 200 mg tramadol-HCl OAD tablet
Test 2 dose: 1 x 200 mg tramadol-HCl OAD tablet]

		Tramadol-HCl/Contramid® (Test 1)			Tramadol-HCl/Contramid® (Test 2)					
VARIABLE	UNIT	ARITHMETIC			ARITHMETIC			MEAN RATIO	90% CONFIDENCE INTERVAL	INTRA INDIVIDUAL
		Mean	SD	Range	Mean	SD	Range	(%)*	(%)**	CV (%)
C_{max}	(ng/ml)	68.0	19.4	8.40 - 96.6	88.4	35.3	19.8 - 168	149	134; 167	24
T_{max}#	(h)	9.00		3.00 - 24.0	7.00		4.50 - 12.0	-3.00	-3.51; 0.00	
AUC(0 - t_{last})	(ng·h/ml)	1366	388	247 - 2111	1401	434	315 - 2250	105	97.0; 107	10
AUC(0 - ∞)	(ng·h/ml)	1430	389	288 - 2174	1418	434	325 - 2348	100	93.6; 105	10
C_{max}/AUC(0 - ∞)	(1/h)	0.04	0.01	0.03 - 0.07	0.06	0.02	0.04 - 0.10	149	135; 163	20
$t_{1/2}$	(h)	7.51	1.39	5.51 - 11.5	6.49	1.05	4.96 - 8.56	86.1	83.0; 89.4	8
MRT	(h)	17.7	3.51	11.6 - 30.6	14.2	2.06	10.4 - 18.0			
BVD	(h)	28.6	3.39	9.44 - 23.8	14.4	4.38	6.20 - 21.8	67.0	58.7; 77.3	31

* : Point estimate of "test 2/test 1" mean ratio from analysis of log-transformed data.

** : 90% Conventional confidence interval for the "test 2/test 1" mean ratio from analysis of variance of log-transformed data.

: Medians, ranges, nonparametric point estimate of "test 2-test 1" median difference and corresponding confidence interval.

Conclusions:
Food did not influence extent of tramadol absorption; the 90% confidence intervals of geometric mean ratio (GMR) (Fed/Fast) of AUC(0-∞) for tramadol and M1 were within 80% to 125%. The maximum plasma concentration of tramadol and M1, however, increased by 54% and 49%, respectively, when Tramadol Contramid® OAD tablets were taken with food. Food has no effect on Tmax.

Appendix for Study MDT-01-006. Demographic Information.

Table A1. Demographic Data for All Subjects.

Subject	Sex	Age (years)	Height (cm)	Body mass (kg)	BMI (kg/m²)
1	Male	20.000	179.000	71.000	22.346
2	Male	20.000	180.000	77.700	21.752
3	Male	22.000	185.000	72.500	21.125
4	Male	19.000	184.000	72.000	21.444
5	Male	27.000	184.000	81.000	24.161
6	Male	25.000	174.000	71.000	23.748
7	Male	19.000	168.000	71.000	25.766
8	Male	19.000	182.000	84.000	25.743
9	Male	19.000	186.000	76.400	24.198
10	Male	20.000	181.000	84.100	25.671
11	Male	22.000	180.000	71.000	21.914
12	Male	19.000	176.000	76.300	29.766
13	Male	19.000	181.000	82.700	25.243
14	Male	22.000	186.000	74.700	21.626
15	Male	22.000	180.000	72.000	22.407
16	Male	19.000	194.000	73.000	19.000
17	Male	18.000	183.000	77.400	23.112
18	Male	20.000	174.000	70.200	23.187
19	Male	22.000	186.000	75.000	21.678
20	Male	19.000	184.000	79.200	23.393
21	Male	27.000	176.000	78.000	25.181
22	Male	19.000	182.000	87.000	26.266
23	Male	20.000	190.000	77.400	21.440
24	Male	28.000	182.000	90.000	27.261
25	Male	22.000	185.000	87.700	25.625
26	Male	20.000	182.000	72.200	21.797
27	Male	22.000	188.000	86.100	24.361
28	Male	20.000	178.000	75.000	23.665
29	Male	28.000	182.000	76.000	22.944
Mean		21.034	182.207	77.458	23.486
SD		2.882	5.741	5.489	1.851
CV%		12.000	3.151	6.252	7.886
Geometric		20.000	182.119	77.043	23.489
Geom SD		1.125	1.032	1.064	1.082
Median		20.000	182.000	76.000	23.393
Min		18.000	168.000	70.200	19.000
Max		28.000	194.000	94.000	27.261
N	29	29	29	29	29

4.2.4 Study MDT1-016: Randomized, open-label, 3-way crossover, bioequivalence study of two tramadol Contramid® OAD 300 mg controlled-release tablets from two different manufacturing sites following a 300 mg dose in healthy subjects under fasting and fed conditions

---

Study Period: February 27, 2006 to April 18, 2006
Sample Analysis Period: April 5, 2006 to April 24, 2006
Principle Investigator: Dr. Richard Larouche
Study Center:

Analytical Site: b(4)

Reviewer's Note: This study was conducted during the review cycle to address potential review issues identified during the filing review: 1. Product used in pivotal clinical trials and product proposed to be commercially marketed are manufactured in two completely different manufacturing sites. There is inadequate data linking the product manufactured at these two sites. 2. Food effect was determined on the 200 mg strength. b(4)

food effect for the 300 mg strength may be different. As such, potential dose dumping of the 300 mg strength due to food effect has not been completely ruled out.

Objectives: To compare the rate and extent of absorption of two Tramadol Contramid® OAD 300 mg controlled-release tablets from two different manufacturing sites, administered as 1 x 300 mg controlled-release tablet under fasting conditions. The effect of food on the to-be-marketed formulation was also assessed.

Study Design: The study was an open-label, laboratory-blind, single-center, single-dose, randomized, three-period, six sequence crossover study in thirty-six (36) healthy, non-smoking male (15) and female (21) subjects. There was a 8 and 9 day washout period between Treatments. Two subjects (Subjects 09 and 28) were withdrawn from the study after Period 1 due to AEs, and two subjects (Subjects 13 and 30) withdrew from the study before Period 3 for personal reasons. Thirty-two subjects (13 males and 19 females) completed the study (Table 1). Twenty-seven were Caucasians and five were American Hispanic. Please refer to Tables A1 in the Appendix for demographic information.

Treatment A: Manufactured at Confab Laboratories, Canada (new site for commercial manufacturing) and administered under fasting conditions.
Treatment B: Manufactured at Confab Laboratories, Canada and administered under fed conditions (after a standardized high-fat high-caloric breakfast) b(4)
Treatment C: Manufactured at (old site for previous batches used in clinical and PK trials) and administered under fasting conditions.

Table 1. Demographic Data.

		Age (years)	Height (cm)	Body mass (kg)	BMI (kg/m²)
All subjects	Mean	39 2	166	68.1	24 7
(n = 32)	Range	19 - 55	155 - 179	50.4 - 94 2	19.7 - 29.8
Males	Mean	37.8	171	75 5	25.8
(n = 13)	Range	19 - 51	163 - 179	61.0 - 94.2	20.7 - 29 4
Females	Mean	40 2	162	63.0	24.0
(n = 19)	Range	20 - 55	155 - 172	50 4 - 81 5	19 7 - 29.8

Test Articles:
Test Product:
Tramadol Contramid® OAD 300 mg Tablets; Manufacturer: Confab Laboratories (Saint-Hubert, Quebec)
Lot #: 104490P1; Expiration Date: March 2008

Reference:
Tramadol Contramid® OAD 300 mg Tablets; Manufacturer: ———— b(4)
————
Lot #: RX87203P1; Expiration Date: January 2009

Sample Collection: Venous blood samples for the determination of tramadol and O-desmethyltramadol concentrations were taken at the following time points: prior to drug administration and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, and 48 hours post-dose.

Sample Analysis: All plasma samples were delivered to———— b(4)
————
for the analysis of tramadol and O-desmethyltramadol (M1) using a validated LC/MS/MS method (Validation No. ———— 79081, March 2006). ————was used as an internal standard. The method provides an acceptable degree of accuracy and precision over the concentration ranges 3.00 -775 ng/mL for tramadol and 0.7902 – 204 ng/mL for O-desmethyltramadol based on peak area ratios with Wagner calibration curves ($\ln(y)=a(\ln(x))^2+b(\ln(x))+c$).

Samples from all subjects completing two periods or more (necessarily including treatment A) were to be analyzed for quantitation of tramadol and O-desmethyltramadol; upon sufficient justification (e.g., vomiting during the dosing interval), some subjects could have been excluded from the analyses.

All BLQ values were substituted by zero for calculation of the descriptive statistics of the concentrations and were deleted for the calculation of the pharmacokinetic variables.

Pharmacokinetic and Statistical Analysis: Treatment A (fasting condition) was compared to Treatment B (fed condition) and to Treatment C (fasting condition) with respect to the pharmacokinetic variables Cmax, t1/2,z, AUC(0-tlast) and AUC(0-∞) for tramadol and O-desmethyltramadol using an analysis of variance with sequence, subject(sequence), product and period effects after logarithmic transformation of the data. Parametric point estimates and 90% confidence intervals for the "Treatment A/Treatment C" and "Treatment B/Treatment A" mean ratios of the variables mentioned above were calculated for each dataset. Tmax was subjected to a non-parametric Wilcoxon test and the p-value is reported for each dataset.

Bioequivalence of test product (A) and the reference product (C) was assessed on the basis of the confidence intervals for the primary variables AUC(0-∞), AUC(0-tlast) and Cmax for tramadol and O-desmethyltramadol in relation to the bioequivalence range of 80% to 125%.

The effect of food (Treatment B, fed vs Treatment A, fasting) was assessed on the basis of the confidence intervals for the variables AUC(0-∞), AUC(0-tlast) and Cmax, in relation to the conventional bioequivalence range of 80% to 125%

Pharmacokinetic Results:

Reviewer's Note: Because there were significant protocol deviations and subjects vomited, the Sponsor did analysis based on 3 datasets (Table 2). The Reviewer selected data analysis from Data Set 1 because it contains the most clean data with subjects who did not vomit and had no significant protocol deviations and the sample size was reasonable (N ≥ 19) for each treatment. Data from other datasets showed similar trend.

Table 2. Summary of Subjects Included in Pharmacokinetic and Statistical Analyses.

	Subjects included in Pharmacokinetic and Statistical Analyses		
Dataset No.	Treatment A	Treatment B	Treatment C
1 - Subjects who had no significant protocol deviations and who did not vomit during the dosing interval	01-08, 10, 12, 14, 16, 19, 20, 22, 23, 25-27, 29-36 (◆n = 26 for AUC(0-∞), $t_{1/2}$ and K_el) (n = 27 for all other variables)	01-03, 05, 07, 12, 14-16, 18, 20, 22, 24-27, 33, 34 (n = 19)	01, 02, 04-08, 12, 14, 18-20, 22, 23, 25-27, 29-36 (n = 26)
2 - Subjects who had no significant protocol deviations and vomited > 4 hours post-dose (under fasting conditions) or > 12 hours post-dose (under fed conditions)	01-08, 10-16, 18-27, 29-36 (◆n = 32 for AUC(0-∞), $t_{1/2}$ and K_el) (n = 33 for all other variables)	01-03, 05, 07, 12, 14-16, 18, 20, 22, 24-27, 31, 33, 34 (n = 19)	01, 02, 04-08, 10-12, 14-16, 18-27, 29-36 (n = 31)
3 - All subjects who completed at least two periods of the study	01-08, 10-27, 29-36 (◆n = 33 for AUC(0-∞), $t_{1/2}$ and K_el) (n = 34 for all other variables)	01-08, 10-27, 29, 31-36 (n = 33)	01-08, 10-12, 14-27, 29-36 (n = 33)

◆Subject 19 are excluded from the calculation of these variables.

A: Labopharm Inc., Canada (Tramadol Contramid® OAD), tramadol 1 x 300 mg tablet manufactured at Confab Laboratories, Canada and administered under fasting conditions.

B: Labopharm Inc., Canada (Tramadol Contramid® OAD), tramadol 1 x 300 mg tablet manufactured at Confab Laboratories, Canada and administered under fed conditions

C: Labopharm Inc., Canada, (Tramadol Contramid® OAD), tramadol 1 x 300 mg tablet manufactured at [redacted] and administered under fasting conditions.

b(4)

PK Profiles

The mean plasma concentration-time profiles of the drug and M1 metabolite after different treatments are shown in Figures 1 and 2 (Based on Dataset No. 3: All subjects who completed at least 2 periods of study).

b(4)

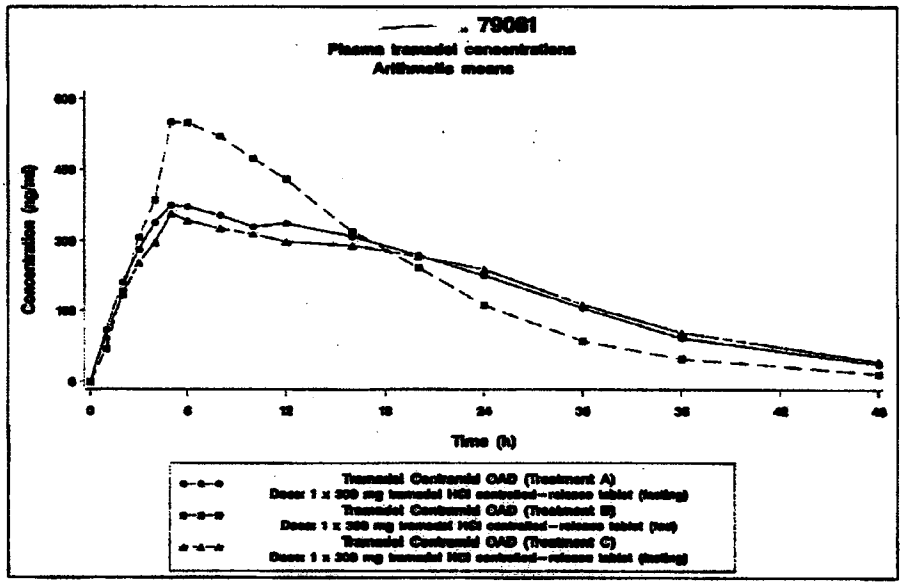


Figure 1. Mean Plasma Tramadol Concentrations after Various Treatments.

b(4)

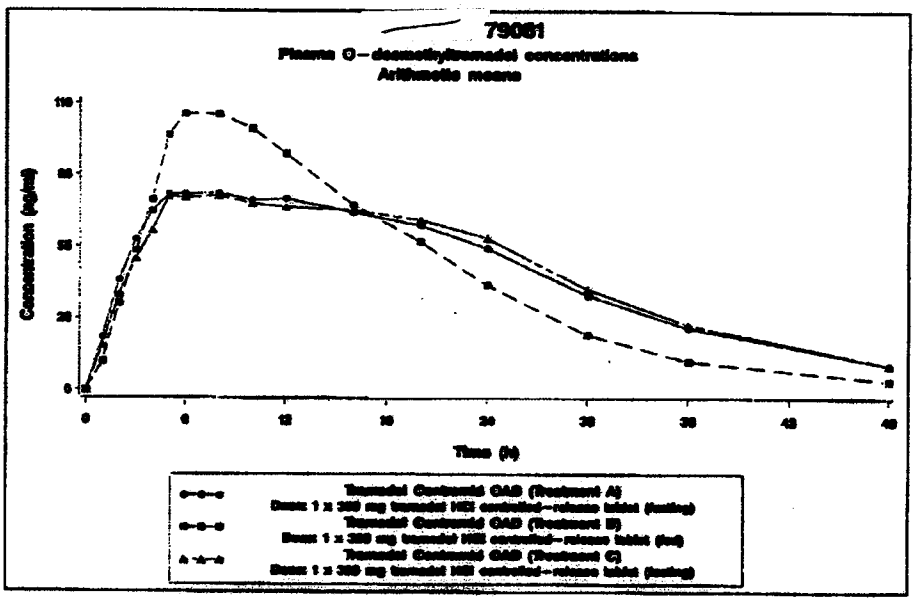


Figure 2. Mean Plasma M1 Concentrations after Various Treatments.

Relative Bioavailability

The mean pharmacokinetic parameters for tramadol and O-desmethyltramadol (M1) following various treatments are summarized in Tables 3 to 6.

Compared Treatment A (300 mg tablets manufactured at the new site) vs. Treatment C (300 mg tablets manufactured at the old site), the 90% confidence intervals for the test/reference ratio of AUC(0-∞) for tramadol and M1 are within the interval [80-125]% (Tables 3 and 4), indicating that in terms of extent of exposure, the test product is equivalent to the reference product. However, the Cmax of tramadol for the test product (new site) is 13% higher than the reference product (old site) (90% CI: 93.6%-137%).

Table 3. Pharmacokinetic Parameters for Tramadol (Dataset No.1:Treatment A vs Treatment C -Arithmetic Means).

[N = 27 (*N = 26): Product A dose: 1 x 300 mg tramadol HCl controlled-release tablet (fasting)
N = 26: Product C dose: 1 x 300 mg tramadol HCl controlled-release tablet (fasting)]

		Tramadol Contramid® OAD (Product A)			Tramadol Contramid® OAD (Product C)					
VARIABLE	UNIT	ARITHMETIC			ARITHMETIC			MEAN RATIO	90% CONFIDENCE INTERVAL	INTRA INDIVIDUAL
		Mean	SD	Range	Mean	SD	Range	(%)*	(%)**	CV (%)
C_{max}	(ng/ml)	454	210	237 - 1087	400	206	242 - 1029	113	93.6 ; 137	43
T_{max}#	(h)	8.00		3.00 - 24.0	12.0		3.02 - 24.0		p - 0.3387	
AUC(0 - t_{max})	(ng· h/ml)	10315	3445	6122 - 18081	9054	3193	5948 - 17635	105	92.6 ; 119	28
AUC(0 - ∞)*	(ng· h/ml)	10488	3468	6417 - 19458	10083	4179	6085 - 21122	108	88.5 ; 116	30
$t_{1/2}$*	(h)	7.97	1.79	5.15 - 12.1	8.48	3.01	4.40 - 15.9	98.7	88.3 ; 110	24
K_e*	(1/h)	0.09	0.02	0.06 - 0.14	0.09	0.03	0.04 - 0.16			

* : Point estimate of "test/reference" mean ratio from analysis of log-transformed data.

** : 90% Conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

: Medians, ranges, p-value for non-parametric Wilcoxon two-sample test.

Dataset No.1: Subjects who had no significant protocol deviations and did not vomit during the dosing interval

Table 4. Pharmacokinetic Parameters for M1 (Dataset No.1: Treatment A vs Treatment C -Arithmetic Means).

[N = 27 (*N = 26): Product A dose: 1 x 300 mg tramadol HCl controlled-release tablet (fasting)
N = 26: Product C dose: 1 x 300 mg tramadol HCl controlled-release tablet (fasting)]

		Tramadol Contramid® OAD (Product A)			Tramadol Contramid® OAD (Product C)					
VARIABLE	UNIT	ARITHMETIC			ARITHMETIC			MEAN RATIO	90% CONFIDENCE INTERVAL	INTRA INDIVIDUAL
		Mean	SD	Range	Mean	SD	Range	(%)*	(%)**	CV (%)
C_{max}	(ng/ml)	85.7	47.9	19.7 - 203	83.0	53.0	20.2 - 225	105	81.5 ; 130	54
T_{max}#	(h)	12.0		4.00 - 24.0	16.0		4.00 - 24.0		p - 0.1325	
AUC(0 - t_{last})	(ng· h/ml)	2136	847	442 - 3757	2095	872	611 - 3806	99.3	84.6 ; 117	35
AUC(0 - ∞)*	(ng· h/ml)	2318	886	474 - 3939	2347	907	754 - 4028	99.3	85.5 ; 115	32
$t_{1/2}$*	(h)	9.97	2.26	5.86 - 13.3	10.1	4.86	5.79 - 24.0	108	89.0 ; 127	29
K_e*	(1/h)	0.08	0.02	0.06 - 0.12	0.08	0.03	0.03 - 0.12			

* : Point estimate of "test/reference" mean ratio from analysis of log-transformed data.

** : 90% Conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

: Medians, ranges, p-value for non-parametric Wilcoxon two-sample test.

Compared Treatment B (fed) vs. Treatment A (fasting) for 300 mg tablets manufactured at the new site, the 90% confidence intervals for the test/reference ratio of AUC(0-∞) for tramadol and M1 are within the interval [80-125]% (Tables 5 and 6), indicating that in terms of extent of exposure, the test product is equivalent to the reference product. However, the Cmax of tramadol for the test treatment (fed) is 67% higher than the reference treatment (fasting) (90% CI: 130-214%) indicating that food increased rate of absorption. Tmax did not change much between treatments. The results were similar to the food effect finding for the 200 mg tablets (Study MDT1-006, Section 4.2.3).

Table 5. Pharmacokinetic Parameters for Tramadol (Dataset No.1:Treatment B vs Treatment A - Arithmetic Means).

[N = 27 (*N = 26): Product A dose: 1 x 300 mg tramadol HCl controlled-release tablet (fasting)
N = 19: Product B dose: 1 x 300 mg tramadol HCl controlled-release tablet (fed)]

		Tramadol Contramid® OAD (Product A)			Tramadol Contramid® OAD (Product B)					
VARIABLE	UNIT	ARITHMETIC			ARITHMETIC			MEAN RATIO	90% CONFIDENCE INTERVAL	INTRA INDIVIDUAL
		Mean	SD	Range	Mean	SD	Range	(%)*	(%)**	CV (%)
C_{max}	(ng/ml)	454	210	237 - 1087	755	313	272 - 1345	167	130 ; 214	43
T_{max}#	(h)	8.00		3.00 - 24.0	10.0		3.00 - 20.0		p - 0.0036	
AUC(0 - t_{last})	(ng· h/ml)	10315	3445	6122 - 18081	10890	2779	6143 - 15865	105	89.1 , 124	28
AUC(0 - ∞)*	(ng· h/ml)	10480	3488	6417 - 19438	11260	3079	6227 - 19681	104	87.4 ; 124	30
$t_{1/2}$*	(h)	7.97	1.79	5.15 - 12.1	7.87	1.86	4.66 - 10.9	87.7	76.1 , 101	24
K_e*	(1/h)	0.09	0.02	0.06 - 0.14	0.10	0.03	0.06 - 0.15			

* : Point estimate of "test/reference" mean ratio from analysis of log-transformed data.

** : 90% Conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

: Medians, ranges, p-value for non-parametric Wilcoxon two-sample test.

Dataset No.1: Subjects who had no significant protocol deviations and did not vomit during the dosing interval

Table 6. Pharmacokinetic Parameters for M1 (Dataset No.1:Treatment B vs Treatment A - Arithmetic Means).

[N = 27 (*N = 26): Product A dose: 1 x 300 mg tramadol HCl controlled-release tablet (fasting)
N = 19: Product B dose: 1 x 300 mg tramadol HCl controlled-release tablet (fed)]

		Tramadol Contramid® OAD (Product A)			Tramadol Contramid® OAD (Product B)					
VARIABLE	UNIT	ARITHMETIC			ARITHMETIC			MEAN RATIO	90% CONFIDENCE INTERVAL	INTRA INDIVIDUAL
		Mean	SD	Range	Mean	SD	Range	(%)*	(%)**	CV (%)
C_{max}	(ng/ml)	35.7	47.9	19.7 - 203	131	75.4	24.8 - 262	151	112 ; 204	54
T_{max}'	(h)	12.0		4.00 - 24.0	18.0		5.00 - 20.0		p - 0.0318	
AUC(0 - t_{last})	(ng· h/ml)	2136	847	442 - 3757	2194	952	632 - 3441	105	85.8 ; 130	35
AUC(0 - ∞)"	(ng· h/ml)	2318	886	474 - 3939	2246	952	702 - 3473	100	82.9 ; 121	32
$t_{1/2}$°	(h)	9.57	2.28	5.86 - 13.3	7.76	1.51	5.57 - 12.5	78.8	66.3 ; 93.7	29
K_e°	(1/h)	0.08	0.02	0.06 - 0.12	0.09	0.02	0.06 - 0.12			

* . Point estimate of "test/reference" mean ratio from analysis of log-transformed data.

** . 90% Conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

: Medians, ranges, p-value for non-parametric Wilcoxon two-sample test.

Discussion and Conclusions: 300 mg tablets manufactured at the new site were equivalent to the 300 mg tablets manufactured at the old site in terms of AUC. However, the new tablets had higher C_{max} (~15% higher) (90% CI: 93.6, 137). Dissolution profiles for tablets manufactured at the new site and old site were comparable (Table 7). Although in general slightly higher % values at each timepoint were observed for tablets manufactured at the new site, the difference were small (<10%).

Table 7. Dissolution Comparison for 300 mg Tablets Manufactured at the New Site (Confab) vs. Old Site ——— Representative Batches).

Batch No.	104490 (Used in this study)	RX-52187 (Used in Study MDT1-011)
Mfg Date	April 2005	October 2002
Manufacturer	Confab	———
Dissolution (Reported as mean (min-max))		
2 hr	23%	22%
7 hr	48%	44%
12 hr	71%	-
20 hr	93%	89%

(Data source: Module 2.3, Table 71 and Table 75)

b(4)

Available information suggests that the ~15% higher Cmax may not lead to additional safety concerns;

- The design of the study to dose 300 mg to healthy subjects may have contributed to the variability. Nausea and vomiting are adverse events associated with tramadol. To build tolerability, patients are normally titrated to their desired dose. In this case, subjects were administered the 300 mg dose directly. Several subjects reported incidences of nausea and vomiting.

- The C_{max} of Tramadol Contramid OAD manufactured at the old site is about 20% lower compared to a corresponding total daily dose of Ultram.
- Tablets manufactured at the old site at doses of 300 mg and 400 mg (2X200 mg) have been studied in patients for up to 12 weeks (700 patients with 300 mg dose and 24 patients with 400 mg dose). These studies were conducted without regard to food and food is known to increase Cmax by at least 50%.
- In addition, 400 mg (2X200 mg) dose have been studied in 48 healthy subjects after a single dose under fasting conditions.
- Overall adverse event profile for 400 mg was similar to those of 100 to 300mg but with higher intensity as expected.
- Ultram IR was approved for use up to 400 mg/day (100 mg QID).

As observed before for 200 mg tablets, food increased Cmax (67% increase) but not AUC for 300 mg tablets. Food also does not have an effect on Tmax.

Appendix for Study MDT-01-016. Demographic Information.
Table A1. Demographic Data for All Subjects.

Subject No.[1]	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Race	Sterile[2]	Sex
01	24	177.0	69.1	22.1	Caucasian	N/A	Male
02	33	179.0	94.2	29.4	Caucasian	N/A	Male
03	52	164.0	74.5	27.7	Caucasian	Yes	Female
04	43	167.0	67.5	24.2	Caucasian	Yes	Female
05	43	159.5	52.1	20.5	Caucasian	Yes	Female
06	47	160.5	56.2	21.8	Caucasian	No	Female
07	20	171.5	81.2	27.6	Caucasian	No	Female
08	32	165.5	81.5	29.8	Caucasian	Yes	Female
09*	46	162.5	56.1	21.2	Caucasian	No	Female
10	55	159.5	75.4	29.6	Caucasian	Yes	Female
11	54	157.5	54.1	21.8	Caucasian	Yes	Female
12	39	174.5	85.0	27.9	Caucasian	N/A	Male
13*	30	161.0	70.4	27.2	Caucasian	No	Female
14	45	154.5	66.2	27.7	Caucasian	No	Female
15	34	158.0	52.5	21.0	Caucasian	No	Female
16	49	170.5	66.5	22.9	Caucasian	Yes	Female
17	38	161.0	59.6	23.0	Caucasian	No	Female
18	42	163.0	53.6	20.2	Caucasian	Yes	Female
19	52	158.0	55.5	22.2	Caucasian	Yes	Female
20	32	162.0	69.0	26.3	American Hispanic	Yes	Female
21	50	155.0	62.5	26.0	Caucasian	No	Female
22	49	165.0	79.6	29.2	American Hispanic	N/A	Male
23	25	167.0	59.6	21.4	Caucasian	No	Female
24	26	160.0	50.4	19.7	American Hispanic	No	Female
25	24	161.5	59.1	22.7	Caucasian	No	Female
26	51	166.5	61.0	22.0	Caucasian	N/A	Male
27	44	165.0	75.9	27.9	Caucasian	N/A	Male
28*	45	173.0	76.9	25.7	Caucasian	N/A	Male
29	50	165.5	74.3	27.1	Caucasian	N/A	Male
30*	23	176.0	69.0	22.3	Caucasian	N/A	Male
31	40	171.5	77.9	26.5	Caucasian	N/A	Male
32	27	174.5	73.3	24.1	Caucasian	N/A	Male
33	19	176.0	64.0	20.7	American Hispanic	N/A	Male
34	49	179.0	89.3	27.9	Caucasian	N/A	Male
35	29	162.5	69.3	26.2	Caucasian	N/A	Male
36	38	167.5	68.7	24.5	American Hispanic	N/A	Male
Mean	38.9	165.9	68.1	24.7			
Minimum	19.0	154.5	50.4	19.7			
Maximum	55.0	179.0	94.2	29.8			

[1] All subjects were non-smokers.
*Subject did not complete the study
[2] Surgically-sterile or post-menopausal female subject.

N/A = Not Applicable
BMI = Body Mass Index

4.3 OCP Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	21-745	Brand Name	Cotramid® OAD
OCPB Division	DCPB2	Generic Name	Tramadol Hydrochloride
Medical Division	DAARP	Drug Class	Centrally Acting Analgesic
OCPB Reviewer	Lei Zhang, Ph.D.	Indication(s)	Management of moderate to moderately severe pain
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	100, 200, and 300 mg tablets
		Dosing Regimen	Once daily. Treatment should be initiated at a dose of 100 mg/day of TRAMADOL CONTRAMID® OAD and may then be increased by 100 mg/day increments every 2 days, up to a maximum dose of 300 mg/day, to achieve a balance between adequate pain control and tolerability for the individual patient. For patients requiring the 300 mg dose, titration should take 4 days. The daily dose should be individualized for each patient. Patients should be maintained on the lowest effective dose.
Date of Submission	11/28/2005	Route of Administration	Oral
Estimated Due Date of OCPB Review	7/15/2006	Sponsor	Labopharm Canada, Inc.
PDUFA Due Date	9/28/2006	Priority Classification	New Formulation (5-S)
Division Due Date	7/28/2006		IND 64,317 505 b(2); Reference Ultram (NDA 20-281)

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		Study MDT1-011 (single dose, fasting, 100, 200 and 300 mg tablets)

multiple dose:	X	1		MDT1-009 (steady-state vs. Ultram at 200 mg daily dose for 5 days) 200 mg tablet
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		Study MDT1-011 (single dose, fasting, 100, 200 and 300 mg tablets) Pilot: MDT1-004 (300 mg is not the marketed formulation)
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
in-vivo effects on primary drug:				
in-vivo effects of primary drug:				
in-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
[redacted]				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	4		MDT1-009 (steady-state vs. Ultram at 200 mg daily dose for 5 days) Supportive (Compare with non-US approved-Topalgic and Zytram): 1. Study MDT1-005 (single dose, 200 and 400 mg, Topalgic 100 and 200 mg BID) 2. Study MDT1-007 (steady-state, 200 mg for 6 days, Topalgic 50 mg QID) 3. Study MDT1-010 (steady-state, 200 mg for 6 days, Topalgic 100 mg BID) 4. Study MDT1-012 (single dose, 200 mg, Zytram 200 mg QD)
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		MDT1-013 (single dose, coated vs. uncoated, 200 mg tablet) MDT1-016 (single dose, 200 mg tablet at Cenfah vs.
replicate design; single / multi dose:				

Food-drug interaction studies:	X	2		Study MDT1-006 (200 mg tablet, single dose) Pilot: MDT1-062
Dissolution:	X			Apparatus 1 (baskets) at a speed of 100 rpm at pH 6.8 (3.2.P.2, Vol. 2 of 10)
(IVIVC):	X			Project MDT RP-0167.1 (Vol. 33 of 99)
Bio-wavier request based on BCS				
BCS class				
[redacted]				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		10-11	4	

Filability and QBR comments		
	"X" if yes	1) Comments
Application filable?	X	
Comments sent to firm?	X	The following comments were included in the filing letter as potential review issues: 1. Product used in pivotal clinical trials and product proposed to be commercially marketed are manufactured in two completely different manufacturing sites. There is inadequate data linking the product manufactured at these two sites. 2 Food effect was determined on the 200 mg strength [redacted] food effect for the 300 mg strength may be different. As such, potential dose dumping of the 300 mg strength due to food effect has not been completely ruled out.
QBR questions (key issues to be considered)	• What is PK profile of 100, 200 and 300 mg CONTRAMID® OAD tablets? Is PK dose proportional? • What is steady state PK of the highest dose strength tablet (300 mg)? • How does exposure of the CONTRAMID® OAD tablets compare to Ultram at steady state for both tramadol and O-desmethylated M1 metabolite at equivalent doses? • Is there a food effect (done with 300 mg tablet)? • Does PK of the new CONTRAMID® OAD formulation support the proposed indication? • Is there an alcohol interaction?	
Other comments or information not included above	This is a 505 b(2) application. The sponsor did not conduct the bioequivalence study to RLD with the 300 mg tablet (highest dose strength). This is considered acceptable because tramadol has narrow therapeutic window and it is unethical to give 300 mg to healthy volunteers for multiple dose studies. The sponsor used 200 mg daily dose that represents the most common dose given to patients. A teleconference was conducted on Jan 23 with the sponsor to bring up the above mentioned two comments in the filing letter to the Sponsor. The Sponsor agreed to conduct BE study to link the to-be-marketed formulation with the formulation used in the pivotal clinical trials (300 mg tablets). In addition, the Sponsor will conduct food effect study with the 300 mg strength tablet. They will submit the full study report during the review cycle (by June 30, 2006).	
Primary reviewer Signature and Date	Lei Zhang (Suresh Deddapaneni did the majority of the filing review.)	
Secondary reviewer Signature and Date	Suresh Deddapaneni	

b(4)

CC: NDA 21-745, DAARP (Balcer), DCPB2 (L. Zhang, Deddapaneni, Hunt, Malinowski), CDR

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

/s/

Lei K Zhang
8/24/2006 03:02:20 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
8/24/2006 03:21:11 PM
BIOPHARMACEUTICS