CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-692

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-692
Submission Dates	9/30/2004, 3/7/2005 (Complete response to approvable letter dated October 29, 2004), 8/23/2005
Brand Name	To-be-determined
Generic Name	Tramadol Hydrochloride
Reviewers	Lei Zhang, Ph.D.
Team Leader	E. Dennis Bashaw, Pharm. D.
OCPB Division	DPE III
OND Division	DAAODP (HFD-550)
Applicant	Bioavail Laboratories, Inc.
Relevant IND	IND 59,023
Type of Submission; Code	505 (b)(2); 5S
Reference Listed Drug	Ultram, 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 chronic pain in adults

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

NDA 21-692 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 not an approved extended-release formulation of tramadol HCl. The original NDA was submitted on Dec 3, 2003 and the Sponsor received an approvable letter on October 29, 2004. The major deficiency cited in the approvable letter was a lack of efficacy of the proposed doses to support the proposed indication. In this resubmission, the Sponsor provided additional analysis based on the existing data and did not conduct new clinical studies. In addition, the Sponsor included a new proposed indication for the management of moderate to moderately severe chronic pain. The intended doses and dosing interval are 100 and 200 mg once daily (not to exceed 300 mg daily).

The major action items listed in the approvable letter related to Clinical Pharmacology and Biopharamceutics are:

- Provide a statistical analysis of the results of Cmin testing, to include the calculation of 90% confidence intervals, in the studies where Cmin was available.
- Acceptance of the dissolution specifications is pending upon the review of in vitro-in vivo correlation (IVIVC) results.
- Provide a more detailed explanation on how final conclusions regarding dosage reduction in renal and hepatic impairment patients were reached in each condition.
- Further evaluate age effect and provide additional data on TRADENAME ER exposure-response in elderly (65-75 yrs) and older elderly (>75 yrs) subjects.

On December 3, 2004, a post-action meeting was taken place. At this meeting the Sponsor clarified the issues raised in the approvable letter and a path forward. With respect to Clinical Pharmacology and Biopharmaceutics, in addition to the issues identified in the approvable letter the following issues came from the Dec. 2004 meeting:

1. The lack of bioequivalence of TRADENAME ER to the Reference Listed Drug (RLD), Ultram.
2. The plasma concentration versus time profile of TRADENAME ER did not appear to show adequate coverage over 24 hours when compared to Ultram given q6h. Particular attention was drawn to the first 5-6 hours and 18 to 24 hours after the TRADENAME ER dose when the steady state mean plasma Tramadol concentrations of TRADENAME ER are lower than those of Ultram. The FDA expressed concern that the lower plasma concentrations achieved as a result of the lag time may result in lack of efficacy.

On March 7, 2005, the Sponsor submitted the complete response to the approvable letter and to the issues raised in the Dec. 2004 meeting. In addition to these issues, a new analysis of the IVIVC data was submitted on September 30, 2004 and was reviewed by Dr. Patrick Marroum during this review cycle (see Appendix 3.2).

At this point in time the Sponsor has not evaluated the pharmacokinetics (PK) of TRADENAME ER in subjects older than 65 years. They submitted summary of adverse events in subjects who are older than 65 years collected from the TRADENAME ER clinical trials and the data were reviewed by Dr. Villalba. The rate of adverse events among the elderly (>65 years) and older elderly (>75 years) were somewhat greater than among the < 65 year population, particularly for the 300 and 400 mg doses. Please refer to Dr. Villalba's safety review for details.

1.1 Recommendations

From a Clinical Pharmacology and Biopharmaceutics perspective, the application is acceptable with the following comments.

1. A decision could not be made on the acceptability of the IVIVC (Level A) as there are still outstanding data requests at this time. Without an IVIVC, the Sponsor should revise their dissolution specifications as an interim specification as shown in the table below (based on the mean dissolution profile obtained from the clinical/bioavailability lots-see previous OCPB review in DFS), until such time that a final review of their IVIVC can be completed:

Time	Applicant's Proposed Dissolution Limits (Dated 8/16/2005)	Agency's Revised Proposed Dissolution limits
2 hours		
4 hours		
8 hours		
10 hours		
16 hours		

2. The labeling recommendation is in Section 2.

1.2 Phase 4 Commitments

None.

1.3 Review of Resubmission

Bioequivalence (BE) and C_{min} Calculations:

In addition to Study B01-567Pk-TRAP03 where BE of TRADENAME ER were compared to Ultram dosed every 6 hours after single- and multiple-doses, the Sponsor cited data from two pilot BE studies with Ultram dosed as 100 mg TID (approximately 7 am, 12 pm and 6 pm) (Study B99-424PK-TRAP03; 2282) or 50 mg QID (7 am, 12 pm, 6 pm and 10 pm) (Study B99-416PK-TRAP03; 99103) after single- and multiple-doses to determine relative bioavailability between TRADENAME ER and Ultram. The later two studies were viewed as supportive because the dose interval for Ultram is not well-controlled as every 6 hours.

The BE of TRADENAME ER to Ultram was demonstrated after single daily dose in all the studies based on Cmax and AUC of tramadol and M1.

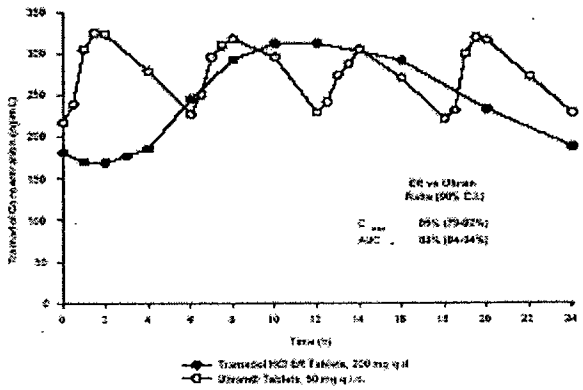
However, the criteria for BE was not met for C_{max} of tramadol when TRADENAME ER was compared to Ultram dosed every 6 hours (Q6h) at steady-state (Table 1) (C_{max} was somewhat lower after TRADENAME ER administration). In addition, C_{min} of tramadol was also lower after TRADENAME ER administration in comparison to Ultram Q6h. Consistent with the extended release nature, Tmax at steady-state is longer for TRADENAME ER than for Ultram (mean Tmax 12 hour vs. 1.5 hr). The PK profile difference between TRADENAME ER and Ultram, i.e., low concentration in absorption phase (0-6 hr) and terminal phase (18-24 hr) was observed. The clinical significance of these findings is unknown (Figure 1). This data alone is insufficient to support the efficacy of TRADENAME ER.

Table 1. Steady-state tramadol point estimates, 90% C.I.'s & Degree of Fluctuation.

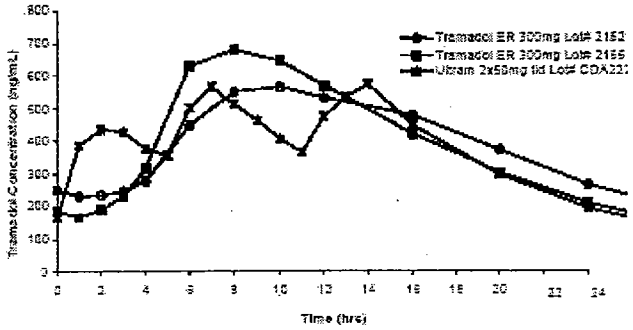
Study # & Type	Comparison	AUC_τ	C_{max}	C_{min}	Fluctuation†, %
B99-416PK-TRAP03 (99103) Pilot 2-Way Steady State Fasting Study	Steady-state, Day 5 Test (2162) 2x100 mg vs Ultram®50 mg q.i.d	107.9 102.8 – 113.4	103.8 96.4 – 111.8	117.1 94.6 – 144.9	70.19 ± 16.98 (TRA) 81.82 ± 16.60 (ULT)
B99-424PK-TRAP03 (2282) Pilot 3-Way Steady State Fasting Study	Steady State Day 5 Test A (2162) 3x100 mg vs Ultram®2x50 mg t.i.d	102 95 – 109	93 84 – 103	135 121- 150	90.20 ±29.14 (TRA) 119.25 ± 25.65 (ULT)
B01-567PK-TRAP03 (2551) 2-Way Single and Multiple Dose Fasting Study	Steady State Day 10 Test 200 mg pivotal batch vs Ultram® 50 mg q6h	88.7 84.0 – 93.8	84.9 78.6 – 91.6	78.8 70.4 – 88.2	61.03 ± 34.51 (TRA) 59.36 ± 20.77 (ULT)

TRA = TRADENAME ER; ULT = Ultram

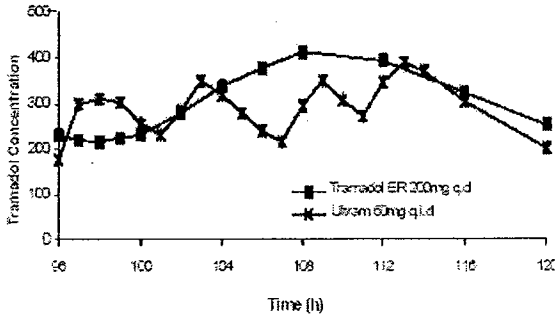
† Fluctuation = $((Cmax-Cmin)/(AUC_\tau/\tau))*100$; where τ is the dosing interval of 24 h.



Study 567PK (Q6h)



Study 416PK (TID)
(Lot 2162 was scaled up for clinical program)



Study 424 PK QID

Figure 1. Mean Steady-State Tramadol Plasma Concentration-Time Profile.

Dosage recommendation for special populations:

Severe renal and hepatic impairment:
We do not agree with Sponsor's dose recommendations for these patients based on the Ultram labeling to reduce dose and increase dose interval. Because of the limited dose strengths of TRADENAME ER, starting TRADENAME ER doses lower than 100 mg for these patients is not possible. Nor has the sponsor studied alternative dosing regimens in this population, i.e., q36hr or q48hr dosing. The use of TRADENAME ER in patients with either severe renal impairment and/or severe hepatic impairment is not recommended.

Elderly:
The effect of age on the absorption of TRADENAME ER in subjects older than 65 years has not been studied and is unknown. From the Ultram Labeling, exposure and elimination half-life of tramadol after Ultram administration are similar in healthy subjects 65-75 years compared to healthy subjects younger than 65 years. Exposure of tramadol is higher in subjects older than 75 years compared to subjects 65-75 years. In general, dosing of an elderly patient (over 65 years of age) should be initiated cautiously, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. TRADENAME ER should be administered with even

greater caution in patients over 75 years, due to the greater frequency of adverse events seen in this population.

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2 DETAILED LABELING RECOMMENDATIONS

The labeling recommendations that are related to Clinical Pharmacology are shown below. Please refer to the approval letter for the final labeling.

CLINICAL PHARMACOLOGY

Mechanism of Action

TRADENAME ER 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. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. 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.

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol. The relationship between exposure of tramadol and M1 and efficacy has not been evaluated in the TRADENAME ER clinical studies.

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids. In contrast to morphine, tramadol has not been shown to cause histamine release. At therapeutic doses, tramadol has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

Pharmacokinetics

The analgesic activity of tramadol is due to both parent drug and the M1 metabolite. TRADENAME ER is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation.

The pharmacokinetics of TRADENAME ER are approximately dose-proportional over a 100-400 mg dose range in healthy subjects. The observed tramadol AUC values for the 400-mg dose were 26% higher than predicted based on the AUC values for the 200-mg dose.

Absorption

In healthy subjects, the bioavailability of a TRADENAME ER 200 mg tablet relative to a 50 mg every six hours dosing regimen of the immediate-release dosage form (ULTRAM) was approximately 85-90%. Consistent with the extended-release nature of the formulation, there is a lag time in drug absorption following TRADENAME ER administration. The mean peak plasma concentrations of tramadol and M1 after administration of TRADENAME ER tablets to healthy volunteers are attained at about 12 h and 15 h, respectively, after dosing (See Table 1 and Figure 2). Following administration of the TRADENAME ER, steady-state plasma concentrations of both tramadol and M1 are achieved within four days with once daily dosing.

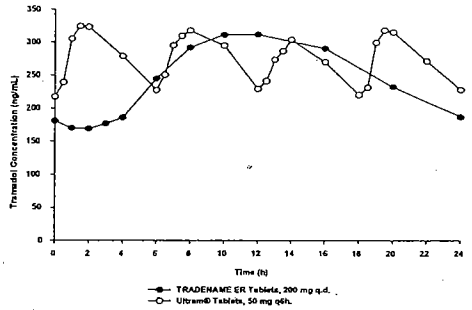
The mean (%CV) pharmacokinetic parameter values for TRADENAME ER 200 mg administered once daily and tramadol HCl immediate-release (ULTRAM) 50 mg administered every six hours are provided in Table 1.

Table 1. Mean (%CV) Steady-State Pharmacokinetic Parameter Values (n=32)

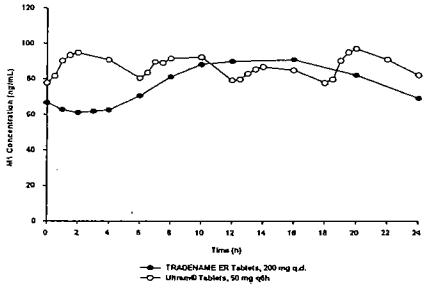
Pharmacokinetic Parameter	Tramadol		M1 Metabolite	
	TRADENAME ER 200-mg Tablet Once-Daily	ULTRAM 50-mg Tablet Every 6 Hours	TRADENAME ER 200-mg Tablet Once-Daily	ULTRAM 50-mg Tablet Every 6 Hours
AUC_{0-24} (ng·h/mL)	5975 (34)	6613 (27)	1890 (25)	2095 (26)
C_{max} (ng/mL)	335 (35)	383 (21)	95 (24)	104 (24)
C_{min} (ng/mL)	187 (37)	228 (32)	69 (30)	82 (27)
T_{max} (h)	12 (27)	1.5 (42)	15 (27)	1.9 (57)
% Fluctuation	61 (57)	59 (35)	34 (72)	26 (47)

AUC_{0-24}: Area Under the Curve in a 24-hour dose interval; C_{max}: Peak Concentration in a 24-hour dose interval; C_{min}: Trough Concentration in a 24-hour dose interval; T_{max}: Time to Peak Concentration

Figure 2: Mean Steady-State Tramadol (a) and M1 (b) Plasma Concentrations on Day 8 Post Dose after Administration of 200 mg TRADENAME ER Once-Daily and 50 mg ULTRAM Every 6 Hours.



a. Tramadol



b. M1

Food Effects

After a single dose administration of 200 mg TRADENAME ER tablet with a high fat meal, the C_{max} and $AUC_{0-\infty}$ of tramadol decreased 28% and 16%, respectively, compared to fasting conditions. Mean T_{max} was increased by 3 hr (from 14 hr under fasting conditions to 17 hr under fed conditions). While TRADENAME ER may be taken without regard to food, it is recommended that it be taken in a consistent manner.

Distribution
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.

Metabolism
Tramadol is extensively metabolized after oral administration. The major metabolic pathways appear to be N – (mediated by CYP3A4 and CYP2B6) and O – (mediated by CYP2D6) demethylation and glucuronidation or sulfation in the liver. One metabolite (O-desmethyl tramadol, denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and is subject to inhibition, which may affect the therapeutic response (see **CLINICAL PHARMACOLOGY-Drug Interactions** and **PRECAUTIONS - Drug Interactions**).

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. Based on a population PK analysis of Phase I studies with immediate-release tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower.

Elimination
Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 after administration of TRADENAME ER are approximately 7.9 and 8.8 hours, respectively.

Special Populations

Renal
Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. The pharmacokinetics of tramadol were studied in patients with mild or moderate renal impairment after receiving multiple doses of TRADENAME ER 100 mg. There is no consistent trend observed for tramadol exposure related to renal function in patients with mild (CLcr: 50-80 mL/min) and moderate (CLcr: 30-50 mL/min) renal impairment in comparison to patients with normal renal function. However, exposure of M1 increased 20-40% with increased severity of the renal impairment (from normal to mild and moderate). TRADENAME ER has not been studied in patients with severe renal impairment (CLcr < 30 mL/min). The limited availability of dose strengths of TRADENAME ER does not permit the dosing flexibility required for safe use in patients with severe renal impairment. Therefore, TRADENAME ER should not be used in patients with severe renal impairment (see **WARNINGS, Use in Renal and Hepatic Disease** and **DOSAGE AND ADMINISTRATION**).

The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose.

Hepatic

Pharmacokinetics of tramadol was studied in patients with mild or moderate hepatic impairment after receiving multiple doses of TRADENAME ER 100 mg. The exposure of (+)- and (-)-tramadol was similar in mild and moderate hepatic impairment patients in comparison to patients with normal hepatic function. However, exposure of (+)- and (-)-M1 decreased ~50% with increased severity of the hepatic impairment (from normal to mild and moderate). The pharmacokinetics of tramadol after the administration of TRADENAME ER has not been studied in patients with severe hepatic impairment. After the administration of tramadol immediate-release tablets to patients with advanced cirrhosis of the liver, tramadol area under the plasma concentration time curve was larger and the tramadol and M1 half-lives were longer than subjects with normal hepatic function. The limited availability of dose strengths of TRADENAME ER does not permit the dosing flexibility required for safe use in patients with severe hepatic impairment. Therefore, TRADENAME ER should not be used in patients with severe hepatic impairment (see **WARNINGS, Use in Renal and Hepatic Disease** and **DOSAGE AND ADMINISTRATION**).

Geriatric

The effect of age on the absorption of tramadol from TRADENAME ER in patients over the age of 65 years has not been studied and is unknown (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Gender

Based on pooled multiple-dose pharmacokinetics studies for TRADENAME ER in 166 healthy subjects (111 males and 55 females), the dose-normalized AUC values for tramadol were somewhat higher in females than in males. There was a considerable degree of overlap in values between male and female groups. Dosage adjustment based on gender is not recommended.

Drug Interactions

The formation of the active metabolite, M1, is mediated by CYP2D6. Concomitant therapy with inhibitors of CYP2D6 such as fluoxetine, paroxetine and quinidine could result in significant drug interactions. *In vitro* drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 (fluoxetine, norfluoxetine, amitriptyline, and quinidine) inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown.

Tramadol is also metabolized by CYP3A4. Administration of CYP3A4 inhibitors, such as ketoconazole and clarithromycin, or inducers, such as rifampin and St. John's Wort, with TRADENAME ER may affect the metabolism of tramadol leading to altered tramadol exposure (see **PRECAUTIONS, drug interactions**).

Quinidine

Tramadol is metabolized to M1 by CYP2D6. A study was conducted to examine the effect of quinidine, a selective inhibitor of CYP2D6, on the pharmacokinetics of tramadol by administering 200 mg quinidine two hours before the administration of TRADENAME ER 100 mg. The results demonstrated that the exposure of tramadol increased 50-60% and the exposure of M1 decreased 50-60% (see **PRECAUTIONS, drug interactions**). In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

Carbamazepine

Carbamazepine, a CYP3A4 inducer, increases tramadol metabolism. Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Because of the seizure risk associated with tramadol, concomitant administration of TRADENAME ER and carbamazepine is not recommended (see **PRECAUTIONS, drug interactions**).

Cimetidine

Concomitant administration of tramadol immediate-release tablets with **cimetidine** does not result in clinically significant changes in tramadol pharmacokinetics. No alteration of the TRADENAME ER dosage regimen with cimetidine is recommended.

WARNINGS

Use in Renal and Hepatic Disease

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. TRADENAME ER has not been studied in patients with severe renal impairment (CLcr < 30 mL/min). The limited availability of dose strengths of TRADENAME ER does not permit the dosing flexibility required for safe use in patients with severe renal impairment. Therefore, TRADENAME ER should not be used in patients with severe renal impairment (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**). Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. The pharmacokinetics of TRADENAME ER has not been studied in patients with severe hepatic impairment. The limited availability of dose strengths of TRADENAME ER does not permit the dosing flexibility required for safe use in patients with severe hepatic impairment. Therefore, TRADENAME ER should not be used in patients with

severe hepatic impairment (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

PRECAUTIONS

Drug Interactions

Use With Carbamazepine
Patients taking **carbamazepine**, a CYP3A4 inducer, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of TRADENAME ER and carbamazepine is not recommended.

Use With Quinidine
Coadministration of quinidine with TRADENAME ER resulted in a 50-60% increase in tramadol exposure and a 50-60% decrease in M1 exposure(see **CLINICAL PHARMACOLOGY-drug interactions**). The clinical consequences of these findings are unknown.

Use With MAO Inhibitors

Interactions with **MAO Inhibitors**, due to interference with detoxification mechanisms, have been reported for some centrally acting drugs (see **WARNINGS, Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors)**

Use With Digoxin and Warfarin

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity and alteration of warfarin effect, including elevation of prothrombin times.

Potential for Other Drugs to Affect Tramadol
In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.

Administration of CYP3A4 inhibitors, such as ketoconazole and clarithromycin, or inducers, such as rifampin and St. John's Wort, with TRADENAME ER may affect the metabolism of tramadol leading to altered tramadol exposure.

Potential for Tramadol to Affect Other Drugs
In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism. In vitro studies indicate that tramadol is unlikely to inhibit the

CYP3A4-mediated metabolism of other drugs when administered concomitantly at therapeutic doses. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

DOSAGE AND ADMINISTRATION

TRADENAME ER should not be used in patients with:

- creatinine clearance less than 30 mL/min,
- severe hepatic impairment (Child-Pugh Class C)

(See WARNINGS, Use in Renal and Hepatic Disease).

Adults (17 years of age and over)

TRADENAME ER should be initiated at a dose of 100 mg once daily and titrated up as necessary by 100-mg increments every five days to relief of pain and depending upon tolerability. TRADENAME ER should not be administered at a dose **exceeding 300 mg per day.**

Individualization of Dose

Good pain management practice dictates that the dose be individualized according to patient need using the lowest beneficial dose. Start at the lowest possible dose and titrate upward as tolerated to achieve an adequate effect. Clinical studies of TRADENAME ER have not demonstrated a clinical benefit at a total daily dose exceeding 300 mg.

In general, dosing of an elderly patient (over 65 years of age) should be initiated cautiously, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. TRADENAME ER should be administered with even greater caution in patients over 75 years, due to the greater frequency of adverse events seen in this population.

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3.2 IVIVC Review

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John Lazor
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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 21-692 Submission date: September 29, 2004
Tramadol extended release tablets
Biovail Corporation
Reviewer: Patrick J Marroum.

Type of submission: Validation of the In Vivo/In Vitro Correlation.

Background:

Biovail Corporation has developed an extended release tablet formulation of tramadol. During the review of the initial submission, the proposed IVIVC model was not accepted due to the fact that the model did not account for differences in bioavailability for the three formulations with different release rates. A conference call was held with the sponsor on September 1st 2004 to discuss the acceptability of the IVIVC. In this submission, the sponsor reanalyzed the data using a model that takes into consideration the time scale difference as well as the difference in bioavailability among these formulations.

Study Design:

The data used in this analysis was obtained from a crossover study with 16 subjects each taking 100 mg tramadol ER formulations with different levels of rate controlling coat. Additionally, 2x 50 mg immediate release tablets of tramadol were given to each subject as a reference.
The dissolution profiles were obtained using USP apparatus 1 at a speed of [redacted] HCl.

Development of the IVIVC model:

1-A unit impulse function for each subject was determined from the IR reference formulation.

2-The amount of drug released in vivo for each subject was determined by deconvolution (the procedure used is deconvolution by convolution which involves nonlinear regression analysis of the convolution integral) of the individual plasma concentration time profiles.

3-The average amount of drug released for each of the formulation was plotted against the mean in vitro dissolution data to obtain the IVIVC relationship.

The fitting of the IR concentration time data as well as the deconvolution and convolution was performed using PDx-IVIVC version 1. The exploration of time scaling was conducted in SPlus 2000 Professional Release 3.

Results:

Figure 1 shows the average dissolution profile for the 3 formulations while Figure 2 shows the corresponding mean plasma concentration time profiles. Figure 3 shows the % dissolved as well as the % absorbed vs time. Figure 4 shows the time course of both in vitro and in vivo release vs time and fitted quadratic equation. Figure 5 shows the relationship between the % released in vitro vs the % released in vivo. Figure 6 shows the time scaled % in vitro release vs % in vivo
Release while Figure 7 shows the relationship between in vitro and in vivo release after time scaling. Figures 8 and 9 show the observed and predicted plasma concentrations for all 3 formulations using both the linear and extended IVIVC model. Figure 10 shows the observed vs predicted plasma concentration for the target formulation in Study 2553 (external predictability).
Figures 11 and 12 shows the plasma concentration time profiles corresponding to the upper and lower limit of the dissolution specifications respectively. Table 1 shows the statistics for the internal validation for the linear model while Table 2 shows the statistics for the internal validation for the extended model. Table 3 shows the statistics for the external validation for the extended model. Table 4 shows the predicted PK parameters that correspond to the upper and lower limit of the dissolution specifications. Table 5 and 6 show the mean parameters of the mean unit impulse response function for Ultram for both studies 2553 and 2677.

Discussion and Comments:

1-For the linear model, the intercept and slope were estimated to be -1.27 and 0.946 indicated that the time scaled in vitro in vivo relationship was 1 to 1. This linear model fails to predict the lower bioavailability of the slower formulation of tramadol. This why the sponsor opted to use an extended model which was developed by Dr. Gillespie which incorporates a time dependent extent of absorption. Drug released after a certain time is not absorbed. The slope and intercept were estimated to be 0.985 and -2.7 respectively. The time at which no further absorption takes place was estimated to be 23 hours.

2-The sponsor did not provide either the mathematical models or the control files that they used for their calculations. The sponsor is requested to provide all the control files as well as the equations for all the models they used to develop the models as well as predicting the plasma concentration time profiles.

3-The sponsor only predicted the target formulation from study 2553 for their external validation even though the study included 3 formulations with different release rates. In order to validate their time dependent model, the sponsor is requested to predict the plasma concentration time profiles for both the fast and slow formulations in study 2553.
It is important to show that the extended model proposed by the sponsor is able to show that indeed it is predictive of slower formulation since the linear model had difficulty predicting the slower formulation. Moreover, the premise that this model which accounts for the non absorption of drug after a certain time in the body could only be validated with slower formulations.

4-The sponsor is proposing the following dissolution specifications:

2hours:
4 hours:
8 hours:
10 hours
16 hours %

Assuming that the proposed IVIVC extended model is acceptable, the predicted plasma concentration time profiles corresponding to the upper and lower limit of the dissolution specifications result in more than % difference (25 % difference for Cmax and 23.35 % for AUC). The sponsor is requested to tighten the specifications in such a way that the maximum difference in the predicted Cmax and AUC between the upper and lower limit is no more than .

Recommendations:

Before a decision can be made on the acceptability of the IVIVC, the sponsor should address the above comments and submit all the requested information. However, if the application is approved the sponsor should tighten the dissolution specifications in a such a way as recommended in the IVIVC guidance.

Patrick J Marroum Ph.D.

RD/FT initialed by Mehul Mehta Ph.D._____

cc: NDA 21-692, HFD 550, HFD 860 (Marroum, Mehta, Rahman, Zeng)

Table 22. The internal validation statistics for the linear IVIVC model for Tramadol ER formulations in Study 2677.

Treatment	C_{max} (ng/mL)				AUC (ng*hr/mL)			
	Obs.	Pred.	Ratio	|%PE|	Obs.	Pred.	Ratio	|%PE|
[redacted]	168.0	152.8	0.909	9.05	2786.9	2688.8	0.965	3.52
Target	127.5	122.6	0.961	3.88	2716.1	2581.7	0.951	4.95
[redacted]	103.0	105.0	1.019	1.92	2300.9	2511.1	1.091	9.13
MAPPE				4.95				5.87

Table 1

Table 25. The internal validation statistics for the extended IVIVC model for Tramadol ER formulations in Study 2677.

Treatment	C_{max} (ng/mL)				AUC (ng*hr/mL)			
	Obs.	Pred.	Ratio	|%PE|	Obs.	Pred.	Ratio	|%PE|
[redacted]	168.0	158.9	0.946	5.41	2786.9	2762.4	0.991	0.88
Target	127.5	127.5	1.000	0.02	2716.1	2560.3	0.943	5.73
[redacted]	103.0	107.7	1.046	4.56	2300.9	2318.2	1.008	0.75
MAPPE				3.33				2.46

Table2

Table 27. The external validation statistics for the extended IVIVC model for Tramadol ER Target formulation in Study 2553.

Treatment	C_{max} (ng/mL)				AUC (ng*hr/mL)			
	Obs.	Pred.	Ratio	|%PE|	Obs.	Pred.	Ratio	|%PE|
Target	125.9	136.1	1.081	8.07	2746.5	2704.2	0.985	1.54
MAPPE				8.07				1.54

Table 3

Table 28. Predicted pharmacokinetic parameters for proposed dissolution specifications and Tramadol ER Target formulation (Lot # 02H218).

[redacted]

Table 15. Parameters of the mean unit impulse response function for Ultram in Study 2553.

Study	Coefficient (ng/mL)	Exponent (h^{-1})	Lag-time (hr)
2553	3.42649	0.10867	0.43122
	-3.42649	1.56419	0.43122

Table 5

Table 14. Parameters of the mean unit impulse response function for Ultram in Study 2677.

Study	Coefficient (ng/mL)	Exponent (h^{-1})	Lag-time (hr)
2677	3.16650	0.10929	0.43064
	-3.16650	3.60421	0.43064

Table 6

Figure 1. Mean in vitro dissolution profiles for Tramadol ER formulations.

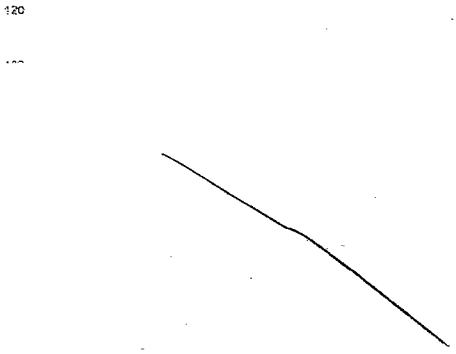

Figure 1

Figure 8. **Mean tramadol hydrochloride concentration-time profiles for Tramadol ER and Ultram formulations (Study 2677 and 2553).**

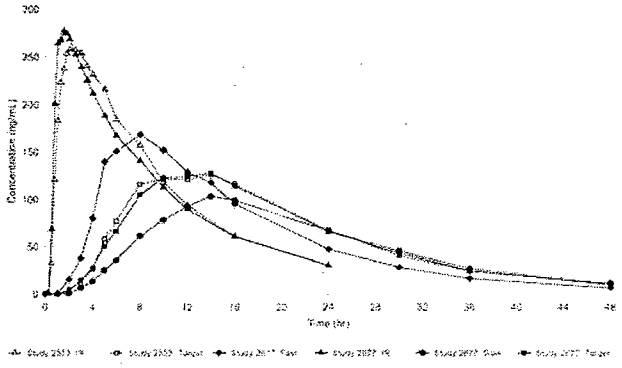

Figure 2

14. The % released in vitro and % absorbed in vivo plotted against time (Tramadol ER formulations in Study 2677.

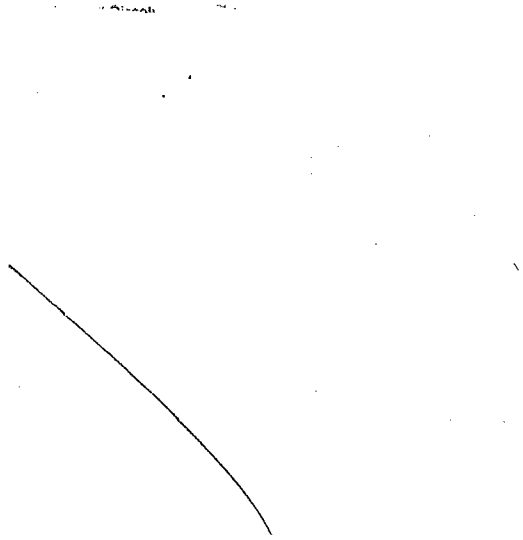

Figure 16. The % released in vivo plotted against % released in vitro with line for Tramadol ER formulations in Study 2677.

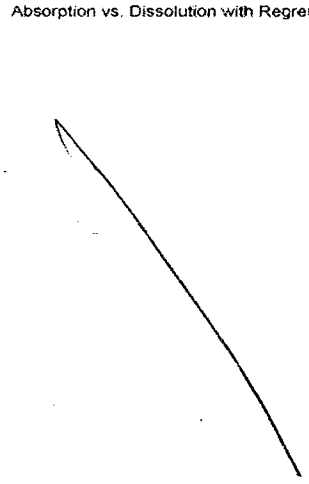

Figure 4

Figure 17. Time course of in vitro and in vivo release and fitted quadratic equation for Tramadol ER formulations in Study 2677.

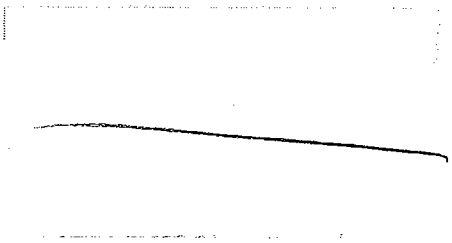

Figure5

Figure 18. The % released in vitro and % absorbed in vivo plotted against Tramadol ER formulations in Study 2677 after time-scaling.

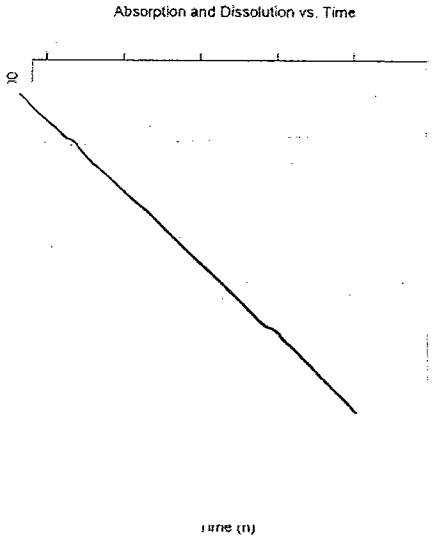

Figure 6

Figure 20. The % released in vivo plotted against % released in vitro with regression line for Tramadol ER formulations in Study 2677 after time-scaling.

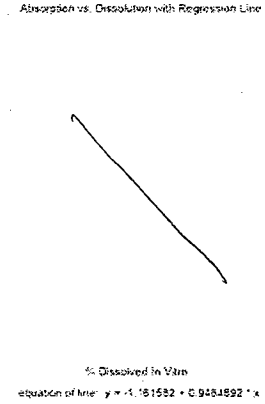

Figure 7

Figure 22. The observed mean plasma concentration profiles (points) and concentration profiles predicted by the linear IVIVC model (solid line) for Tramadol ER formulations in Study 2677.

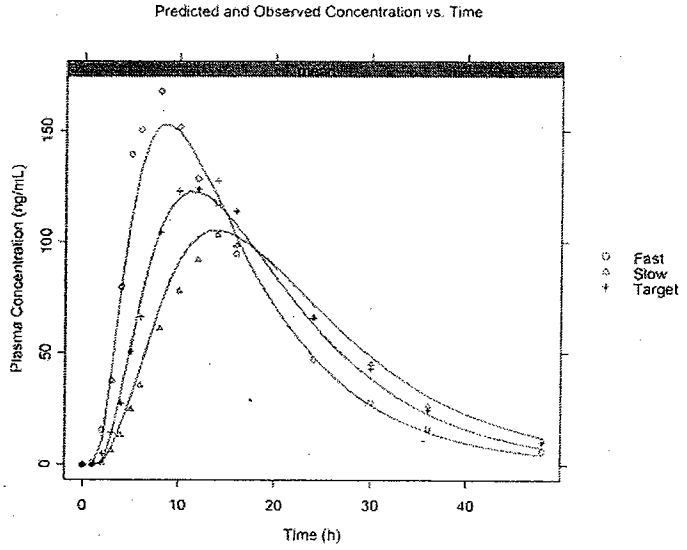

Figure 8

Figure 24. The observed mean plasma concentration profiles (points) and concentra profiles predicted by the extended IVIVC model (solid line) for Tramadol formulations in Study 2677.

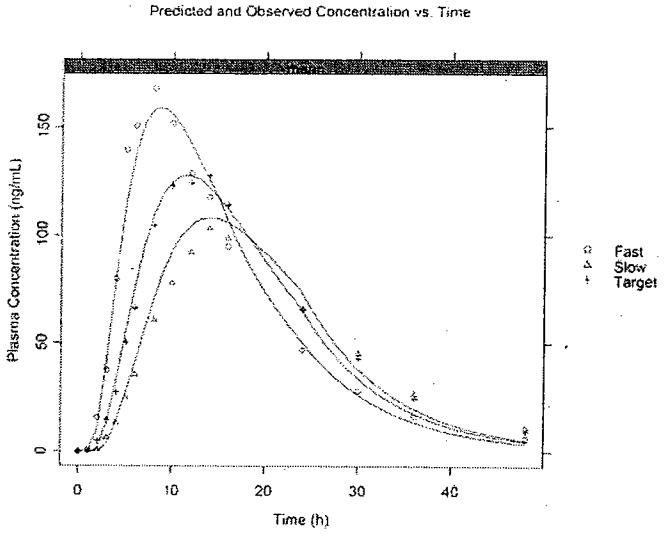

Figure 9

Figure 25. **The observed mean plasma concentration profiles (points) and concentration profiles predicted by the extended IVIVC model (solid line) for Tramadol ER Target formulation in Study 2553.**

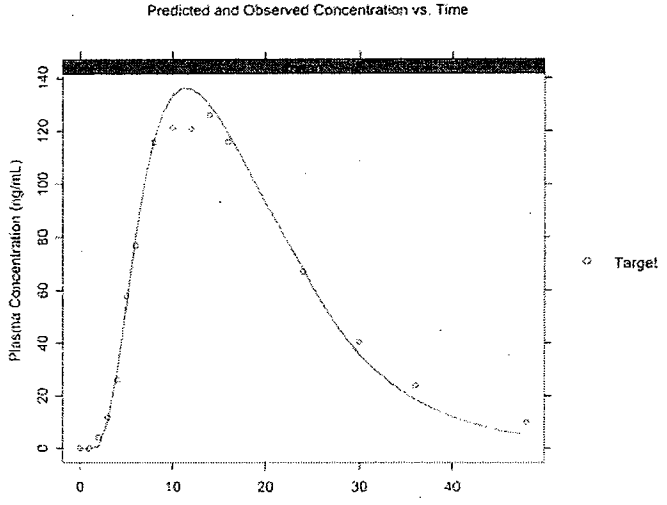

Figure 10

Figure 27. Predicted tramadol hydrochloride concentration-time profiles for proposed upper dissolution specification and Tramadol ER Target formulation (Lot # 021I218).

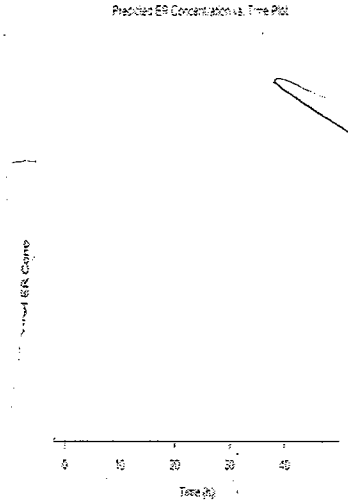

Figure 11

Figure 26. Predicted tramadol hydrochloride concentration-time profiles for pr lower dissolution specification and Tramadol ER Target formulation 021I218).

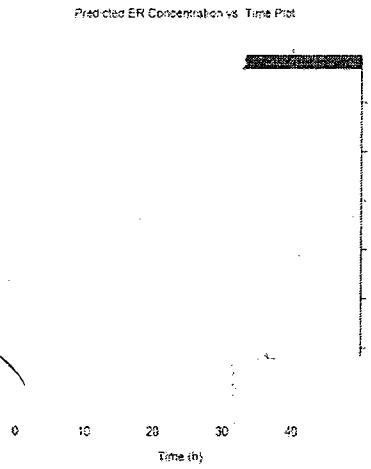

Figure 12

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/s/

Patrick Marroum
7/1/05 01:09:21 PM
BIOPHARMACEUTICS

Mehul Mehta
7/1/05 03:40:05 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-692
Submission Dates	12/31/2003; 8/20/2004; 8/26/2004; 9/24/2004
Brand Name	Ralivia ER™
Generic Name	Tramadol Hydrochloride
Reviewers	Lei Zhang, Ph.D. (Primary) and Abimbola Adebowale, Ph.D.
Team Leader	Dennis Bashaw, Pharm.D.
OCPB Division	DPE III
OND Division	DAAODP (HFD-550)
Applicant	Bioavail Laboratories, Inc.
Relevant IND	IND 59,023
Type of Submission; Code	505 (b)(2); 5S
Reference Listed Drug	Ultram, 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 product of tramadol hydrochloride tablets, Ralivia ER™. The reference product is Ultram® (tramadol hydrochloride tablets), which is currently marketed under approved NDA 20-281. Currently, there is no approved extended-release formulation of tramadol HCl. The Sponsor is seeking the same indication as Ultram® for Ralivia ER™, i.e., for the management of moderate to moderately severe pain. There are three dosage forms for Ralivia ER, 100, 200 and 300 mg tablets.

To support human PK and biopharmaceutics requirement, Ralivia ER was studied in a total of 17 *in vivo* PK studies. The *in vitro* and *in vivo* correlation has been investigated. Dissolution method and specification were proposed. Among these studies, 8 studies were considered pivotal and were reviewed in detail. These studies included the assessment of bioequivalence of Ralivia ER compared to Ultram after single and multiple doses, dose proportionality, dosage form equivalence, food effect, morning dosing vs. evening dosing, the potential for a drug interaction with quinidine in healthy subjects, and studies in patients with renal and hepatic impairments.

Because 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 QID to QD regimen, the primary focus of the Clinical Pharmacology and Biopharmaceutics (CPB) 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
(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)
(6) *In Vitro-In Vivo* Correlation (not a requirement, but an important issue)

While the sponsor has undertaken an extensive PK program, they have not evaluated Ralivia ER in subjects older than 65 years. Because of the effect of age on gastrointestinal systems, e.g., permeability, pH and transit time change, there may be a significant age effect on the PK of Ralivia ER. In addition, the Sponsor did not conduct exposure-response studies with Ralivia ER. Because of the PK profile difference between Ralivia ER and Ultram, i.e., low concentrations in absorption phase (0-6 hr) and terminal phase (18-24 hr) following ER QD dosing compared to Ultram QID dosing, it is questionable whether Ralivia ER supports the same indication as Ultram.

To support clinical efficacy and safety for Ralivia ER, four 12-week efficacy studies in patients with chronic moderate to severe painful conditions, one open-label one year safety study, and one pilot dental pain study were included in the submission. From an efficacy standpoint, the development program was lacking in that it did not include any comparison of efficacy to Ultram. Three 12-week efficacy trials (Study 015, 021, and 023) were conducted in patients with osteoarthritis (OA) of the knee/hip and the other one (Study 014) was conducted in patients with chronic low back pain. The two pivotal trials (Study 021 and 023) in OA patients failed to support an indication of , however, one of them (Study 023) succeeded in the primary analysis for a chronic pain claim. Additional sensitivity analyses conducted by the Statistical Reviewer for this study did not support the Sponsor's claim. Study 015 succeeded in demonstrating efficacy in pain score primary analysis but failed additional analyses (BOCF [baseline observation carried forward]). Study 014 failed to demonstrate efficacy. Based on information from the clinical studies, at best the application is "approvable". From an efficacy standpoint, additional efficacy studies will be required for this application to be approved. Please refer to Dr. Lourdes Villalba (Medical Reviewer) and Dr. Yongman Kim (Statistical Reviewer)'s reviews for details.

1.1 Recommendations

From a Clinical Pharmacology and Biopharmaceutics perspective, the Sponsor has adequately characterized the pharmacokinetic performance of the new ER formulation.

Given the current status of the clinical efficacy database, the following studies would be useful in determining both individual dose-response and the effect of special populations on the variability seen in dose-response in the clinical efficacy database for Ralivia ER.

Please convey the following comments to the Sponsor:

1. In order to better understand the role of Ralivia ER in chronic pain, you should consider undertake a definitive exposure-response study, using an appropriate chronic pain model. Ideally this trial should include Ultram as an active comparator agent. Such a study would allow for a better understanding of results from chronic pain efficacy trials and how they relate back to the Ultram database.
2. Study age effect on Ralivia ER exposure-response in elderly (65-75 yrs) and older elderly (>75 yrs) subjects.

General Comments:

3. In your re-submission you should provide a statistical analysis of the results of C_{min} testing, to include the calculation of 90% confidence intervals, in the studies where C_{min} was available.
4. Acceptance of the dissolution specifications is pending upon the review of *in vitro-in vivo* correlation (IVIVC) results.

Labeling:

The labeling recommendation is deferred pending the completion of a successful clinical development program. The following feedback on the special populations section of the label is

being provided to the sponsor so that they can better address the labeling in their next submission:

5. For patients with renal or hepatic impairment, you relied on Ultram labeling along with your studies to develop dosing recommendations. Please provide a more detailed explanation on how final conclusions regarding dosage reduction in these patients were reached in each condition.

1.2 Phase 4 Commitments

None. (Not Applicable.)

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

This application consists of 17 *in vivo* PK studies. Among these studies, 8 studies were considered pivotal and were reviewed in detail (See Appendix 4.2 for individual study reviews). The synopses of those studies conducted with the to-be-marketed formulation that were not reviewed are included in Section 4.3 for reference.

Relative Bioavailability to Ultram (IR product) (Study 567PK)

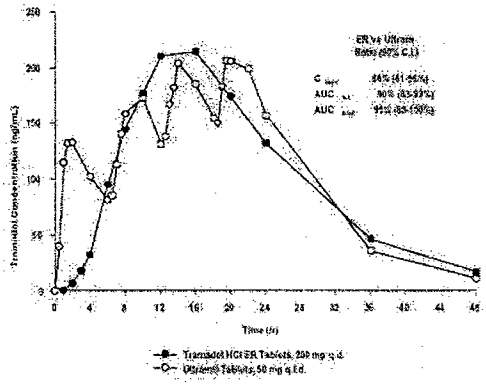
Single Dose:

After a single daily dose of Tramadol HCl 200 mg Extended Release Tablets and Ultram® 50 mg Tablets (Q6h) under fasting conditions, the 90% confidence intervals (CIs) of geometric mean ratio (GMR) (Ralivia ER/Ultram) of $AUC_{0\text{-}inf}$ and C_{max} for tramadol and its active metabolite, M1, were within the 80.00% to 125.00% boundary for bioequivalence. Consistent with its extended release nature, T_{max} is longer for Ralivia ER than for Ultram (Mean T_{max} 13.6 hr vs. 2.2 hr) (Figure 1).

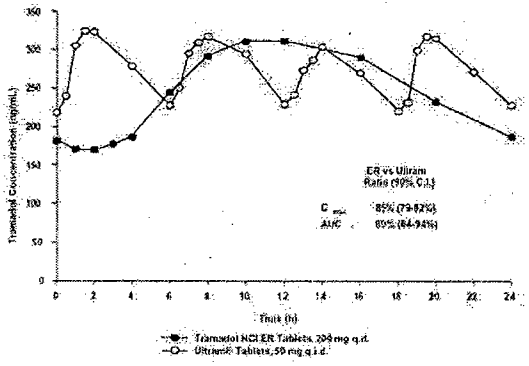
Multiple Doses:

At steady state, the 90% CIs of the geometric mean ratio (GMR) (Ralivia ER/Ultram) of AUC_{τ} for tramadol and 90% CIs of GMR of AUC_{τ} and C_{max} for M1 were within the [redacted] boundary for bioequivalence. However, the lower limit of 90% CI of GMR of C_{max} for tramadol is slightly lower than 80% [redacted]. The clinical significance of this finding is unknown. Consistent with extended release nature, T_{max} at steady state is also longer for Ralivia ER than for Ultram (Mean T_{max} 11.9 hr vs. 1.5 hr) (Figure 1).

Figure 1.



Single Dose



Multiple Dose

For C_{min}, the statistical results indicate that the values were not equivalent between ER and IR products and lower trough concentrations were achieved with 200-mg Tramadol HCl ER tablets QD compared with 50-mg Ultram® tablets Q6h. Consequently, greater fluctuations were observed over 24 hours with the ER regimen than with the corresponding Ultram® regimen.

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, making it questionable as to whether or not Ralivia ER would support the same indication as Ultram.

[redacted]

Food Effect (Study 568PK)

Food effect was studied in two studies: one is 200 mg single dose (Study 568PK) and the other is 300 mg multiple dose (Study 629PK). Only the first study was reviewed in detail because a single dose study is considered the more sensitive testing condition.

Results from Study 2550 suggest that food (a high fat meal) decreases both the rate and extent of absorption of tramadol after a single dose of Ralivia ER (200 mg). The C_{max} and $AUC_{0\text{-}inf}$ of tramadol decreased 28% and 16%, respectively in the presence of food (based on geometric mean ratio of fed vs. fasting). Mean T_{max} increased by 3 hours (from 14 hr fasting to 17 hr fed). Similar results were observed for M1. Therefore, there was a food-effect on the rate and extent of the absorption of tramadol from this extended release product. The clinical significance of the food effect is unknown.

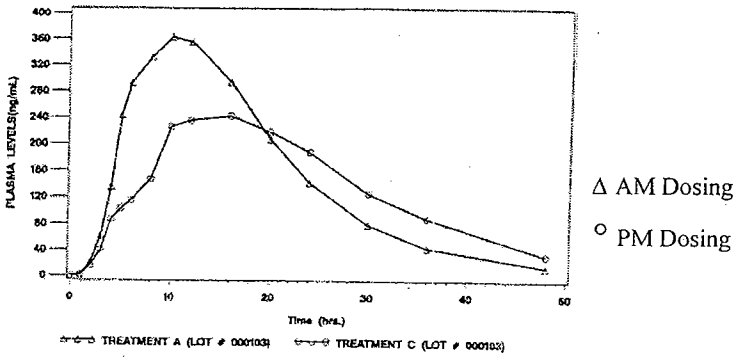
Dosage Form Bioequivalence (Study 623PK)

The active and inactive components for the tablet core are proportional similar for 100, 200 and 300 mg tablets. 100 mg tablets were used in all the clinical trials. 100 mg and 300 mg Tramadol HCl ER tablets are dosage strength equivalent. 100 and 200 mg tablets are also dosage strength equivalent (Study 570PK).

Morning (AM) Dosing vs. Evening (PM) Dosing (Study 426PK)

Evening administration of the ER formulation resulted in a significant reduction and delay in the rate of drug absorption but did not reduce the total amount absorbed (Figure 2). Compared to morning dosing, C_{max} and $AUC_{0\text{-}inf}$ of tramadol decreased 29% and 6%, respectively after evening administration of the tablet. T_{max} increased by 5 hr (15 hr PM vs. 10 hr AM). The differences in the profiles may be related to a slowing in gastrointestinal transit during the night compared with the daytime. This diurnal effect in drug PK may have implications in the pharmacodynamic effect of the drug and should be included in the labeling.

Figure 2.



Tramadol (AM vs. PM)

Renal Impairment (Study 589PK)

Impaired renal function resulted in a decreased renal clearance of tramadol and its metabolites, M1 and M5. An increase in systemic exposure (up to ~ 40%) and about a 50% reduction in renal clearance was observed for the metabolites in patients with mild and moderate renal impairment. The effect on the systemic exposure of tramadol in this population was not consistent. The data suggests that dosage adjustment may be needed in patients with mild and moderate renal impairment.

Liver Impairment (Study 590PK)

In the patients with hepatic impairment, systemic exposure of the (+) and (-) enantiomers for the parent drug were similar in patients with mild or moderate hepatic impairment when compared to the healthy volunteers. By contrast, systemic exposure of the (+) and (-) enantiomers for the M1 metabolite in both groups of hepatically-impaired patients were ~50% less than those observed in the healthy volunteers, indicating lower formation of the metabolite in the patients with hepatic impairment. The (+)/ (-) enantiomeric ratios for tramadol and M1 were similar in all 3 groups, indicating that stereoselective metabolism was not affected in hepatic impairment. Due to the observed reduction of M1 formation in patients with mild or moderate hepatic impairment dosage adjustment may be required to maintain adequate analgesic effect.

Interaction with Quinidine (Study 591PK)
The metabolism of tramadol to its active metabolite, M1, is mediated by CYP2D6. An evaluation of the effect of quinidine on the exposure of tramadol and its metabolites (M1 andM5) demonstrated that quinidine inhibits the metabolism of tramadol resulting in a higher systemic exposure of the parent tramadol and lower systemic exposure of the M1 metabolite.

In Vitro-In Vivo Correlation (IVIVC, Study 619PK)
The study report for IVIVC (Report 2003-14) was consulted to Dr. Patrick Marroum. His review of the report indicates that the analysis method was not acceptable because the scaling factor used in the Report 2003-14 was formulation dependent. Therefore, the Level A *in-vitro/in-vivo* correlation that was obtained for Ralivia ER Tablets in the study report was not acceptable. Subsequently, a teleconference was held between the Agency and the Sponsor. Dr. Marroum recommended that the Sponsor should re-do the computations using the method of Gillespie (Adv Exp Med Biol. 1997;423:53-65) to correct for differences between *in-vitro* and *in-vivo* release profiles. The Sponsor submitted a new IVIVC analysis report (Report RA612005) on Oct 1, 2004. This report will be reviewed at the next review cycle. The conclusion of IVIVC is pending.

Dissolution
The proposed dissolution method is acceptable. The dissolution specifications may need to be revised based on the review of IVIVC results.

Abimbola O. Adebowale, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III

Lei Zhang, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III

Concurrence:

E. Dennis Bashaw, Pharm.D.
Clinical Pharmacology Team Leader
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

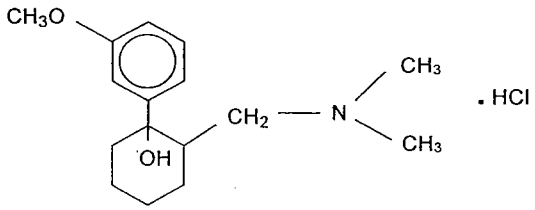
An OCPB briefing (Required Inter-Divisional Level) was held on October 18, 2004.

2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Table 2.1.1.1. Physical-Chemical Properties of Tramadol HCl.

Drug Name	Tramadol Hydrochloride
Chemical Name	(±) cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride
Structure and Molecular Formula	 $C_{16}H_{25}NO_2 \cdot HCl$
Molecular Weight	299.8
pKa	9.41
Appearance	White, bitter, crystalline and odorless powder
Solubility	Readily soluble in water and ethanol

Tramadol Hydrochloride Extended-Release Tablets, 100 mg, 200 mg and 300 mg are diffusion controlled tablets consisting of a tablet core surrounded by a semi-permeable coating. This coating forms a membrane that is responsible for controlling the release of tramadol hydrochloride *in vivo*. The active and inactive components for the tablet core are proportionally similar for 100, 200 and 300 mg tablets (See Section 2.5.1).

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

Tramadol HCl is a centrally acting synthetic 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 for Ultram (tramadol IR product), i.e., indicated for the management of moderate to moderately severe pain in adults.

2.1.3 What are the proposed dosage recommendations and route of administration of Ralivia ER for the proposed indication?

Ralivia ER™ is taken orally.

Ralivia ER is proposed for patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect. Ralivia ER is started at a dose of 100 mg QD and titrated up if required by 100 mg increments every 5 days as necessary for pain relief and depending on tolerability. Ralivia ER is administered for pain relief at a **dose not to exceed** [redacted] **mg/day**. Dose is reduced in patients with renal impairment, liver impairment and who are over 65 years.

[redacted]

The proposed dosage recommendations will be reviewed pending the completion of a successful clinical development program.

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, Ralivia ER was studied in a total of 17 *in vivo* PK studies involving about 350 subjects. These studies included the assessment of bioequivalence of Ralivia ER compared to Ultram after single and multiple doses, dose proportionality, dosage form equivalence, food effect, morning dosing vs. evening dosing, and potential drug interaction with quinidine in healthy subjects, and studies in patients with renal and hepatic impairments.

To support clinical efficacy and safety for Ralivia ER, four 12-week efficacy studies in patients with chronic moderate to severe painful conditions, one open-label one year safety study, and one pilot dental pain study were included in the submission (Table 2.2.1.1). There are about 3000 patients received Tramadol ER in these studies.

Three 12-week efficacy trials (Study 015, 021, and 023) were conducted in patients with osteoarthritis (OA) of the knee/hip and the other one (Study 014) was conducted in patients with chronic low back pain. Study 021 and Study 023 that were considered pivotal for an OA indication. Study 021 is a placebo- and active-controlled study, and Study 023 is a placebo-controlled study. Celecoxib (200 mg QD) was the active control. The dose range for Ralivia ER was 100 to 300 mg QD in Study 021, and 100 to 400 mg QD in Study 023.

The pain intensity visual analog scale (VAS) admission criteria were the same for the three studies conducted in patients with OA and the one study conducted in patients with chronic low back pain.

Table 2.2.1.1. List of Clinical Studies

Study Type	Population	Study Number
Chronic Pain		
12-Week Studies	Chronic low back pain	B00.CT3.014.TRA P03
	Qsteoarthritis (OA) pain	B00.CT3.015. TRA P03 **B02.CT3.021.TRA P03** **B02.CT3.023.TRA P03**
Long-Term Safety Study	Chronic low back pain, osteoarthritis, and other patients with chronic, non-malignant pain	B00.CTOL.003.TRA P03
Pre-emptive Treatment of Acute Dental Pain	Acute dental pain	B00.CT2PC.009. TRA P03

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

Studies 021 and 023 used Western Ontario and McMaster Universities (WOMAC) pain, WOMAC function and patient global pain assessment as co-primary endpoints. VAS scores are the secondary endpoints. Pain VAS scores are primary endpoints for Study 014 and 015.

The two pivotal trials (Study 021 and 023) in patients with OA of the knee/hip conducted by the Sponsor failed to support an indication of [redacted] however, one of them (Study 023) succeeded in the primary analysis for a chronic pain claim. Additional sensitivity analyses conducted by the Statistical Reviewer for this study did not support the Sponsor's claim. Study 015 succeeded in demonstrating efficacy in pain score primary analysis but failed additional analyses (BOCF). Study 014 failed to demonstrate efficacy. From an efficacy standpoint, additional efficacy studies will be required for this application to be approved. Please refer to Dr. Lourdes Villalba (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 two metabolites, M1 (O-desmethyltramadol) and M5 (O, N-di-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 Ralivia ER in terms of efficacy and safety?

Exposure-response relationship of Ralivia ER in terms of efficacy and safety has not been studied by the Sponsor.

The affinity of tramadol for the μ-opioid receptor is weaker by a factor of approximately 6000 compared with that of morphine in the same system. However, the (+)-enantiomer of the M1 metabolite has an affinity for the μ-opioid receptor that is about 220 times greater than that of (+)-tramadol. In a direct comparison, (+)-M1 was only 4 times less potent than morphine. The (-)-enantiomers of both tramadol and its O-desmethyl metabolite have much weaker affinity for the μ-opioid receptor. The effect of tramadol on the reuptake of norepinephrine and on the release and reuptake of serotonin are mediated primarily by tramadol alone. Effects related to the monoaminergic component are probably mediated by (+)- and (-)-tramadol, and the opioid component is mediated by the (+)-enantiomer of the O-desmethyl metabolite.

In various experimental pain models using healthy subjects, tramadol appears to be a better analgesic in extensive metabolizers (EMs) than in poor metabolizers (PMs) possibly due to the higher concentrations of M1 in EMs than in PMs.

Per the Ultram labeling, analgesic activity of Ultram (IR form of tramadol) is attributed to tramadol and its metabolite M1. Analgesia in humans after administration of Ultram begins within approximately one hour after administration and reaches a peak in approximately two to three hours. Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of opioids.

However, direct correlations between plasma drug and metabolite concentrations and relief of pain have not been consistently demonstrated.

2.2.5 What are the PK characteristics of Ralivia ER?

2.2.5.1 What are single dose and multiple dose PK parameters of Ralivia ER?

In Study B01-567PK-TRAP03, PK parameters for tramadol and M1 were studied in healthy subjects after single and multiple dose of 200 mg Ralivia ER QD.

Single Dose

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

	Tramadol	M1
AUC_{0-t} (ng.hr/mL)	4792.17 ± 2017.83	1856.01 ± 596.66
AUC_{0-inf} (ng.hr/mL)	4999.94 ± 2139.00	1984.59 ± 636.68
C_{max} (ng/mL)	234.23 ± 90.43	83.42 ± 27.52
T_{max} (hour)	13.57 ± 3.76	15.57 ± 3.16
$t_{½}$ (hour)	7.66 ± 1.76	8.95 ± 2.20
K_{el} ($hour^{-1}$)	0.096 ± 0.024	0.082 ± 0.022
MRT (hours)	2.22 ± 1.47	3.91 ± 2.70
M/P Ratio		0.4747 ± 0.2121

Multiple Doses

Table 2.2.5.1.2. Summary of PK Parameters (Mean ± SD) for Tramadol and M1 after Multiple Doses

	Tramadol	M1
AUC_{τ} (ng.hr/mL)	5975.03 ± 2027.42	1889.96 ± 481.47
C_{max} (ng/mL)	335.44 ± 116.11	95.44 ± 23.09
C_{min} (ng/mL)	186.54 ± 69.51	69.14 ± 20.70
T_{max} (hour)	11.88 ± 3.17	14.63 ± 3.92
Degree of Fluctuation (%)	61.03 ± 34.51	33.50 ± 24.21
Degree of Swing (%)	103.76 ± 103.14	45.56 ± 46.27
C_{avg} (ng/mL)	248.96 ± 84.48	78.75 ± 20.06
M/P Ratio		0.3610 ± 0.1192

2.2.5.2 What are the ADME (absorption, distribution, metabolism and elimination) characteristics of Ralivia ER?

Because Ralivia ER 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, there is a lag time in drug absorption. T_{max} of tramadol is longer for Ralivia ER than for Ultram (Mean T_{max} 13.6 hr vs. 2.2 hr) after a singe dose. T_{max} at steady state is also longer for Ralivia ER than for Ultram (Mean T_{max} 11.9 hr vs. 1.5 hr).

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 (Literature)

Tramadol undergoes extensive hepatic metabolism through 2 main metabolic pathways involving isoenzymes CYP2D6 and CYP3A4 to produce the primary metabolites, O-desmethyl-tramadol (M1, via CYP2D6) and N-desmethyl-tramadol (M2, via CYP3A4), respectively (Figure 2.2.5.2.1). M1 is the major metabolite and possesses analgesic activity in animal and human models for experimental pain. The 2 metabolites, M1 and M2, are further converted to secondary metabolites, N, N-didesmethyltramadol (M3), N, N, O-tridesmethyltramadol (M4), and N, O-didesmethyltramadol (M5). The formation of M5 from M2 is mediated by CYP2D6, while formation of M5 from M1 and M3 from M2 is mediated by CYP2D6 and CYP3A4, respectively. Both primary and secondary metabolites undergo additional Phase II reactions to form glucuronide and sulfate conjugates.

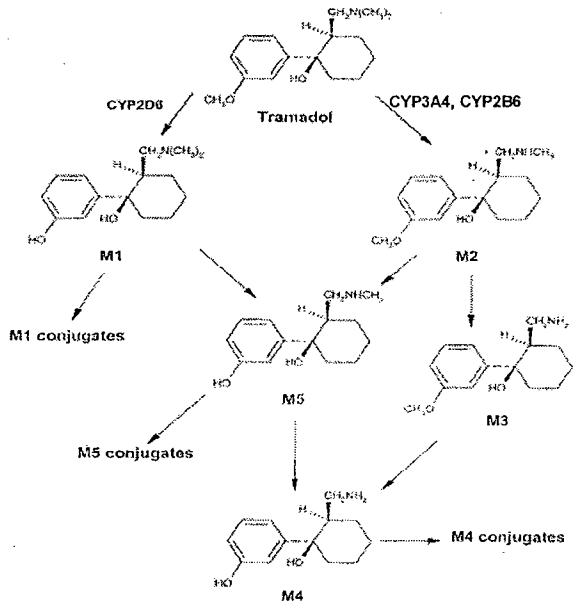


Figure 2.2.5.2.1. Main Metabolism Pathways for Tramadol.

Elimination

The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 after administration of Ralivia ER are approximately 7.9 and 8.8 hours, respectively.

2.2.5.3 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

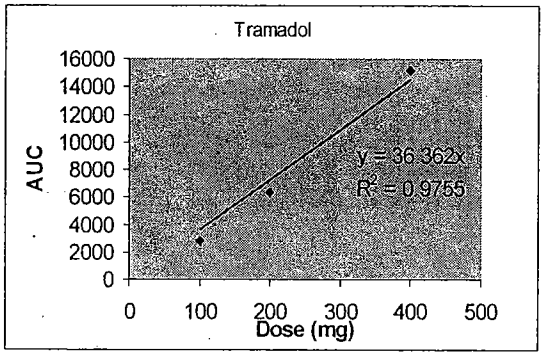
Ralivia ER is intended to be administered at doses ranging from 100 mg to ——mg per day. Dose proportionality was evaluated in a multiple-dose study (B01-569PK-TRAP03) in which 100-mg, 200-mg, and 2 x 200-mg tablets were administered under steady-state conditions. PK parameters for tramadol and M1 at different doses are listed in Tables 2.2.5.3.1 and 2.2.5.3.2. The Linear regression analysis of the pharmacokinetic data as well as ANOVA of dose corrected pharmacokinetic data indicated that AUC_τ and C_{max} of tramadol and M1 increased proportionally with dose within the investigated dose range (Figures 2.2.5.3.1 and 2.2.5.3.2, and Tables 2.2.5.3.3 and 2.2.5.3.4).

Table 2.2.5.3.1. Steady State Pharmacokinetic Parameters for Tramadol at Doses of 100, 200 and 400 mg.

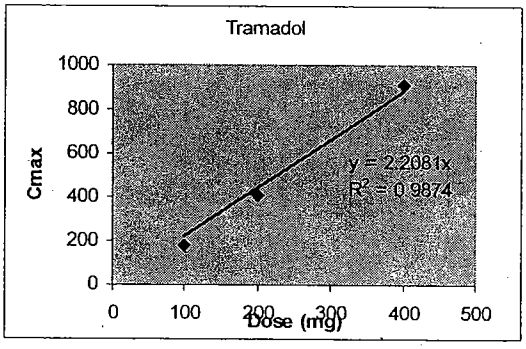
Pharmacokinetic Parameter	Tramadol HCl 100 mg Extended Release Tablets 1 x 100 mg (A) n = 25 Mean ± SD	Tramadol HCl 200 mg Extended Release Tablets 1 x 200 mg (B) n = 25 Mean ± SD	Tramadol HCl 200 mg Extended Release Tablets 2 x 200 mg (C) n = 25 Mean ± SD
AUC_τ (ng·hr/mL)	2778.41 ± 1141.24	6364.89 ± 2755.19	15212.75 ± 5754.59
C_{max} (ng/mL)	179.24 ± 62.68	408.99 ± 177.71	910.05 ± 319.71
C_{min} (ng/mL)	73.84 ± 42.63	168.58 ± 72.58	438.70 ± 213.20
T_{max} (hours)	11.68 ± 2.43	12.16 ± 2.23	12.00 ± 2.38
Degree of Fluctuation (%)	98.979 ± 41.628	94.697 ± 36.879	81.785 ± 38.392
C_{ave} (ng/mL)	115.77 ± 47.55	265.20 ± 114.80	633.86 ± 239.77

Table 2.2.5.3.2. Steady State Pharmacokinetic Parameters for O-desmethyltramadol (M1) at Doses of 100, 200 and 400 mg.

Pharmacokinetic Parameter	Tramadol HCl 100 mg Extended Release Tablets 1 x 100 mg (A) n = 25 Mean ± SD	Tramadol HCl 200 mg Extended Release Tablets 1 x 200 mg (B) n = 25 Mean ± SD	Tramadol HCl 200 mg Extended Release Tablets 2 x 200 mg (C) n = 25 Mean ± SD
AUC_τ (ng·hr/mL)	846.73 ± 210.51	1640.53 ± 574.72	3189.17 ± 973.87
C_{max} (ng/mL)	48.01 ± 11.53	91.29 ± 34.19	169.06 ± 48.75
C_{min} (ng/mL)	26.95 ± 10.71	53.42 ± 19.00	107.23 ± 39.88
T_{max} (hours)	12.32 ± 2.50	13.16 ± 2.70	14.00 ± 2.83
Degree of Fluctuation (%)	62.399 ± 32.222	56.637 ± 33.742	49.717 ± 26.325
C_{ave} (ng/mL)	35.28 ± 8.77	68.36 ± 23.95	132.88 ± 40.58

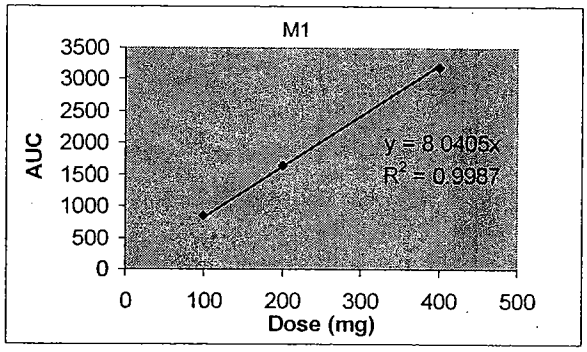


a. AUCτ

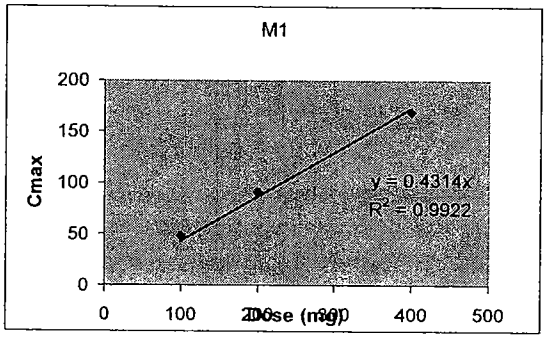


b. Cmax

Figure 2.2.5.3.1. Relationship between Tramdol AUCτ (a) and dose, and C_{max} (b) and dose.



a. AUCτ



b. Cmax

Figure 2.2.5.3.2. Relationship between M1 AUCτ (a) and dose, and C_{max} (b) and dose.

Table 2.2.5.3.3. P Value for Paired Comparison Among 100 (Trt A), 200 (Trt B) and 400 mg (Trt C) for Tramadol.

Parameter	Trt A - Trt B	Trt A - Trt C	Trt B - Trt C
C_{max}	0.4532	0.0627	0.2597
AUC_τ	0.4675	0.0319	0.1491

Table 2.2.5.3.4. P Value for Paired Comparison Among 100 (Trt A), 200 (Trt B) and 400 mg (Trt C) for M1.

Parameter	Trt A - Trt B	Trt A - Trt C	Trt B - Trt C
C_{max}	0.3011	0.1267	0.6162
AUC_τ	0.4490	0.4168	0.9560

2.2.5.4 How do the PK parameters change with time following chronic dosing?

The accumulation index was quantified by the following formula:

Accumulation Index = AUC(0-24hr) (multiple dose)/ AUC(0-24hr) (single dose)

The results presented in Table 2.2.5.4.1 indicate that accumulation index of tramadol for Tramadol ER (1.9) is somewhat higher than what is estimated from its apparent half life of 9 hr (1.2) assuming one-compartment model.

Table 2.2.5.4.1. Accumulation Index Following Tramadol ER Dosing.

	Tramadol ER
Tramadol	1.89 ± 0.48
M1	1.73 ± 0.59

2.2.6 What is the relative bioavailability of Ralivia ER vs. Ultram following single and multiple doses?

Single Dose

After a single daily dose of Tramadol HCl 200 mg Extended Release Tablets and Ultram® 50 mg Tablets (Q6h) under fasting conditions, the 90% confidence intervals (CIs) of geometric mean ratio (GMR) (Ralivia ER/Ultram) of $AUC_{0\text{-}inf}$ and C_{max} for tramadol and its active metabolite, M1, were within 80.00% to 125.00% boundary for bioequivalence (Table 2.2.6.1).

Table 2.2.6.1. Pharmacokinetic Parameter Values for Tramadol and its M1 Metabolite and the Key Statistical Results for the Comparison of a Single Daily-Dose of 200-mg Tramadol HCl ER Tablets QD and 50-mg Ultram® Tablets Q6h

Pharmacokinetic Parameter	Tramadol HCl ER 200-mg Tablets QD	Ultram® 50-mg Tablets Q6h	Ratio of Least Square Means	90% Confidence Interval
Tramadol				
$AUC_{0\text{-}inf}$ (ng·h/mL)	4999.94 ± 2139.00	5174.38 ± 1687.68	91.01%	83.28% - 99.46%
C_{max} (ng/mL)	234.23 ± 90.43	257.98 ± 69.04	91.01%	81.21% - 95.84%
T_{max} (h)	13.57 ± 3.76	2.22 ± 1.36	NR	NR
M1 Metabolite				
$AUC_{0\text{-}inf}$ (ng·h/mL)	1984.59 ± 636.68	2168.12 ± 527.97	88.95%	80.03% - 98.87%
C_{max} (ng/mL)	83.42 ± 27.52	88.79 ± 21.21	90.54%	83.50% - 98.17%
T_{max} (h)	15.57 ± 3.16	2.97± 1.57	NR	NR

NR = Not reported.

Multiple Doses

At steady state, the 90% CIs of geometric mean ratio (GMR) (Ralivia ER/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 bioequivalence. However, the lower limit of 90% CI of GMR of C_{max} for tramadol is slightly lower than 80% (78.6%) (Table 2.2.6.2). The clinical significance of this finding is unknown.

Table 2.2.6.2. Pharmacokinetic Parameter Values for Tramadol and its M1 Metabolite and the Key Statistical Results for the Comparison of Multiple Doses of 200-mg Tramadol HCl ER Tablets QD and 50-mg Ultram® Tablets Q6h

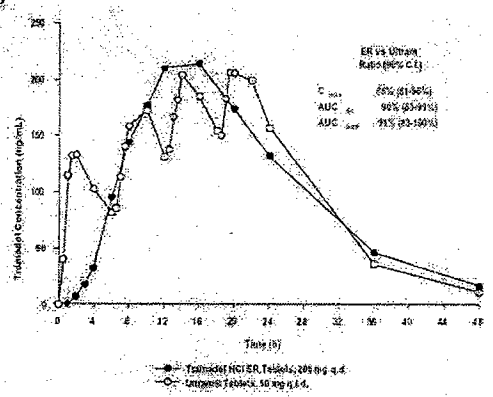
Pharmacokinetic Parameter	Tramadol HCl ER 200-mg Tablets QD	Ultram® 50-mg Tablets Q6h	Ratio of Least Square Means	90% Confidence Interval
Tramadol				
AUC_{0-24} (ng·h/mL)	5975.03 ± 2027.43	6612.66 ± 1790.04	88.73%	83.97% - 93.75%
C_{max} (ng/mL)	335.44 ± 116.11	382.49 ± 79.86	84.88%	78.63% - 91.63%
C_{min} (ng/mL)	186.54 ± 69.51	227.68 ± 72.36	NR	NR
T_{max} (h)	11.88 ± 3.17	1.49 ± 0.63	NR	NR
M1 Metabolite				
AUC_{0-24} (ng·h/mL)	1889.96 ± 481.47	2095.37 ± 539.58	90.35%	85.18% - 95.85%
C_{max} (ng/mL)	95.44 ± 23.09	104.35 ± 24.57	91.01%	85.05% - 97.75%
C_{min} (ng/mL)	69.14 ± 20.70	81.98 ± 22.36	NR	NR
T_{max} (h)	14.63 ± 3.92	1.94 ± 1.10	NR	NR

NR = Not reported.

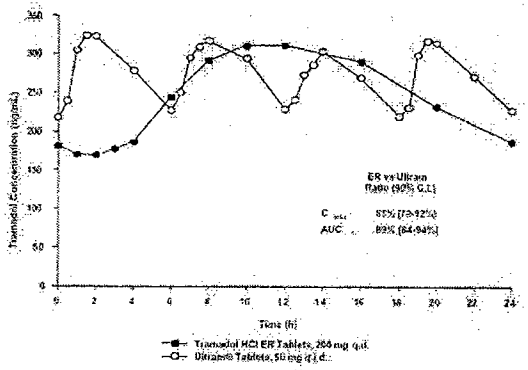
For C_{min}, the statistical results indicate that the values were not equivalent between ER and IR products and lower trough concentrations were achieved with 200-mg Tramadol HCl ER tablets QD compared with 50-mg Ultram® tablets Q6h. Consequently, greater fluctuations are observed over 24 hours with the ER regimen than the corresponding Ultram® regimen. 90% CIs were not calculated for C_{min}. C_{min} is considered an important parameter in maintaining the analgesic effect of tramadol. The Sponsor is asked to provide this information during further development of Ralivia ER.

PK profiles of tramadol following Ralivia ER 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 that makes it questionable as to whether Ralivia ER would support the same indication as Ultram. The clinical significance of this exposure difference needs to be explored.

Figure 2.2.6.1.



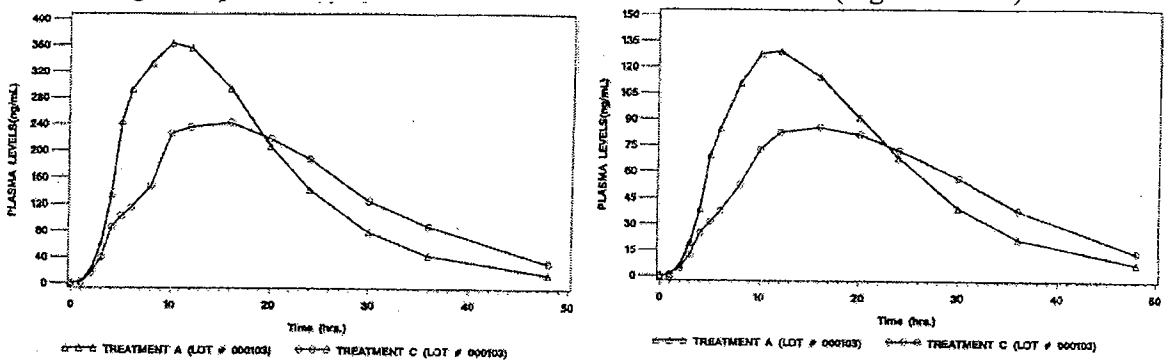
Single Dose



Multiple Dose

2.2.7 What is comparison of PK for Ralivia after AM and PM dosing (Is there a diurnal effect)?

Evening administration of the ER formulation resulted in a significant reduction and delay in the rate of drug absorption but did not reduce the total amount absorbed (Figure 2.2.7.1).



a. Tramadol b. M1

Figure 2.2.7.1. Mean Plasma Tramadol (a) and M1 (b) Concentrations After Single Dosing With 3 x 100-mg Tramadol HCl ER Tablets Dosing at AM (Treatment A) and PM (Treatment C) Under Fasting Conditions.

Compared to morning dosing, C_{max} and $AUC_{0\text{-}inf}$ of tramadol decreased 29% and 6%, respectively after evening administration of the tablet (Table 2.2.7.1). T_{max} increased by 5 hr (15 hr PM vs. 10 hr AM). The differences in the profiles may be related to a slowing in gastrointestinal transit during the night compared with the daytime. This diurnal effect in drug PK may have implications in the pharmacodynamic effect of the drug and should be included in the labeling.

Table 2.2.7.1. Relative Bioavailability Analysis (PM/AM) for Tramadol, M1, and M5 Following Tramadol HCl ER 1 x 300 mg Tablet (PM) versus Tramadol HCl ER 3 x 100 mg Tablet (AM) Administration.

Tramadol

	AUC (0 - t)	AUC (0 - infinity)	C_{max}
90% Geometric C.I.[4]	84% - 96%	87% - 101%	65% - 77%
Ratio of Means[5]	90%	94 %	71 %
CV[6]	13.51%	13.79 %	16.85 %

M1

	AUC (0 - t)	AUC (0 - infinity)	C_{max}
90% Geometric C.I.[4]	82% - 92%	85% - 96%	63% - 74%
Ratio of Means[5]	87%	90 %	69 %
CV[6]	11.76%	12.24 %	15.38 %

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence PK of Ralivia ER?

Tramadol is eliminated primarily through metabolism by liver and the metabolites are eliminated primarily by the kidney. The Sponsor evaluated the effect of renal impairment and hepatic impairment on exposure to tramadol and its metabolites M1 and M5 with this new formulation of tramadol HCl. As described below both renal and hepatic impairment affected the exposure of the M1 metabolite.

Renal Impairment

Impaired renal function resulted in a decreased renal clearance of tramadol and its metabolites, M1 and M5. An increase in systemic exposure was observed for the metabolites in patients with mild and moderate renal impairment. The effect on the systemic exposure of tramadol in this population was not consistent.

Study B02-589PK-P03P1, a multiple dose study compared the pharmacokinetics of Tramadol HCl ER tablets in healthy individuals and patients with mild and moderate renal failure. The study population consisted of groups of 6 healthy controls, 6 patients with mild renal failure, and 6 patients with moderate renal failure. Subjects received a single dose of Tramadol HCl ER on 6 consecutive mornings after they had fasted for 10 hours overnight. The mean pharmacokinetic parameter values for Tramadol and its metabolites in healthy subjects and patients with mild or moderate renal impairment are reported in the table below:

Table 2.3.1.1. PK Parameters for Tramadol.

Table 9A – Pharmacokinetic Parameters for Tramadol

Pharmacokinetic Parameter	Group 1 (Healthy Volunteers) Mean ± SD N = 6	Group 2 (MiRF Subjects) Mean ± SD N = 5	Group 3 (MoRF Subjects) Mean ± SD N = 6
AUC_τ (ng·hr/mL) (τ = 24 hours)	2726.83 ± 625.07	3360.98 ± 976.03	2776.24 ± 1207.48
C_{max} (ng/mL)	173.86 ± 28.80	193.56 ± 46.18	174.07 ± 66.76
C_{min} (ng/mL)	67.66 ± 24.10	89.42 ± 34.23	60.02 ± 39.94
C_{av} (ng/mL)	113.62 ± 26.04	140.04 ± 40.67	115.68 ± 50.31
T_{max} (hr)	9.67 ± 3.20 (10.00)*	12.40 ± 6.89 (12.00)*	10.33 ± 1.97 (11.00)*
Degree of Fluctuation (%)	96.59 ± 24.79	76.28 ± 29.21	107.28 ± 28.14
A_e (mg)	14.25 ± 2.80	14.75 ± 6.12	8.95 ± 2.43
CL_R (mL/min)	90.32 ± 26.07	77.23 ± 33.25	59.02 ± 15.88

*This is the median value

The results in Table 2.3.1.1 show that the effects of renal impairment on the systemic exposure of tramadol were not consistent in the 2 groups of renally impaired patients when compared with healthy volunteers. Patients with mild renal impairment (MiRF) had increased systemic exposure while patients with moderate renal impairment (MoRF) had similar systemic exposure when compared to the healthy volunteers. In addition, the renal clearance of tramadol decreased in the MoRF patients while that of the MiRF patients was similar to that of healthy volunteers.

Table 2.3.1.2. PK Parameters for M1 and M5.

Table 9B – Pharmacokinetic Parameters for O-desmethyltramadol (M1)

Pharmacokinetic Parameter	Group 1 (Healthy Volunteers) Mean ± SD N = 6	Group 2 (MiRF Subjects) Mean ± SD N = 5	Group 3 (MoRF Subjects) Mean ± SD N = 6
AUC_τ (ng·hr/mL) (τ = 24 hours)	778.42 ± 228.60	996.64 ± 597.67	1036.22 ± 407.04
C_{max} (ng/mL)	40.88 ± 11.02	51.32 ± 26.95	60.37 ± 20.06
C_{min} (ng/mL)	24.47 ± 10.15	31.07 ± 23.04	27.07 ± 14.00
C_{av} (ng/mL)	32.43 ± 9.53	41.53 ± 24.90	43.18 ± 16.96
T_{max} (hr)	10.33 ± 2.94 (11.00)*	12.00 ± 0.00 (12.00)*	10.67 ± 2.07 (12.00)*
A_e (mg)	7.49 ± 1.21	3.83 ± 1.69	3.93 ± 2.03
CL_r (mL/min)	164.25 ± 18.39	88.90 ± 56.93	70.60 ± 40.34
M/P ratio (for AUC_τ)	0.314 ± 0.109	0.324 ± 0.207	0.416 ± 0.157

*This is the median value

Table 9C – Pharmacokinetic Parameters for O,N-di-desmethyltramadol (M5)

Pharmacokinetic Parameter	Group 1 (Healthy Volunteers) Mean ± SD N = 6	Group 2 (MiRF Subjects) Mean ± SD N = 5	Group 3 (MoRF Subjects) Mean ± SD N = 6
AUC_τ (ng·hr/mL) (τ = 24 hours)	424.65 ± 138.15	660.78 ± 402.05	741.12 ± 418.30
C_{max} (ng/mL)	21.69 ± 5.75	28.93 ± 19.50	39.74 ± 20.51
C_{min} (ng/mL)	13.71 ± 5.58	21.26 ± 13.85	20.55 ± 12.19
C_{av} (ng/mL)	17.69 ± 5.76	27.53 ± 16.75	30.88 ± 17.43
T_{max} (hr)	11.00 ± 2.76 (12.00)*	14.00 ± 2.83 (13.00)*	13.00 ± 5.90 (12.00)*
A_e (mg)	6.83 ± 1.68	5.05 ± 2.21	5.27 ± 3.32
CL_r (mL/min)	272.56 ± 23.71	143.52 ± 38.37	120.06 ± 31.17
M/P ratio (for AUC_τ)	0.182 ± 0.069	0.219 ± 0.123	0.293 ± 0.111

*This is the median value

By contrast, the systemic exposure for the M1 and M5 metabolites increased (~20-40%) with the severity of the renal impairment. In addition, the metabolic ratio for both M1 and M5 increased with the severity of renal disease. Systemic exposure did not significantly correlate with creatinine clearance in the patient population for the M1 metabolite and M5 metabolite. The renal clearance of the M1and M5 metabolites in patients with mild or moderate impairment was decreased by about 50%, when compared to healthy volunteers. The renal clearance showed a significant ($p<0.002$) correlation with creatinine clearance in the renally impaired patients for both the M1 and M5 metabolites. The applicant concluded that despite the lack of significance of these observations, dosage adjustment may be needed when administering Tramadol HCl ER to renally-impaired patients.

However, in the proposed labeling, the applicant only recommended adjustment of the dosing regimen of Tramadol ER in patients with creatinine clearances of less than 30 mL/min (i.e. those with severe renal impairment). In all patients with creatinine clearance less than 30 mL/min, it was recommended that the maximum daily dose should not exceed 200 mg . The Sponsor did not provide rationale for this dose reduction recommendation.

The exposure-response relationship with regards to toxicity for tramadol and its metabolites is not well defined at this time so one cannot really use it for dosage adjustment. This reviewer

believes that it might be difficult to recommend a dosage adjustment for tramadol in the mild and moderate renally impaired patients due to the inconsistency observed with the data. However, if one bases it on the data obtained for the metabolites especially M1, the active metabolite, where an increase in systemic exposure (up to ~ 40%) and a 50% reduction in renal clearance was observed, it could be recommended that the maximum daily dose should not exceed 200 mg in patients with mild and moderate renal impairment.

Hepatic Impairment

In the patients with hepatic impairment, systemic exposure of the (+) and (-) enantiomers for the parent drug were similar in patients with mild or moderate hepatic impairment when compared to the healthy volunteers. By contrast, systemic exposure of the (+) and (-) enantiomers for the M1 metabolite in both groups of hepatically-impaired patients were ~50% less than those observed in the healthy volunteers, indicating lower formation of the metabolite in the patients with hepatic impairment. The (+)/ (-) enantiomeric ratios for tramadol and M1 were similar in all 3 groups, indicating that stereoselective metabolism was not affected in hepatic impairment.

This was shown in Study B02-590PK-P03P1, a multiple dose study that examined the stereospecific pharmacokinetics of Tramadol HCl ER in patients with mild or moderate hepatic impairment. The study population consisted of 3 groups of 6 healthy controls, 6 patients with mild hepatic impairment, and 6 patients with moderate hepatic impairment. Subjects received a single dose of Tramadol HCl ER on 6 consecutive mornings after they had fasted for 10 hours overnight. The mean pharmacokinetic parameters for (+) tramadol, (-) tramadol, (+)-M1, and (-)-M1 are reproduced in Table 2.3.1.3 below:

Table 2.3.1.3. Mean (%CV) Pharmacokinetic Parameters for Racemic Tramadol and M1 Metabolite in patients with Hepatic Impairment and Healthy Volunteers.

Population/ Dosage Regimen[a]	Parent Drug/Metabolite	Area Under the Curve (ng·mL/h)	Peak Conc. (ng/mL)	Time to Peak (h)
Healthy Adults, 100 mg MD	(+)Tramadol	1698 (27)	90.4 (26.0)	11.7 (31.5)
	(-) Tramadol	1520 (33)	81.2 (30.0)	11.0 (34.0)
	(+) M1	362 (38)	18.4 (37.1)	12.0 (21.1)
	(-) M1	367 (29)	18.9 (28)	10.3 (31.0)
Hepatic Impairment, Mild, 100 mg racemate (50 mg of each enantiomer) MD	(+) Tramadol (-) Tramadol	1409 (31) 1292 (35)	78.4 (19.2) 72.4 (21.4)	14.3 (35.0) 14.3 (35.0)
	(+) M1	195 (87)	10.5 (81.4)	15.6 (35.6)
	(-) M1	217 (82)	11.8 (70.5)	15.0 (34.5)
Hepatic Impairment, Moderate, 100 mg racemate (50 mg of each enantiomer) MD	(+) Tramadol	1539 (34)	84.5 (30.6)	12.7 (30.7)
	(-) Tramadol	1434 (40)	79.5 (34.8)	12.0 (25.8)
	(+) M1	156 (88)	7.8 (84.6)	13.2 (27.5)
	(-) M1	184 (63)	9.5 (56.5)	14.3 (36.8)

As show in the table above, hepatic impairment resulted in a lower systemic exposure of M1, the active metabolite, in patients with hepatic impairment. There was no statistically significant ($p > 0.12$) difference in the stereoselective systemic exposure of tramadol and M1 between the three groups. The (+)/(-) enantiomeric ratios for tramadol and M1 were similar in all 3 groups, indicating that stereoselective metabolism was not affected in hepatic impairment. Due to the observed reduction of M-1 formation in patients with mild or moderate hepatic insufficiency dosage adjustment may be required to maintain adequate analgesic effect.

In the Ultram labeling, dose of Ultram for patients with cirrhosis is 50 mg every 12 hours. The Sponsor proposed 100 mg Ralivia every 48 hours for patients with cirrhosis. The Sponsor did not provide rationale for this dose reduction recommendation. As mentioned earlier, the exposure-response relationship with regards to efficacy and toxicity for tramadol and its metabolites is not well defined at this time so one cannot really determine dose adjustment based on exposure.

Age
According to the Ultram labeling, maximum serum concentration of tramadol increased (208 vs. 162 ng/mL) in subjects over 75 years compared to subjects 65 to 75 years.

In this application, the Sponsor has not evaluated Ralivia ER in subjects older than 65 years nor in subjects over 75 years. Because of the effect of age on gastrointestinal systems, e.g., permeability, pH and transit time change, there may be a significant age effect on the PK of Ralivia ER. The Sponsor will be asked to study age effect on Ralivia ER exposure-response in elderly (65-75 yrs) and older elderly (>75 yrs) subjects.

Dose recommendations for special population patients (e.g., renal impairment, hepatic impairment, over 65 years) will be determined after a successful completion of the clinical program.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence PK of Ralivia ER?

Formation of the M1 metabolite is dependent on hepatic CYP2D6 that is expressed [redacted] Approximately 7% to 10% of Caucasians and 1% of Asians are homozygous for mutant CYP2D6 [redacted]. These individuals are classified "poor metabolizers". Based on a population PK analysis of Phase 1 studies in healthy subjects (Ultram labeling), concentrations of tramadol were approximately 20% higher in "poor metabolizers" vs. "extensive metabolizers", while M1 concentrations were 40% lower. Inhibitors for CYP2D6 would affect Ralivia ER PK.

The Sponsor conducted one drug interaction study with quinidine (a CYP2D6 inhibitor) to evaluate its effect on the exposure of tramadol and its metabolites (M1 and M5). It was found that quinidine inhibited the metabolism of tramadol resulting in a higher systemic exposure of tramadol and lower systemic exposure of the M1 metabolite.

Study B02-591PK-P03P1 examined the influence of CYP2D6 inhibition on the pharmacokinetics of 100-mg Tramadol HCl ER tablets in 24 healthy non-smoking male and female subjects. In this study, subjects were assigned to 1 of 2 treatments in 2 study periods separated by a 1-week washout. With the first treatment, subjects were given a single dose of 100 mg of Tramadol HCl ER at 8:00 am after a 10-hour overnight fast. With the second treatment, subjects were given a single dose of 200 mg of quinidine sulfate at 6:00 pm after a 2-hour fast and at 6:00 am after an 8-hour overnight fast. Thereafter, a single dose of the 100-mg

ER formulation was given at 8:00 am after a 2-hour fast. The mean pharmacokinetic parameters for tramadol and its M1 metabolite are reproduced in the table below:

Table 9D – Pharmacokinetic Parameters for Tramadol

Pharmacokinetic Parameter	Tramadol HCl 100 mg ER Tablets (A) (n=19) (mean ±SD)	Tramadol HCl 100 mg ER Tablets with Quinidine Sulfate Tablets 200mg (B) (n=19) (mean ±SD)
AUC_{0-t} (ng·hr/mL)	2503.24 ± 856.06	3930.38 ± 1085.11
AUC_{0-inf} (ng·hr/mL)	2576.22 ± 1016.54	4227.24 ± 1296.42
C_{max} (ng/mL)	122.82 ± 29.23	184.65 ± 44.34
T_{max} (hours)	13.69 ± 3.85	13.37 ± 2.00
$t_{1/2}$ (hours)	7.65 ± 2.32	9.35 ± 1.94
K_{el} ($hour^{-1}$)	$9.76 \times 10^{-2} \pm 2.57 \times 10^{-2}$	$7.68 \times 10^{-2} \pm 1.39 \times 10^{-2}$
MRT (hours)	20.78 ± 4.10	22.86 ± 3.18
Cl (mL/min)	729.68 ± 241.81	429.94 ± 130.06
Vd (L)	446.60 ± 86.59	335.27 ± 79.60

Table 9G – Estimated 90% CI, Ratio of Means, and p-Values for Tramadol following administration of Tramadol HCl 100 mg ER Tablets (A) or a combination of Tramadol HCl 100 mg ER Tablets and Quinidine Sulfate Tablets 200 mg (B)

Parameter	Tramadol		
	90% C.I.	Ratio of Means	P-value
AUC_{0-t}	143.49% - 177.73%	159.69%	<0.0001
AUC_{0-inf}	145.81% - 184.43%	163.99%	<0.0001
C_{max}	135.36% - 167.37%	150.52%	<0.0001
$T_{1/2}$	N/AP	N/AP	0.0006

As shown in table 9D, co-administration of the 2 drugs produced about a 50% to 60% increase in the plasma concentrations of tramadol as compared with the concentration achieved with tramadol alone. This increase was associated with about a 41% decrease in the total plasma clearance of tramadol and a prolongation of its mean terminal half-life from 7.6 to 9.3 hours. This increased systemic exposure was also reflected in the 90% CI (table 9G)

Table 9E – Pharmacokinetic Parameters for O-Desmethyltramadol (M1)

Pharmacokinetic Parameter	Tramadol HCl 100 mg ER Tablets (A) (n=19) (mean ±SD)	Tramadol HCl 100 mg ER Tablets with Quinidine Sulfate Tablets 200mg (B) (n=19) (mean ±SD)
AUC_{0-t} (ng·hr/mL)	790.93 ± 221.31	304.65 ± 80.97
AUC_{0-inf} (ng·hr/mL)	850.01 ± 255.61	345.24 ± 89.38
C_{max} (ng/mL)	34.37 ± 9.89	12.27 ± 3.55
T_{max} (hours)	16.11 ± 3.80	15.79 ± 3.12
$t_{1/2}$ (hours)	8.85 ± 2.74	11.44 ± 2.75
K_{el} ($hour^{-1}$)	$8.50 \times 10^{-2} \pm 2.38 \times 10^{-2}$	$6.35 \times 10^{-2} \pm 1.31 \times 10^{-2}$
MRT (hours)	23.88 ± 4.72	27.46 ± 4.67
Cl (mL/min)	2117.54 ± 607.24	5313.83 ± 2255.31
Vd (L)	1588.88 ± 562.86	5113.41 ± 1876.61
M/P Ratio (AUC_{0-inf})	0.3781 ± 0.1722	0.0907 ± 0.0290

Table 9H – Estimated 90% CI, Ratio of Means, and p-Values for O-desmethyltramadol (M1) following administration of Tramadol HCl 100 mg ER Tablets (A) or a combination of Tramadol HCl 100 mg ER Tablets and Quinidine Sulfate Tablets 200 mg (B)

Parameter	O-desmethyltramadol (M1)		
	90% C.I.	Ratio of Means	P-value
AUC_{0-t}	32.41% - 45.32%	38.33%	<0.0001
AUC_{0-inf}	34.67% - 47.48%	40.57%	<0.0001
C_{max}	30.38% - 42.16%	35.79%	<0.0001
$T_{1/2}$	N/AP	N/AP	0.0001

As shown in table 9E above, the increase in plasma tramadol concentrations was linked with a corresponding decrease of 50% to 60% in the formation of the M1 metabolites. This decreased systemic exposure of M1 was also reflected in the 90% CI (table 9H).

Becasue co-administration of quinidine with tramadol has opposite effects on plasma concentrations of tramadol and its M1 metabolite, the clinical implications of the interaction are difficult to predict because analgesic activity is probably dependent on the systemic exposure of both moieties. However, the results indicate that potential interactions may occur with drugs that are metabolized by cytochrome CYP2D6 isoenzyme.

2.4.2 What drug-drug interactions have been studied for Ultram?

CYP2D6 and CYP3A4 are the two major P450s involved in the metabolism of tramadol. Tramadol is unlikely an inhibitor and inducer of CYP3A4. In the Ultram labeling, potential interactions with carbamazepine, quinidine, CYP2D6 inhibitors (such as fluoxetine, paroxetine), cimetidine, MAO inhibitors, digoxin and warfarin were described. Concomitant administration of Ultram and carbamazepine (a known CYP3A4 inducer) is not recommended.

2.5 General Biopharmaceutics

2.5.1 What is formulation (quantitative composition) of Ralivia ER 100, 200 and 300 mg tablets?

The extended-release formulation consists of the drug and inert excipients in a solid core that is surrounded with a release-controlling coating comprising water soluble and water insoluble polymers and a plasticizer. Drug release from the dosage form can be adjusted by changing the porosity of the coating surrounding the core. The compositions of the drug products (100, 200 and 300 mg extended release tables) are listed in Tables 2.5.1.1 to 2.5.1.3.

Table 2.5.1.1. Quantitative Composition of 100 mg Ralivia ER Tablet.

Component	% w/w	100 mg/tablet
Tramadol HCl ER Tablet Granulation		
Tramadol Hydrochloride, House	82.0	100.00
[redacted]		
Tablet Core Weight		
Tablet Coating Solution		
[redacted]		
Target Weight Gain		
Weight Gain Range		
Theoretical Total Coated Tablet Weight	100.0	122.00

[redacted] used for the manufacture of the bulk blend is essentially removed during the manufacturing process. The finished product contains NM.

[redacted] used for the manufacture of the coating solution is essentially removed during the manufacturing process. The finished product contains NMT [redacted]

[redacted] used for the manufacture of the coating solution is essentially removed during the manufacturing process. The finished product contains NMT [redacted]

Table 2.5.1.2. Quantitative Composition of 200 mg Ralivia ER Tablet.

Component	% w/w	200 mg/tablet
Tramadol HCl ER Tablet Granulation		
Tramadol Hydrochloride, House	85.4	200.00
[redacted]		
Tablet Core Weight		
Tablet Coating Solution		
[redacted]		
Target Weight Gain		
Weight Gain Range		
Theoretical Total Coated Tablet Weight	100.0	234.00

[redacted] used for the manufacture of the bulk blend is essentially removed during the manufacturing process. The finished product contains NMT [redacted]

[redacted] used for the manufacture of the coating solution is essentially removed during the manufacturing process. The finished product contains NMT [redacted]

[redacted] used for the manufacture of the coating solution is essentially removed during the manufacturing process. The finished product contains NMT [redacted]

Table 2.5.1.3. Quantitative Composition of 300 mg Ralivia ER Tablet.

Component	% w/w	300 mg/tablet
Tramadol HCl ER Tablet Granulation		
Tramadol Hydrochloride, House	87.2	300.00
[redacted]		
Tablet Core Weight		
Tablet Coating Solution		
[redacted]		
Target Weight Gain		
Weight Gain Range		
Theoretical Total Coated Tablet Weight	100.0	344.00

[redacted] used for the manufacture of the bulk blend is evaporated during the manufacturing process. The finished product contains NMT [redacted]

[redacted] used for the manufacture of the coating solution is evaporated during the manufacturing process. The finished product contains NMT [redacted]

[redacted] used for the manufacture of the coating solution is evaporated during the manufacturing process. The finished product contains NMT [redacted]

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

Food effect was evaluated in Study B01-568PK-TRAP03 with 200 mg tablet, single dose. Food (a high fat meal) decreased both rate and extent of absorption of tramadol. C_{max} and $AUC_{0\text{-}inf}$ of tramadol decreased 28% and 16%, respectively in the presence of food (based on geometric mean ratio of fed vs. fasing). Mean T_{max} was increased by 3 hours (from 14 hr fasting to 17 hr fed). Similar results were observed for M1 and M5. Therefore, there was a food-effect on the rate and extent of the absorption of tramadol from this extended release product. The clinical significance of the food effect is unknown.

Table 2.5.2.1. Relative Bioavailability Analysis of Fed (Test) versus Fasing (Reference) for Tramadol and M1 Following 200 mg Tramadol ER Administration.

Parameter	Tramadol		
	90% C.I.	Ratio of Means	Intra-Subject CV
$AUC_{0\text{-}t}$	64.38% - 95.79%	78.53%	36.05%
$AUC_{0\text{-}inf}$	62.96% - 116.69%	85.71%	41.38%
C_{max}	56.97% - 91.70%	72.27%	43.18%

Parameter	O- desmethyltramadol (M1)		
	90% C.I.	Ratio of Means	Intra-Subject CV
$AUC_{0\text{-}t}$	63.59% - 94.84%	77.66%	36.26%
$AUC_{0\text{-}inf}$	73.68% - 114.40%	91.81%	18.45%
C_{max}	60.27% - 96.44%	76.24%	42.65%

2.5.3 Dose three dose strength tablets demonstrate dosage form equivalence?

Yes. In Study B03-623PK-P03P1, 100 mg and 300 mg Tramadol HCl ER tablets are shown to be dosage strength equivalent (Table 2.5.3.1). The active and inactive components for the tablet core are proportional similar for 100, 200 and 300 mg tablets. Therefore, 100 mg and 200 mg Tramadol HCl ER tablets should also be dosage strength equivalent. Results form Study 570 PK proved this (Study was not reviewed).

Table 2.5.3.1. Relative Bioavailability Analysis for Tramadol, M1, and M5 Following Tramadol HCl ER 1 x 300 mg Tablet (A) versus Tramadol HCl ER 3 x 100 mg Tablet (B) Administration.

Parameters	Tramadol		
	90% C.I.	Ratio of Means	Intra-Subject CV
$AUC_{0\text{-}t}$	97.48% - 104.84%	101.10%	7.11%
$AUC_{0\text{-}inf}$	99.18% - 106.93%	102.98%	7.35%
C_{max}	91.34% - 106.74%	98.74%	15.22%

Parameters	O-Desmethyltramadol			O-N-di-Desmethyltramadol		
	90% C.I.	Ratio of Means	Intra-Subject CV	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	94.81% - 102.52%	98.59%	7.65%	93.19% - 101.17%	97.09%	8.03%
AUC_{0-inf}	96.13% - 105.81%	100.85%	8.97%	92.63% - 102.55%	97.46%	8.10%
C_{max}	86.69% - 99.16%	92.72%	13.12%	86.02% - 98.41%	92.01%	13.14%

2.5.4 Has the Sponsor established in vitro-in vivo correlation (IVIVC) of Ralivia ER?

The Sponsor submitted a Study Report (2003-14) to claim a Level A IVIVC for Ralivia ER. We did not agree with the conclusion. Specifically, we did not accept the computational approach that used different scaling factors for different release rate formulations. A teleconference was held between the Agency and the Sponsor. The Sponsor was asked to re-do the analysis using the method of Gillespie (Adv Exp Med Biol. 1997;423:53-65) to correct for differences between *in-vitro* and *in-vivo* release profiles. The Sponsor submitted a new IVIVC analysis report (Report RA612005) on September 30, 2004. This report will be reviewed at the next review cycle. The conclusion of IVIVC is pending. The dissolution method and specifications were reviewed without consideration of IVIVC.

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

Yes the applicant developed a dissolution method and specification. The method seems appropriate however, the specifications are not acceptable. Drug Release Method proposed for future commercial formulations of Tramadol HCl ER Tablets, 100 mg, 200 mg, and 300 mg are reproduced in the Table below:

Drug Release Parameters	**Value**
Apparatus	Automated USP Dissolution Apparatus #1
Dissolution medium	[redacted]
Dissolution medium volume	[redacted]
Dissolution medium temperature	[redacted]
Rotation speed	[redacted]
Sampling Time	2, 4, 8 and 16 hours

Effect of medium:

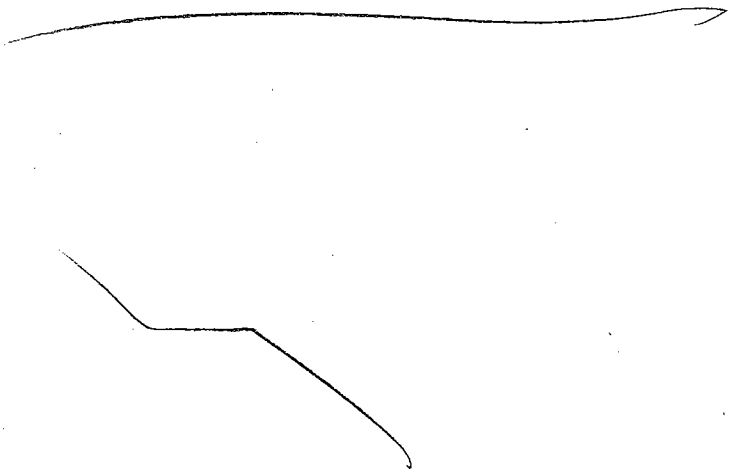


Figure 2.5.5.1. Representative Dissolution profiles for Tramadol HCL ER Tablets, 100 mg (Lot 02C139) in Different Dissolution Media

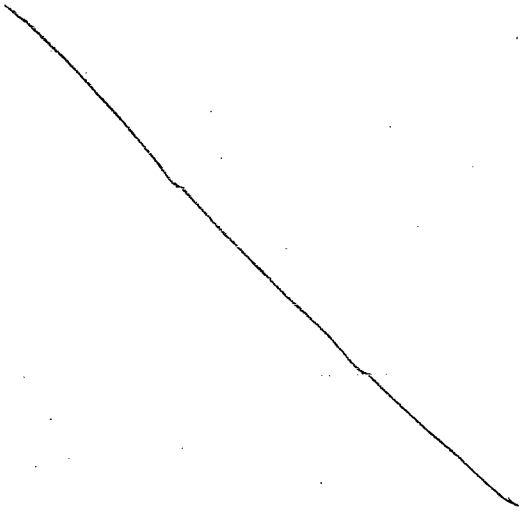


Figure 2.5.5.2. Representative Dissolution profiles for Tramadol HCL ER Tablets, 100 mg, 200 mg and 300 mg in [redacted] (Proposed Commercial Formulations)

Specifications

The applicant stated that based on the properties of the drug substance and its extended release formulation, as well as the robust Level A IVIVC, *in vitro* release specifications wider than the traditional 10% range around the target formulation are justified. Since the level A IVIVC correlation was not acceptable, it cannot be used to justify the proposed specifications. Therefore the acceptance of the specifications will be based on the dissolution profiles obtained for the clinical/bioavailability lots. These dissolution profiles show that the proposed wider than 10% deviation from the mean dissolution profile will not be acceptable for ensuring batch to batch quality. Based on the data provided, this reviewer proposes a tightening of the specifications as follows:

Time	Applicant's Proposed Dissolution Limits	Agency's Revised Proposed Dissolution limits
2 hours		
4 hours		
8 hours		
10 hours		
16 hours		

The dissolution specification may need to be further revised based on the review of IVIVC results.

2.6 Analytical

2.6.1 Were the analytical methods used to determine Tramadol and M-1 and M-5 in biological fluids adequately validated?

Yes. Concentrations of tramadol and its metabolites, M1 and M5, (both bound and free) were adequately measured in human plasma by validated LC/MS/MS assays and summarized in Table 2.6.1.1. The same basic assay was used throughout the development plan and consistent performance was achieved from study to study. The assay is sensitive and selective for the analytes. In this method, tramadol, M1, and M5 and the internal standard, metoprolol, are extracted by into an organic media from 0.50 mL of human plasma. An aliquot of this extract is then injected into a high performance liquid chromatograph (HPLC) with a tandem mass spectrometry (LC-MS/MS) detection system. The analytes are separated by and the resulting chromatographic peaks are quantified by mass spectrometry. Typically, the limit of quantification for racemic tramadol assay was in plasma and in urine. The limits for each of the individual tramadol enantiomers were after the second assay validation. For the M1 metabolite, the limits of quantification were for the racemic mixture and for the individual enantiomers. The limit of quantification for the racemic M1 metabolite in urine was . The limits for racemic the M5 metabolite were identical to those for racemic M1 metabolite in both plasma and urine.

Except for the analysis of samples from Study B02-590PK-P03P1 that was performed by [redacted], all other assays were performed by Bioanalytical Laboratory, Biovail Contract Research (Scarborough, Ontario, Canada).

Long-term stability of tramadol, M1 and M5 in frozen human plasma at -25°C was > 115 days. All samples were analyzed within the115 days of sample collection.

Table 2.6.1.1. Analytical Methods used for the Determinations of Tramadol, M1 and M5 in Each Study (Listed as the biggest value of %CV in each experiment).

Studies	Reference Validation Method	Analytes	LOQ (ng/ml)	Linear Range (ng/ml)	Between Run Precision (%|CV|)	Between Run Bias (%|RE|)	QC Samples (ng/mL) other than LOQ QC
567PK 569PK	T11-04	Tramadol M1 M5			< 7 < 6.1 < 7.4	< 6.4 < 8.0 < 3.5	3.023, 6.045, 193.452, 773.805 1.664, 3.329, 106.519, 426.075 1.455, 2.910, 93.120, 372.48
568PK	T11-02	Tramadol M1			< 17.3 < 17.3	< 7.3 < 8.9	3.002, 6.004, 192.126, 768.503 1.501, 3.002, 96.065, 384.258
426PK	T11-00	Tramadol M1 M5			< 9.2 < 10.9 < 15.9	< 8.4 < 9.3 < 13.3	3.00, 6.00, 159.96, 767.81 1.48, 2.97, 79.19, 380.14 146, 2.91, 77.60, 372.48
623PK	T11-08a	Tramadol M1 M5			< 5.4 < 4.5 < 6.3	< 5.5 < 3.0 < 5.4	6.045, 193.452, 773.805 3.00, 95.991, 383.964 2.91, 93.12, 372.48
591PK	T11-06	Tramadol M1 M5			Please refer to individual study reviews (Section 4.2) for summary of analytical methods for these studies		
590PK	DCN11-502-V1 (Plasma)	(+)/(-)-Tramadol (+)/(-)-M1					
	DCN11-502-V2 (Urine)	(+)/(-)-Tramadol (+)/(-)-M1					
589PK	T20-00a (Plasma)	Tramadol M1 M5					
	T-18-01a (Urine)	Tramadol M1 M5					

3 DETAILED LABELING RECOMMENDATIONS

The labeling recommendation is deferred pending the completion of a successful clinical development program.

21 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

9 § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

4.4 Individual Study Review

4.4.1 Study #2551 (B01-567PK-TRAP03): A Two-Way, Crossover, Open-Label, Fasting, Single-Dose and Multiple-Dose Bioavailability Study of Tramadol Hydrochloride Extended Release 200 mg Tablets (Once Daily) Versus Ultram 50 mg Tablets (Four Times Daily) in Normal Healthy Non-Smoking Male and Female Subjects

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Study Period:	January 15, 2002 to February 19, 2002 Treatment I: January 16, 2002 to January 26, 2002 Treatment II: February 9, 2002 to Feburary 19, 2002
Sample Analysis Period:	March 2002 to April 2002
Principle Investigator:	Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.
Study Center:	Biovail Contract Research (BCR) – 460 Comstock Road, Toronto, ON, M1L 4S4 Canada – 689 Warden Avenue, Units 1 & 2, Toronto, ON, M1L 4R6 Canada
Analytical Site:	Bioanalytical Lab of BCR

Objectives: To determine the relative bioavailability of Tramadol HCl 200 mg Extended Release Tablets administered as a 200 mg dose (once daily) compared to Ultram® 50 mg Tablets administered as 50 mg (four times daily) under single daily-dose and steady-state conditions, and to investigate the extended release characteristics of the novel formulation.

Study Design: The study was performed as a randomized, open-label, analytically blinded, single-dose and multiple-dose, two- way, crossover study in thirty-six (36) normal, healthy, non-smoking male and female subjects under fasting conditions. Thirty-two (32) subjects (27 males and 5 females) completed the study. Please refer to Tables A1 and A2 in the Appendix for demographic information.

Subjects were randomized to Sequence 1 or Sequence 2 (Table 1). There was a 14-day washout period between Treatment A and B.

Table 1. Study Design.

Sequence 1	Treatment A	Washout	Treatment B
Sequence 2	Treatment B	Washout	Treatment A

Treatment A:
Day 1 and Days 3-10: One (1) Tramadol HCl 200 mg Extended Release Tablet at 0 hr with 240 mL water following an overnight fast of at least 10 hrs. (Total daily dose = 200 mg).

Treatment B:
Day 1 and Days 3-10: One (1) Ultram® 50 mg Tablet at 0 hour with 240 mL of water following an overnight fast of at least ten (10) hours. A second dose of one (1) Ultram® 50 mg Tablets given at 6.0 hours with 240 mL of water after a fast of at least one (1) hour. A third dose of one (1) Ultram® 50 mg Tablets given at 12.0 hours with 240 mL of water after a fast of at least one (1) hour. A fourth dose of one (1) Ultram® 50 mg Tablets given at 18.0 hours with 240 mL of water after a fast of at least one (1) hour. (Total daily dose = 200 mg).

Test Articles:
Treatment A:
Tramadol HC1 200 mg Extended Release Tablets
Manufacturer: By: [redacted] For: Biovail Corporation
Lot #: [redacted].0 010704; Manufacturing Date: 07/20/01

Treatment B:
Ultram® 50 mg Tablets
Manufacturer: Ortho-McNeil Pharmaceutical, Inc. OMP Division
Control# 91P0789E; Expiration Date: 6-03

Sample Collection and Handling:
Treatment A:

Days 1-3:	0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0 (Day 2), 36.0, 48.0 (Day 3) hours post-drug administration.
Days 7, 8, and 9:	0.0 (pre-dose)
Day 10:	0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0 and 24.0 (Day 11) hours post-drug administration.
Treatment B:	
Days 1-3:	0.0 (pre-dose), 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 6.5, 7.0, 7.5, 8.0, 10.0, 12.0, 12.5, 13.0, 13.5, 14.0, 16.0, 18.0, 18.5, 19.0, 19.5, 20.0, 22.0, 24.0 (Day 2), 36.0 and 48.0 (Day 3) hours post-drug administration.
Days 7, 8, and 9:	0.0 (pre-dose). Pre-Dose samples were not required for 6.0, 12.0 and 18.0 drug administration.
Day 10:	0.0 (pre-dose), 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 6.5, 7.0, 7.5, 8.0, 10.0, 12.0, 12.5, 13.0, 13.5, 14.0, 16.0, 18.0, 18.5, 19.0, 19.5, 20.0, 22,0 and 24.0 (Day 11) hours post-drug administration.

Approximately 617.5 mL of blood was collected over the two (2) study periods, including the amount for pre-study test, hemoglobin tests done prior to Day 8 for Period II, as well for post-study clinical blood tests.

The blood samples were stored in an ice bath prior to centrifugation and were centrifuged as soon as possible under refrigerated conditions a [redacted]. The collected plasma from each blood collection tube was aliquotted into labeled, duplicate, polypropylene culture tubes, and stored frozen at minus (-) 25°C ± 10°C until assayed.

Sample Analysis: All plasma samples were delivered to the analytical facility (Bioanalytical Lab of BCR) after the completion of the clinical portion of the study for the analysis of tramadol, O-desmethyltramadol (M1) and O, N-di-desmethyltramadol (M5), using a suitably validated and sensitive assay method. Full validation of the method, including precision, accuracy and reproducibility is included in the final report (T11-04, Appendix 6), along with a statement regarding the stability of the frozen samples. The analytical facility was blinded regarding the dosage regimen.

Pharmacokinetic and Statistical Analysis: The arithmetic mean, standard deviation (SD) and inter-subject CV were calculated for plasma tramadol, O-desmethyltramadol (Ml) and O, N-di-

desmethyltramadol (M5) concentrations for each sampling time and formulation and for the following PK parameters:

Under single dose: AUC0-t, AUC0-inf, Tmax, Kel, t1/2, Cmax, MRT, M/P ratio, and r-value (the correlation coefficient of the most linear portion of the terminal elimination phase)

Under multiple-dose: AUCτ, Cmax, Tmax, % fluctuation, % swing, Cmin, Cavg, and M/P ratio and r-value (the correlation coefficient of the most linear portion of the terminal elimination phase).

The Cmax for Q6h dosing of Ultram was calculated irrespective of the dose number. The corresponding Tmax following Ultram dosing was determined by relating it to the time of the last dose of Ultram when Cmax occurred and not relative to the first dose at time zero.

Individual ANOVAs (with the following factors: treatment, period, sequence, and subject within sequence) were performed on the log-transformed data AUC0-t, AUC0-inf, and Cmax for single-dose administration, and AUCτ, Cmax, Cmin, and Cavg for multiple-dose administration. ANOVAs were performed with the SAS General Linear Models (GLM) Procedure. For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than or equal to 0.050.

Bioavailability of the formulations was compared where treatment differences were estimated and 90% confidence intervals (CIs) were estimated and presented for the logarithmically transformed variables. The treatment differences tested were: Treatment A versus Treatment B.

Pharmacokinetic Results:
Reviewer's Note: Although levels of M5 were measured for this study, because M5 is pharmacologically less active than M1, only descriptive PK data are listed in the review. No further analysis of the M5 data was presented.

Steady-State Assessment
Steady state was reached for both tramadol and M1 metabolite following either multiple Tramadol ER (200 mg once-daily) or Ultram (50 mg Q6h) dosing on Day 4 as predose levels were stable from Days 4 to 7 (Tables 2 and 3).

Table 2. Predose Plasma Concentrations Following Tramadol ER (200 mg once-daily) Dosing.

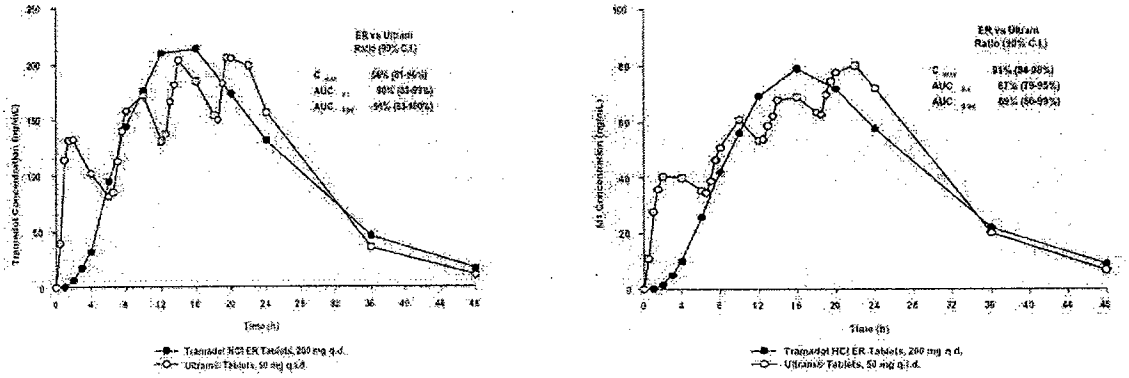
	Day 4 Post Dose	Day 5 Post Dose	Day 6 Post Dose	Day 7 Post Dose
Tramadol (ng/mL)	172 ± 87	166 ± 90	179 ± 70	181 ± 76
M1	64 ± 24	64 ± 27	70 ± 21	67 ± 21

Table 3. Predose Plasma Concentrations Following Ultram (50 mg Q6h) Dosing.

	Day 4 Post Dose	Day 5 Post Dose	Day 6 Post Dose	Day 7 Post Dose
Tramadol (ng/mL)	222 ± 75	208 ± 70	208 ± 67	217 ± 73
M1	81 ± 23	80 ± 22	80 ± 22	78 ± 22

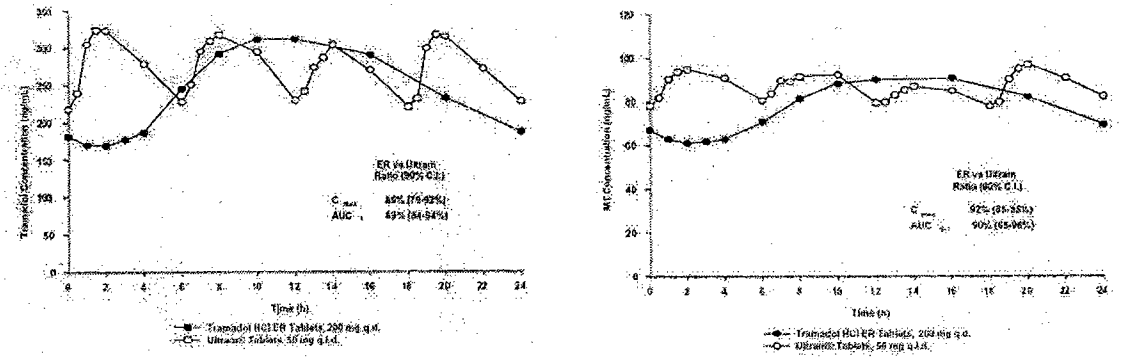
PK Profiles

The mean plasma concentration-time profiles of the drug and M1 metabolite after single daily-dosing are shown in Figure 1 (a and b). The mean steady state plasma concentration-time profiles of the drug and M1 metabolite after multiple dosing are shown in Figure 2 (a and b).



a. Tramadol b. M1

Figure 1. Mean Sinlge Daily-Dose Plasma Tramadol (a) and M1 (b) Concentrations on Day 1 for 200-mg Tramadol HCl ER Tablets QD and 50-mg Ultram® Tablets Q6h.



a. Tramadol b. M1

Figure 2. Mean Steady State Plasma Tramadol (a) and M1 (b) Concentrations on Day 7 Post Dose for 200-mg Tramadol HCl ER Tablets QD and 50-mg Ultram® Tablets Q6h.

The mean pharmacokinetic parameters for tramadol, O-desmethyltramadol (M1), and O,N-di-desmethyltramadol (M5) following single daily-dose and multiple dose results are summarized in Tables 4-9.

Table 4. Pharmacokinetic Parameters for Tramadol After Single Daily-Dose Administration of Tramadol ER (200 mg) and Ultram (50 mg Q6h).

Pharmacokinetic Parameter	Tramadol HCl 200 mg Extended Release Tablets (A) n = 32 Mean ± SD	Ultram® 50 mg Tablets (B) n = 32 Mean ± SD
AUC_{0-t} (ng.hr/mL)	4792.17 ± 2017.83	5095.20 ± 1595.42
AUC_{0-inf} (ng.hr/mL)	4999.94 ± 2139.00	5174.38 ± 1687.68
C_{max} (ng/mL)	234.23 ± 90.43	257.98 ± 69.04
T_{max} (hour)	13.57 ± 3.76	2.22 ± 1.36
$t_{½}$ (hour)	7.66 ± 1.76	5.76 ± 1.15
K_{el} ($hour^{-1}$)	0.096 ± 0.024	0.125 ± 0.025
MRT (hours)	2.22 ± 1.47	1.03 ± 0.69

Note: The observed Tmax (Tmax relating to the first dose at time 0) for Tramadol following Ultram Q6h dosing was 17.2 ± 4.6 hr.

Table 5. Pharmacokinetic Parameters for O-desmethyltramadol (M1) After One Daily-Dose Administration of Tramadol ER (200 mg) and Ultram (50 mg Q6h).

Pharmacokinetic Parameter	Tramadol Hcl 200 mg Extended Release Tablets (A) n = 32 Mean ± SD	Ultram® 50 mg Tablets (B) n = 32 Mean ± SD
AUC_{0-t} (ng.hr/mL)	1856.01 ± 596.66	2063.81 ± 501.78
AUC_{0-inf} (ng.hr/mL)	1984.59 ± 636.68	2168.12 ± 527.97
C_{max} (ng/mL)	83.42 ± 27.52	88.79 ± 21.21
T_{max} (hour)	15.57 ± 3.16	2.97 ± 1.57
$t_{½}$ (hour)	8.95 ± 2.20	6.90 ± 1.22
K_{el} ($hour^{-1}$)	0.082 ± 0.022	0.104 ± 0.020
MRT (hours)	3.91 ± 2.70	1.85 ± 1.10
M/P ratio	0.4747 ± 0.2121	0.4901 ± 0.2056

Note: The observed Tmax (Tmax relating to the first dose at time 0) for M1 following Ultram Q6h dosing was 19.7 ± 3.8 hr.

Table 6. Pharmacokinetic Parameters for O, N-di-desmethyltramadol (M5) After One Daily-Dose Administration of Tramadol ER (200 mg) and Ultram (50 mg Q6h).

Pharmacokinetic Parameter	Tramadol HCl 200 mg Extended Release Tablets (A) n = 32 Mean ± SD	Ultram® 50 mg Tablets (B) n = 32 Mean ± SD
AUC_{0-t} (ng.hr/mL)	684.84 ± 244.04	765.01 ± 239.00
AUC_{0-inf} (ng.hr/mL)	757.34 ± 282.87	804.97 ± 264.89
C_{max} (ng/mL)	29.00 ± 9.09	31.03 ± 9.03
T_{max} (hour)	16.82 ± 3.44	2.92 ± 1.48
$t_{½}$ (hour)	10.07 ± 2.48	8.24 ± 2.07
K_{el} ($hour^{-1}$)	0.074 ± 0.021	0.089 ± 0.021
MRT (hours)	5.53 ± 3.43	3.42 ± 2.49
M/P ratio (based on AUC_{0-Inf})	0.1901 ± 0.0771	0.1926 ± 0.0712

Table 7. Pharmacokinetic Parameters for Tramadol After Multiple-Dose Administration of Tramadol ER (200 mg) and Ultram (50 mg Q6h).

Pharmacokinetic Parameter	Tramadol HCl 200 mg Extended Release Tablets (A) n = 32 Mean ± SD	Ultram® 50 mg Tablets (B) n = 32 Mean ± SD
AUC_τ (ng·hr/mL)	5975.03 ± 2027.42	6612.66 ± 1790.04
C_{max} (ng/mL)	335.44 ± 116.11	382.49 ± 79.86
C_{min} (ng/mL)	186.54 ± 69.51	227.68 ± 72.36
T_{max} (hour)	11.88 ± 3.17	1.49 ± 0.63
Degree of Fluctuation (%)	61.03 ± 34.51	59.36 ± 20.77
Degree of Swing (%)	103.76 ± 103.14	76.30 ± 34.17
C_{avg} (ng/mL)	248.96 ± 84.48	275.53 ± 74.59

Note: The observed Tmax (Tmax relating to the first dose at time 0) for Tramadol following Ultram Q6h dosing was 11.0 ± 5.8 hr.

Table 8. Pharmacokinetic Parameters for O-desmethyltramadol (M1) After Multiple-Dose Administration of Tramadol ER (200 mg) and Ultram (50 mg Q6h).

Pharmacokinetic Parameter	Tramadol HCl 200 mg Extended Release Tablets (A) n = 32 Mean ± SD	Ultram® 50 mg Tablets (B) n = 32 Mean ± SD
AUC_τ (ng·hr/mL)	1889.96 ± 481.47	2095.37 ± 539.58
C_{max} (ng/mL)	95.44 ± 23.09	104.35 ± 24.57
C_{min} (ng/mL)	69.14 ± 20.70	81.98 ± 22.36
T_{max} (hour)	14.63 ± 3.92	1.94 ± 1.10
Degree of Fluctuation (%)	33.50 ± 24.21	26.10 ± 12.23
Degree of Swing (%)	45.56 ± 46.27	30.03 ± 20.41
C_{avg} (ng/mL)	78.75 ± 20.06	87.31 ± 22.48
M/P ratio	0.3610 ± 0.1192	0.3510 ± 0.1041

Note: The observed Tmax (Tmax relating to the first dose at time 0) for M1 following Ultram Q6h dosing was 13.4 ± 7.2 hr.

Table 9. Pharmacokinetic Parameters for O, N-di-desmethyltramadol (M5) After Multiple-Dose Administration of Tramadol ER (200 mg) and Ultram (50 mg Q6h).

Pharmacokinetic Parameter	Tramadol HCl 200 mg Extended Release Tablets (A) n = 32 Mean ± SD	Ultram® 50 mg Tablets (B) n = 32 Mean ± SD
AUC_τ (ng.hr/mL)	984.90 ± 345.84	1078.57 ± 341.59
C_{max} (ng/mL)	49.74 ± 16.87	51.13 ± 15.15
C_{min} (ng/mL)	38.31 ± 17.32	43.58 ± 15.86
T_{max} (hour)	16.69 ± 3.50	2.89 ± 1.41
Degree of Fluctuation (%)	30.43 ± 21.23	18.40 ± 10.52
Degree of Swing (%)	38.59 ± 35.35	19.82 ± 12.08
C_{avg} (ng/mL)	41.04 ± 14.41	44.94 ± 14.23
M/P ratio	0.1998 ± 0.0758	0.1944 ± 0.0708

Relative Bioavailability

The relative bioavailability analysis results for AUC0-t, AUC0-inf and Cmax (single daily-dose) of tramadol and M1, transformed using the natural logarithm, are summarized in Table 10. The relative bioavailability analysis results for AUCτ, and Cmax (multiple-dose) of tramadol and M1, transformed using the natural logarithm, are summarized in Table 11.

Table 10. Relative Bioavailability Analysis of Tramadol HCl 200 mg Extended Release Tablets (A) versus Ultram 50 mg Tablets (B) for Tramadol After Single Daily-Dose Administration.

Parameter	TRAMADOL		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	82.69% - 98.46%	90.23%	20.56%
AUC_{0-inf}	83.28% - 99.46%	91.01%	20.56%
C_{max}	81.21% - 95.84%	88.23%	19.52%

Parameter	O-DESMETHYLTRAMADOL (M1)		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	79.19% - 94.98%	86.73%	21.42%
AUC_{0-inf}	80.03% - 98.87%	88.95%	23.19%
C_{max}	83.50% - 98.17%	90.54%	19.07%

Table 11. Relative Bioavailability Analysis of Tramadol HCl 200 mg Extended Release Tablets (A) versus Ultram 50 mg Tablets (B) for Tramadol After Multiple Dose Administration.

Parameter	TRAMADOL		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_τ	83.97% - 93.75%	88.73%	12.98%
C_{max}	78.63% - 91.63%	84.88%	18.02%

Parameter	O-DESMETHYLTRAMADOL (M1)		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_τ	85.18% - 95.85%	90.35%	13.90%
C_{max}	85.05% - 97.75%	91.18%	16.40%

Accumulation Index
The accumulation index was quantified by the following formula:
Accumulation Index = AUC(0-24hr) (multiple dose)/ AUC(0-24hr) (single dose)

Accumulation index of tramadol for Tramadol ER (1.9) is higher than what is estimated from its apparent half life of 9 hr (1.2).

Table 12. Accumulation Index Following Tramadol ER and Ultram Dosing.

	Tramadol ER	Ultram
Tramadol	1.89 ± 0.48	1.86 ± 0.35
M1	1.73 ± 0.59	1.57 ± 0.25

Overall Conclusions:
The pharmacokinetics of tramadol and its metabolite O-desmethyltramadol (MI) following Tramadol ER and Ultram dosing were assessed under both single and multiple dose conditions. The 90% confidence intervals (CIs) of geometric mean ratio (GMR) (Treatment A/Treatment B) of AUC0-inf and Cmax for tramadol and M1 were within 80.00% to 125.00% after a single daily dose of Tramadol HC1 200 mg Extended Release Tablets (Treatment A) and Ultram® 50 mg Tablets (Q6h) (Treatment B) under fasting conditions. When Tramadol HC1 Extended Release Tablets were compared to Ultram® 50 mg Tablets under the multiple dose regimen, 90% CIs of geometric mean ratio (GMR) (Treatment A/Treatment B) of AUCτ for tramadol and 90% CTs of GMR of AUCτ and Cmax for M1 were within 80.00% to 125.00%. The lower limit of 90% CI of GMR of Cmax for tramdol is slightly lower than 80% (78.6%). The clinical significance of lower Cmax for tramadol at steady state following Tramadol ER compared to Ultram dosing is unknown. For all conditions, 100% was not included in 90% CI indicating that exposure of tramadol and M1 after Tramadol ER dosing is in general lower than that following Ultram (tramadol IR formulation) dosing.

Appendix for Study #2551. Demographic Information.
Table A1. Demographic Data for All Subjects.

Subject No.	Race	Gender	Age (years)	Height (inches)	Weight (pounds)	Frame
01	Caucasian	Male	25	67	164	Medium
02	Caucasian	Female	31	65	131	Medium
03	Caucasian	Male	38	70	177	Medium
04	Asian	Female	26	65	119	Medium
05	Caucasian	Male	45	69	192	Large
06	Caucasian	Female	30	65	137	Medium
07	Caucasian	Male	33	70	138	Medium
08	Black	Female	25	64	164	Large
09	Caucasian	Male	25	74	191	Medium
10	Caucasian	Male	33	67	142	Medium
11	Caucasian	Male	21	69	171	Medium
~~*12~~	~~Caucasian~~	~~Female~~	~~24~~	~~64~~	~~125~~	~~Medium~~
~~*13~~	~~Black~~	~~Male~~	~~32~~	~~67~~	~~165~~	~~Medium~~
~~*14~~	~~Caucasian~~	~~Female~~	~~24~~	~~62~~	~~138~~	~~Medium~~
15	Black	Male	33	71	184	Medium
16	Caucasian	Male	26	68	168	Small
17	Caucasian	Male	34	70	177	Large
18	Black	Female	34	66	170	Large
19	Caucasian	Male	24	71	172	Medium
20	Caucasian	Male	43	68	176	Medium
21	Caucasian	Male	34	73	173	Small
22	Caucasian	Male	38	65	150	Small
23	Caucasian	Male	44	69	174	Medium
24	Caucasian	Male	41	75	198	Medium
25	Caucasian	Male	59	74	205	Medium
26	Caucasian	Male	25	74	184	Medium
27	Caucasian	Male	25	69	144	Medium
28	Caucasian	Male	27	71	173	Medium
29	Caucasian	Male	22	69	156	Medium
30	Caucasian	Male	37	72	160	Medium
31	Black	Male	25	69	159	Medium
~~*32~~	~~Caucasian~~	~~Male~~	~~28~~	~~74~~	~~180~~	~~Medium~~
33	Caucasian	Male	34	75	190	Medium
34	Caucasian	Male	37	66	132	Medium
35	Caucasian	Male	34	70	186	Medium
36	Caucasian	Male	38	70	176	Medium

Mean (All subjects)	**32**	**69**	**165**
S.D. (±)	**8.0**	**3.4**	**21.7**
Mean (Completing subjects*)	**33**	**69**	**167**
S.D. (±)	**8.2**	**3.1**	**21.1**

* Subjects #12, #13, #14 and #32 did not complete the study. Subject #12 was dismissed due to an adverse event on Day 1, Period 1. Subject #13 was dismissed due to an adverse event on Day 2 (pre-Day 3 dosing), Period 2. Subject #14 was dismissed due to non-compliance during the check-in of Period 2. Subject #32 withdrew prior to Period 2 check-in.

Table A2. Demographic Characteristics for Subjects Who Completed the Study.

	N	%
Age (y)		
21-59	32	100
Race		
Caucasian	27	84.4
African American	4	12.5
Asian	1	3.1
Sex		
Male	27	84.4
Female	5	15.6

4.4.2 Study #2552 (B01-569PK-TRAP03): A Three-Treatment, Open-Label, Multiple-Dose, Fasting, Dose-Escalation Study of Tramadol Hydrochloride Extended Release Tablets (100 mg, 200 mg and 400 mg Doses) Given Once Daily in Normal Healthy Non-Smoking Male and Female Subjects

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Study Period: January 24, 2002 to February 12, 2002
Sample Analysis Period: February 2002 to March 2002
Principle Investigator: Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.
Study Center: Biovail Contract Research (BCR) – 460 Comstock Road, Toronto, ON, M1L 4S4 Canada – 689 Warden Avenue, Units 1 & 2, Toronto, ON, M1L 4R6 Canada
Analytical Site: Bioanalytical Lab of BCR

Objectives: To investigate the dose-proportionality of tramadol over the 100 mg – 400 mg dose range for Tramadol HCl Extended Release Tablets (100 and 200 mg), given once daily (as either 100 mg, 200 mg or 2 x 200 mg) under multiple-dose, fasting conditions.

Study Design: The study was performed as an open-label, analytically blinded, multiple-dose, three-treatment study in thirty (30) normal, healthy, non-smoking male and female subjects under fasting conditions. Twenty-five (25) subjects (13 males and 12 females) completed the study. Please refer to Tables A1 and A2 in the Appendix for demographic information.

Subjects were dosed sequentially with 100 mg, 200 mg and 400 mg tramadol dose (Table 1).

Table 1. Study Design.

Treatment A (Days 1-6)	Treatment B (Days 7-12)	Treatment C (Days 13-18)
One (1) Trarnadol HCI Extended Release 100 mg Tablet at 0.0 hour with 240 mL of ambient temperature water following an overnight fast of at least ten (10) hours. (Totat Daily Dose = 100 mg).	One (1) Tramadol HCI Extended Release 200 mg Tablet at 0.0 hour with 240 mL of ambient temperature water following an overnight fast of at least ten (10) hours. (Total Daily Dose = 200 mg).	Two (2) Tramadol HCI Extended Release 200 mg Tablets at 0.0 hour with 240 mL of ambient temperature water after an overnight fast of at least ten (10) hours. The drug was given one or two tablets at a time, but both tablets must be ingested within one (1) minute. (Total Daily Dose = 400 mg).

Test Articles:
Treatment A:
Tramadol HC1 100 mg Extended Release Tablets
Manufacturer: By: [redacted] For: Biovail Corporation
Lot #: [redacted] 010206; Manufacturing Date: 07/23/01

Treatments B and C:
Tramadol HC1 200 mg Extended Release Tablets
Manufacturer: By: [redacted] For: Biovail Corporation
Lot #: [redacted] 010704; Manufacturing Date: 07/20/01

Sample Collection and Handling:
Day 1: 0.0 hour (pre-dose)
Day 2: No blood samples
Day 3, 4, 5: 0.0 hour (pre-dose)
Day 6: 0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0 and 20.0 hours post-0.0 hour drug administration

Day 7: 24.0 hours after 0.0-hour drug administration of Day 6
Day 8: No blood samples
Days 9, 10, 11: 0.0 hour (pre-dose)
Day 12: 0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0 and 20.0 hours post 0.0 hour drug administration

Day 13: 24.0 hours after 0.0-hour drug administration of Day 12
Day 14: No blood samples
Days 15, 16, 17: 0.0 hour (pre-dose;)
Day 18: 0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0 and 20.0 hours post-0.0 hour drug administration
Day 19: 24.0 hours after 0.0-hour drug administration of Day 18

Approximately 549.5 mL of blood was collected over the entire study periods, including the amount for pre-study test, hemoglobin tests done prior to dosing on Day 16 and post-study clinical blood tests.

The blood samples were stored in an ice bath prior to centrifugation and were centrifuged as soon as possible under refrigerated conditions at———————. The collected plasma from each blood collection tube was aliquotted into labeled, duplicate, polypropylene culture tubes, and stored frozen at minus (-) 25°C ± 10°C until assayed.

Sample Analysis: All plasma samples were delivered to the analytical facility (Bioanalytical Lab of BCR) after the completion of the clinical portion of the study for the analysis of tramadol, O-desmethyltramadol (Ml) and O, N-di-desmethyltramadol (M5), using a suitably validated and sensitive assay method. Full validation of the method, including precision, accuracy and reproducibility is included in the final report (T11-04, Appendix 6), along with a statement regarding the stability of the frozen samples. The analytical facility was blinded regarding the dosage regimen.

Pharmacokinetic and Statistical Analysis: Descriptive statistics were performed on the plasma concentrations of tramadol, and its metabolites O-desmethyltramadol (Ml) and O, N-di-desmethyltramadol (M5) at each sampling and for all the PK parameters: AUCτ, Cmax, Tmax, % fluctuation, % swing, Cmin, Cavg, and M/P ratio.

Linear regression analysis was performed to define the functional relationship between the pharmacokinetic parameters (AUCτ and Cmax) and different doses of Tramadol HC1 using SAS regression procedures.

ANOVA (a=0.05) was carried out on the dose-corrected pharmacokinetic parameters. The analysis of variance model included treatment as a factor.

Pharmacokinetic Results:
Reviewer's Note: Although levels of M5 were measured for this study, because M5 is pharmacologically less active than M1, only descriptive PK data are listed in the review. No further analysis of the M5 data was presented.

Steady-State Assessment
Steady state was reached for both tramadol and M1 metabolite at every dose level on Day 4 as predose levels were stable from Days 4 to 6 (Tables 2 and 3).

Table 2. Predose Tramadol Plasma Concentrations (Mean ± SD) Following Tramadol ER (100, 200, and 400 mg once-daily) Dosing.

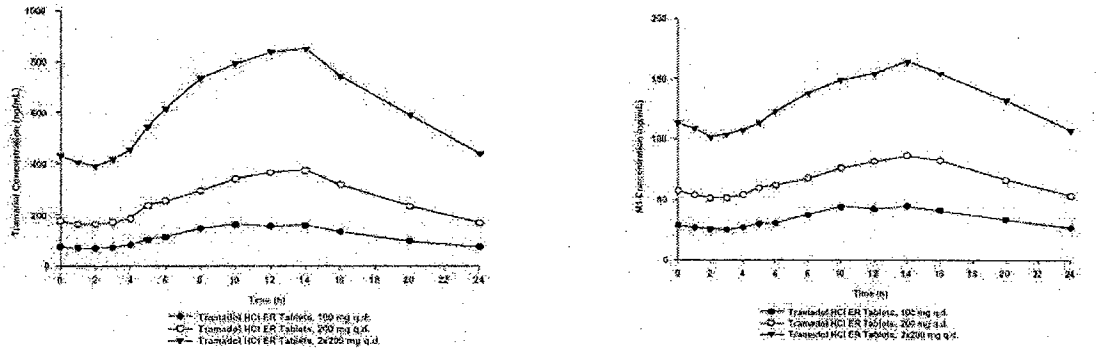
	Day 3 Post Dose	Day 4 Post Dose	Day 5 Post Dose	Day 6 Post Dose
100 mg	64 ± 46	76 ± 41	73 ± 42	74 ± 37
200 mg	141 ± 66	169 ± 88	166 ± 79	176 ± 88
400 mg	396 ± 176	438 ± 188	478 ± 229	431 ± 203

Table 3. Predose M1 Plasma Concentrations (Mean ± SD) Following Tramadol ER (100, 200, and 400 mg once-daily) Dosing.

	Day 3 Post Dose	Day 4 Post Dose	Day 5 Post Dose	Day 6 Post Dose
100 mg	27 ± 10	29 ± 9	29 ± 11	29 ± 9
200 mg	53 ± 18	57 ± 25	56 ± 21	58 ± 21
400 mg	116 ± 38	116 ± 33	122 ± 41	113 ± 38

PK Profiles

The mean steady-state plasma concentration-time profiles of tramadol and its metabolite M1 at 100 mg, 200 mg and 400 mg (2 x 200 mg) are shown in Figures 1a and 1b.



a. Tramadol b. M1

Figure 1. Mean Steady-State Plasma Tramadol (a) and M1 (b) Concentrations for 100-mg, 200-mg, and 2 x 200-mg (400-mg) Tramadol HCl ER Tablets.

The mean pharmacokinetic parameters for tramadol, O-desmethyltramadol (M1), and O,N-di-desmethyltramadol (M5) are summarized in Tables 4-6.

Table 4. Pharmacokinetic Parameters for Tramadol.

Pharmacokinetic Parameter	Tramadol HCl 100 mg Extended Release Tablets 1 x 100 mg (A) n = 25 Mean ± SD	Tramadol HCl 200 mg Extended Release Tablets 1 x 200 mg (B) n = 25 Mean ± SD	Tramadol HCl 200 mg Extended Release Tablets 2 x 200 mg (C) n = 25 Mean ± SD
AUC_τ (ng·hr/mL)	2778.41 ± 1141.24	6364.89 ± 2755.19	15212.75 ± 5754.59
C_{max} (ng/mL)	179.24 ± 62.68	408.99 ± 177.71	910.05 ± 319.71
C_{min} (ng/mL)	73.84 ± 42.63	168.58 ± 72.58	438.70 ± 213.20
T_{max} (hours)	11.68 ± 2.43	12.16 ± 2.23	12.00 ± 2.38
Degree of Fluctuation (%)	98.979 ± 41.628	94.697 ± 36.879	81.785 ± 38.392
C_{ave} (ng/mL)	115.77 ± 47.55	265.20 ± 114.80	633.86 ± 239.77

Table 5. Pharmacokinetic Parameters for O-desmethyltramadol (M1).

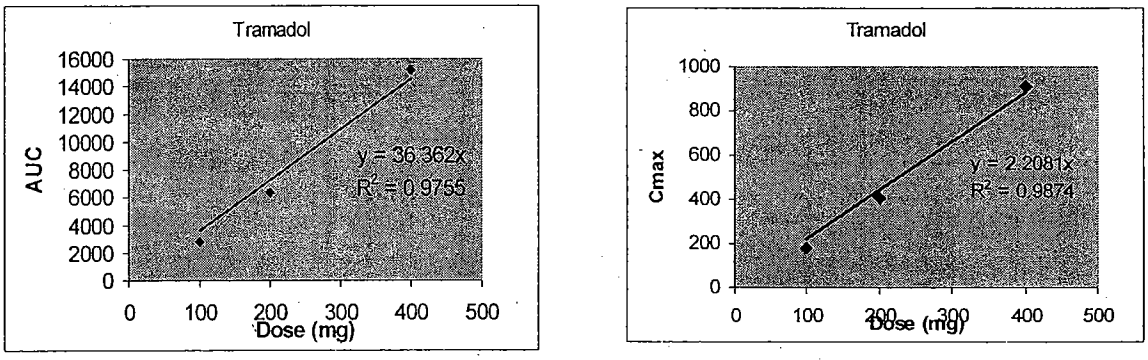
Pharmacokinetic Parameter	Tramadol HCl 100 mg Extended Release Tablets 1 x 100 mg (A) n = 25 Mean ± SD	Tramadol HCl 200 mg Extended Release Tablets 1 x 200 mg (B) n = 25 Mean ± SD	Tramadol HCl 200 mg Extended Release Tablets 2 x 200 mg (C) n = 25 Mean ± SD
AUC_τ (ng·hr/mL)	846.73 ± 210.51	1640.53 ± 574.72	3189.17 ± 973.87
C_{max} (ng/mL)	48.01 ± 11.53	91.29 ± 34.19	169.06 ± 48.75
C_{min} (ng/mL)	26.95 ± 10.71	53.42 ± 19.00	107.23 ± 39.88
T_{max} (hours)	12.32 ± 2.50	13.16 ± 2.70	14.00 ± 2.83
Degree of Fluctuation (%)	62.399 ± 32.222	56.637 ± 33.742	49.717 ± 26.325
C_{ave} (ng/mL)	35.28 ± 8.77	68.36 ± 23.95	132.88 ± 40.58

Table 6. Pharmacokinetic Parameters for O, N-di-desmethyltramadol (M5).

Pharmacokinetic Parameter	Tramadol HCl 100 mg Extended Release Tablets 1 x 100 mg (A) n = 25 Mean ± SD	Tramadol HCl 200 mg Extended Release Tablets 1 x 200 mg (B) n = 25 Mean ± SD	Tramadol HCl 200 mg Extended Release Tablets 2 x 200 mg(C) n = 25 Mean ± SD
AUC_τ (ng·hr/mL)	388.96 ± 99.59	888.78 ± 314.74	2022.09 ± 589.81
C_{max} (ng/mL)	21.23 ± 5.30	47.19 ± 17.49	100.03 ± 27.51
C_{min} (ng/mL)	13.45 ± 4.88	32.66 ± 12.16	78.52 ± 27.41
T_{max} (hours)	13.36 ± 3.09	13.44 ± 3.93	15.36 ± 2.81
Degree of Fluctuation (%)	49.959 ± 30.658	40.952 ± 29.437	28.403 ± 20.472
C_{ave} (ng/mL)	16.21 ± 4.15	37.03 ± 13.11	84.25 ± 24.58

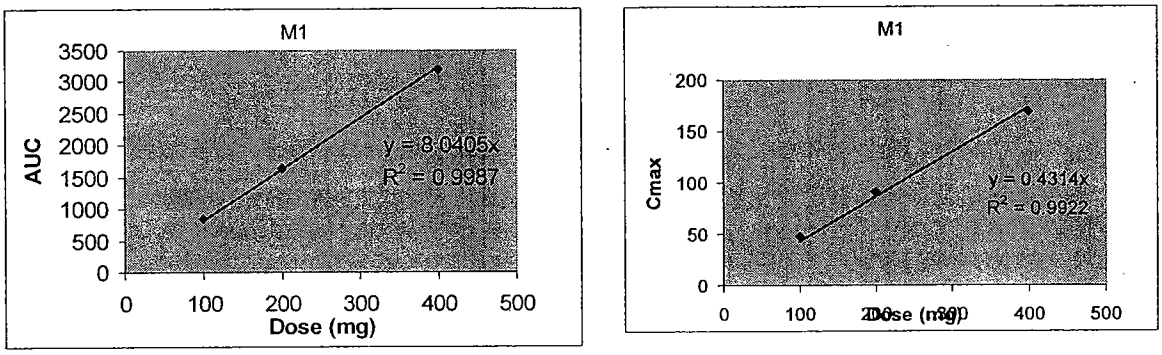
Dose Proportionality Analysis

Both AUCτ and Cmax of Tramdol and M1 exposure were dose-proportional to Tramadol ER doses (100, 200 and 40 mg) at steady state (Figures 2 and 3) as evidenced by the linear relationship between AUCτ and dose, and Cmax and dose.



a. AUCτ **b. Cmax**

Figure 2. Relationship between Tramdol AUCτ (a) and dose, and Cmax (b) and dose.



a. AUCτ **b. Cmax**

Figure 3. Relationship between M1 AUCτ (a) and dose, and Cmax (b) and dose.

The sponsor performed ANOVAs on dose-corrected log-transformed AUCτ and Cmax. The resulting p values of the t-test from the pair-wise comparisons among 100 (Trt A), 200 (Trt B) and 400 mg (Trt C) were summarized in Tables 7 and 8. The p-values for tramadol were greater than 0.05 except for AUCτ of treatments A and C. Most p-values obtained from metabolite M1 were also greater than 0.05. Therefore the ANOVA results on the dose-corrected data indicated that there was no significant differences in the pharmacokinetics among the dosing groups.

Table 7. P Value for Paired Comparison Among 100, 200 and 400 mg for Tramadol.

Parameter	Trt A - Trt B	Trt A - Trt C	Trt B - Trt C
C_{max}	0.4532	0.0627	0.2597
AUC_{τ}	0.4675	0.0319	0.1491

Table 8. P Value for Paired Comparison Among 100, 200 and 400 mg for M1.

Parameter	Trt A - Trt B	Trt A - Trt C	Trt B - Trt C
C_{max}	0.3011	0.1267	0.6162
AUC_{τ}	0.4490	0.4168	0.9560

Discussion and Conclusions:

Linear pharmacokinetics has been observed following multiple doses of 50 and 100 mg at steady state for Ultram (PDR). Results from this study suggest that the mean values of Cmax and AUCτ of tramadol increased as the administered dose increased in the range of 100 to 400 mg. Linear regression analysis of the pharmacokinetic data as well as ANOVA of dose corrected pharmacokinetic data indicated that AUCτ and Cmax increased proportionally with dose within the investigated dose range.

Appendix for Study 2552. Demographic Information.
Table A1. Demographic Data for All Subjects.

Subject No.	Race	Gender	Age (years)	Height (inches)	Weight (pounds)	Frame
01	Black	Female	28	68	174	Large
02	Caucasian	Male	35	67	152	Small
03	Caucasian	Female	30	62	139	Medium
04	Native	Male	34	74	182	Medium
05	Caucasian	Female	44	61	108	Small
06	Caucasian	Male	36	69	180	Medium
07	Caucasian	Male	28	65	144	Medium
08	Black	Male	21	68	131	Medium
09	Black	Female	46	64	158	Medium
10	Caucasian	Male	39	66	141	Medium
~~*11~~	~~Caucasian~~	~~Female~~	~~19~~	~~71~~	~~167~~	~~Large~~
~~*12~~	~~Caucasian~~	~~Male~~	~~29~~	~~68~~	~~176~~	~~Medium~~
13	Caucasian	Female	49	68	153	Medium
14	Caucasian	Male	39	69	170	Small
15	Caucasian	Female	29	65	119	Large
16	Caucasian	Male	33	73	193	Medium
17	Caucasian	Female	34	66	125	Medium
~~*18~~	~~Caucasian~~	~~Male~~	~~41~~	~~71~~	~~191~~	~~Medium~~
19	Caucasian	Female	32	67	143	Medium
20	Black	Male	35	67	148	Medium
21	Caucasian	Female	37	68	182	Large
22	Caucasian	Male	48	69	147	Medium
23	Caucasian	Female	27	68	140	Medium
24	Black	Male	30	74	190	Medium
~~*25~~	~~Caucasian~~	~~Female~~	~~21~~	~~62~~	~~107~~	~~Small~~
26	Caucasian	Male	27	65	140	Small
27	Caucasian	Female	30	64	124	Medium
~~*28~~	~~Caucasian~~	~~Male~~	~~30~~	~~74~~	~~191~~	~~Medium~~
29	Caucasian	Female	37	65	147	Medium
30	Caucasian	Male	36	71	185	Medium

Mean (All subjects)	**33**	**68**	**155**
S.D. (±)	8	4	26
Mean (Completing subjects*)	**35**	**67**	**153**
S.D. (±)	7	3	244

* Subjects #11, #12, #18, #25, and #28 did not complete the study. Subject #11 was dismissed pre-dose Day 3 due to adverse events. Subject #12 withdrew pre-dose Day 11 due to an adverse event. Subject #18 was dismissed post-dose Day 6 due to administrative reasons. Subject #25 withdrew post-dose Day 8 due to personal reasons. Subject #28 was dismissed pre-dose Day 14 due to adverse events.

Table A2. Demographic Characteristics for Subjects Who Completed the Study.

	N	%
Age (y)		
21-49	25	100
Race		
Caucasian	19	76
African American	5	20
NATIVE	1	4
Sex		
Male	13	52
Female	12	48

4.2.3 Study #2550 (B01-568PK-TRAP03): A Two-Way, Crossover, Open-Label, Single-Dose, Comparative Bioavailability Study of Tramadol HCl 200 mg Extended Release Tablets under Fasting and Fed Conditions in Normal Healthy Nan-Smoking Male and Female Subjects

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Study Period: November 27, 2001 to December 7, 2001
Period I: November 28, 2001
Period II: December 5, 2001

Sample Analysis Period: January 8, 2002 to January 17, 2002

Principle Investigator: Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.

Study Center: Biovail Contract Research (BCR) – 460 Comstock Road, Toronto, ON, M1L 4S4 Canada – 689 Warden Avenue, Units 1 & 2, Toronto, ON, M1L 4R6 Canada

Analytical Site: Bioanalytical Lab of BCR

Objectives: To investigate the effect of a high-fat meal on the bioavailability of Tramadol HCl 200 mg Extended Release Tablets given once daily under fasting and fed conditions.

Study Design: The study was performed as a randomized, open-label, analytically blinded, single-dose, two-way, crossover study in twenty-four (24) normal, healthy, non-smoking male and female subjects under fasting and fed conditions. Twenty-two (22) subjects (13 males and 9 females) completed the study. Please refer to Tables A1 and A2 in the Appendix for demographic information. Subjects# 12 and Subject#18 vomited during the dosing interval. PK data from these two subjects were excluded in the analysis.

Subjects were randomized to Sequence 1 or Sequence 2 (Table 1). There was a 7-day washout period between Treatment A and B.

Table 1. Study Design.

Sequence 1	Treatment A	Washout	Treatment B
Sequence 2	Treatment B	Washout	Treatment A

Treatment A:
Day 1: One (1) Tramadol HCl 200 mg Extended Release Tablet at 0.0 hour within five (5) minutes following the complete ingestion of a high-fat content breakfast (Total dose = 200 mg).

The subjects fasted overnight for at least ten (10) hours prior to being served the high fat content breakfast. The standard high-fat content breakfast consisted of the following: one (1) egg (fried), one (1) buttered English muffin, one (1) slice of American cheese, one (1) slice of Canadian bacon, one (1) serving of hash brown potatoes and eight (8) fluid ounces (240 mL) of whole milk. *(Reviewer's Note: This high-fat breakfast is acceptable.)*

Treatment B:
Day 1: One (1) Tramadol HCl 200 mg Extended Release Tablet at 0.0 hour with 240 mL of ambient temperature water following an overnight fast of at least ten (10) hours (Total dose = 200 mg).

Test Articles:
Tramadol HCl 200 mg Extended Release Tablets
Manufacturer: By: [redacted] For: Biovail Corporation
Lot #: [redacted] 010704; Manufacturing Date: 07/20/01

Sample Collection and Handling:
For each Study Perido: 0.0 hour (pre-dose), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0, 24.0, 36.0, and 48.0 hours post-0.0 hour drug administration

Approximately 251 mL of blood was collected over the two study periods, including the amount for pre-study test and post-study clinical blood tests.

The blood samples were stored in an ice bath prior to centrifugation and were centrifuged as soon as possible under refrigerated conditions at [redacted]. The collected plasma from each blood collection tube was aliquotted into labeled, duplicate, polypropylene culture tubes, and stored frozen at minus (-) 25°C ± 10°C until assayed.

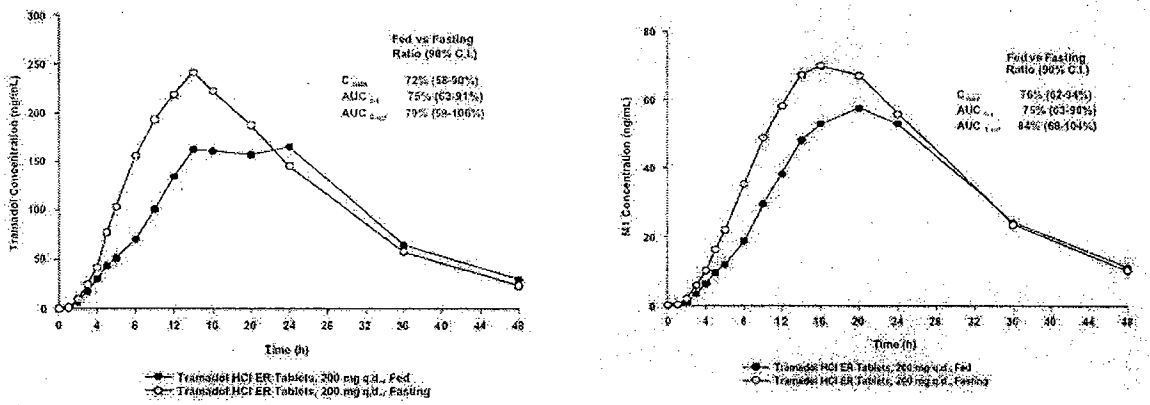
Sample Analysis: All plasma samples were delivered to the analytical facility (Bioanalytical Lab of BCR) after the completion of the clinical portion of the study for the analysis of tramadol, O-desmethyltramadol (Ml) and O, N-di-desmethyltramadol (M5), using a suitably validated and sensitive assay method. Full validation of the method, including precision, accuracy and reproducibility is included in the final report, along with a statement regarding the stability of the frozen samples (T11-02, Appendix 6 of the study report). The analytical facility was blinded regarding the dosage regimen.

Pharmacokinetic and Statistical Analysis: Descriptive statistics were performed on the plasma concentrations of tramadol, and its metabolites O-desmethyltramadol (Ml) and O, N-di-desmethyltramadol (M5) at each sampling and for all the PK parameters outlined in the protocol.

Analysis of variance (ANOVA) was performed on the pharmacokinetic parameters and log-transformed AUC0-t, AUC0-inf and Cmax. Based on the pair-wise comparisons of the log-transformed AUC0-t, AUC0-inf and Cmax data, the intra-subject coefficient of variation (CV), the relative ratios of the geometric means (fed/fast), and the 90% geometric confidence intervals (CI) were determined.

Pharmacokinetic Results:
Reviewer's Note: Although levels of M5 were measured for this study, because M5 is pharmacologically less active than M1, only descriptive PK data for M5 are listed in the review. No further analysis of the M5 data was presented.

PK Profiles
The mean plasma concentration-time profiles of tramadol and its metabolite M1 following Tramadol ER (200 mg) administration under fasting and fed conditions are shown in Figures 1a and 1b.



a. Tramadol b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations After Single Dosing With Tramadol HCl ER Tablets (200 mg) Administered Under Fasting and Fed Conditions.

The mean pharmacokinetic parameters for tramadol, O-desmethyltramadol (M1), and O, N-di-desmethyltramadol (M5) without Subjects #12 and #18 (who vomited during dosing) are summarized in Tables 2-4.

Table 2. Pharmacokinetic Parameters for Tramadol.

Pharmacokinetic Parameter (mean ±SD)	Tramadol HCl 200 mg Extended Release Tablet (Fed) (A) (n=20)	Tramadol HCl 200 mg Extended Release Tablet (Fasting) (B) (n=20)
AUC_{0-t} (ng·hr/mL)	4468.95 ± 2046.52	5331.25 ± 1657.56
AUC_{0-inf} (ng·hr/mL)	5154.17 ± 2426.50	5670.37 ± 1927.20
C_{max} (ng/mL)	207.42 ± 130.14	257.99 ± 75.37
T_{max} (hours)	17.10 ± 4.97	13.80 ± 2.50
$t_{1/2}$ (hours)	10.44 ± 7.45	8.90 ± 2.16
K_{el} (hour $^{-1}$)	0.083 ± 0.031	0.082 ± 0.020
MRT (hour)	25.61 ± 10.14	22.10 ± 3.13

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

Pharmacokinetic Parameter (mean ±SD)	Tramadol HCl 200 mg Extended Release Tablet (Fed) (A) (n=20)	Tramadol HCl 200 mg Extended Release Tablet (Fasting) (B) (n=20)
AUC_{0-t} (ng·hr/mL)	1457.50 ± 529.45	1739.20 ± 415.10
AUC_{0-inf} (ng·hr/mL)	1618.66 ± 477.71	1885.24 ± 495.78
C_{max} (ng/mL)	63.61 ± 27.45	74.92 ± 20.10
T_{max} (hours)	21.01 ± 3.15	17.10 ± 4.18
$t_{1/2}$ (hours)	9.19 ± 2.37	9.75 ± 2.32
K_{el} (hour $^{-1}$)	0.080 ± 0.022	0.075 ± 0.017
MRT (hour)	25.23 ± 3.28	24.44 ± 3.06
M/P Ratio (AUC_{0-inf})	0.4033 ± 0.2088	0.3862 ± 0.1497

Table 4. Pharmacokinetic Parameters for O, N-di-desmethyltramadol (M5).

Pharmacokinetic Parameter (mean ±SD)	Tramadol HCl 200 mg Extended Release Tablet (Fed) (A) (n=20)	Tramadol HCl 200 mg Extended Release Tablet (Fasting) (B) (n=20)
AUC_{0-t} (ng·hr/mL)	618.25 ± 235.60	776.73 ± 261.52
AUC_{0-inf} (ng·hr/mL)	763.61 ± 299.47	873.21 ± 272.23
C_{max} (ng/mL)	23.96 ± 8.25	31.28 ± 11.96
T_{max} (hours)	22.21 ± 4.20	18.20 ± 3.89
$t_{1/2}$ (hours)	11.45 ± 3.76	11.74 ± 2.97
K_{el} (hour $^{-1}$)	0.067 ± 0.022	0.062 ± 0.015
MRT (hour)	28.89 ± 5.60	27.62 ± 4.04
M/P Ratio (AUC_{0-inf})	0.1891 ± 0.0367	0.1959 ± 0.0692

Relative Bioavailability

The relative bioavailability analysis results for AUC0-t, AUC0-inf and Cmax, transformed using the natural logarithm, are summarized without Subject #12 and #18 in Table 5.

Table 5. Relative Bioavailability Analysis of Fed (Test) versus Fasting (Reference) for Tramadol and M1 Following 200 mg Tramadol ER Administration.

Parameter	Tramadol		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	64.38% - 95.79%	78.53%	36.05%
AUC_{0-inf}	62.96% - 116.69%	85.71%	41.38%
C_{max}	56.97% - 91.70%	72.27%	43.18%

Parameter	O- desmethyltramadol (M1)		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	63.59% - 94.84%	77.66%	36.26%
AUC_{0-inf}	73.68% - 114.40%	91.81%	18.45%
C_{max}	60.27% - 96.44%	76.24%	42.65%

Discussion and Conclusions:

This study compared the rate and extent of absorption of Tramadol HCl 200 mg Extended Release Tablet under fed conditions relative to that under fasting conditions. The relative bioavailability of the tramadol from two treatments was assessed by a comparison of AUC_{0-t}, AUC_{0-inf} and C_{max} after a single dose administration. The ratios of test-to-reference on the mean data for the three parameters between the two treatments were not within 80.00% - 125.00% range. Food (a high fat meal) decreased both rate and extent of absorption of tramadol. C_{max} and AUC_{0-inf} of tramadol decreased 28% and 16%, respectively in the presence of food (based on geometric mean ratio of fed vs. fasting). Mean T_{max} increased by 3 hours (from 14 hr fasting to 17 hr fed). Similar results were observed for M1 and M5. Therefore, there was a food-effect on the rate and extent of the absorption of tramadol from this extended release product. The clinical significance of the food effect is unknown. The study results also indicated that there was no dose dumping for this ER product under fed conditions.

Appendix for Study 2550. Demographic Information.

Table A1. Demographic Data for All Subjects.

Subject No.	Race	Gender	Age (years)	Height (inches)	Weight (pounds)	Frame
01	Caucasian	Male	37	74	190	Medium
02	Black	Female	29	70	147	Medium
03	Asian	Male	41	69	182	Medium
04	Caucasian	Female	27	65	133	Medium
05	Caucasian	Male	28	70	153	Medium
06	Black	Female	40	67	126	Medium
07	Caucasian	Male	41	69	182	Medium
08	Caucasian	Female	28	66	129	Medium
09	Caucasian	Male	46	70	140	Medium
10	Caucasian	Male	29	74	184	Medium
11	Asian	Male	22	66	137	Small
12	Caucasian	Female	42	66	139	Medium
13	Caucasian	Male	43	68	184	Large
~~*14~~	~~Caucasian~~	~~Female~~	~~22~~	~~66~~	~~139~~	~~Medium~~
15	Caucasian	Male	34	72	210	Large
16	Caucasian	Female	24	62	125	Medium
17	Black	Male	38	66	157	Medium
18	Black	Female	41	65	136	Medium
~~*19~~	~~Black~~	~~Male~~	~~21~~	~~68~~	~~177~~	~~Medium~~
20	Asian	Female	28	66	132	Medium
21	Black	Male	28	75	217	Large
22	Caucasian	Male	34	69	184	Medium
23	Caucasian	Male	40	71	191	Medium
24	Black	Female	38	64	145	Medium

Mean (All subjects)	33	68	160
S.D. (±)	7.6	3.3	28.2
Mean (Completing subjects*)	34	69	174
S.D. (±)	5.5	4.3	34.8

* Subjects #14 and #19 did not complete the study due to adverse events consisting of an abnormal ECG and a positive urine pregnancy test.

Table A2. Demographic Characteristics for Subjects Who Completed the Study.

	N	%
Age (y)		
22-46	22	100
Race		
Caucasian	13	59.1
African American	6	27.3
Asian	3	13.6
Sex		
Male	13	59.1
Female	9	40.9

4.2.4 Study #2696 (B03-623PK-P03P1): A Two-Way, Crossover, Open-Label, Single-Dose, Fasting, Dosage Strength Equivalence Study of Tramadol HCl ER 1 x 300 mg Tablet Versus Tramadol HCl ER 3 x 100 mg Tablets In Normal Healthy Non-Smoking Male and Female Subjects

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Study Period:	April 24, 2003 to May 8, 2003 Period I: April 26, 2003 Period II: May 2, 200
Sample Analysis Period:	May 7, 2003 to May 20, 2003
Principle Investigator:	Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.
Study Center:	Biovail Contract Research (BCR) – 460 Comstock Road, Toronto, ON, M1L 4S4 Canada – 689 Warden Avenue, Units 1 & 2, Toronto, ON, M1L 4R6 Canada
Analytical Site:	Bioanalytical Lab of BCR

Objectives: To determine the dosage strength equivalence between two strengths of Tramadol HCl Extended Release Tablets (1 x 300 mg q.d. versus 3 x 100 mg q.d.) under fasting conditions.

Study Design: The study was performed as a randomized, open-label, analytically blinded, single-dose, two-way, crossover study in twenty-six (26) normal, healthy, non-smoking male and female subjects under fasting conditions. Twenty-three (23) subjects (13 males and 10 females) completed the study. Please refer to Tables A1 and A2 in the Appendix for demographic information.

Subjects were randomized to Sequence 1 or Sequence 2 (Table 1). There was a 5-day washout period between Treatment A and B.

Table 1. Study Design.

Sequence 1	Treatment A	Washout	Treatment B
Sequence 2	Treatment B	Washout	Treatment A
Treatment A: Day 1: One Tramadol HCl Extended Release 300 mg Tablet with 240 mL of ambient temperature water following an overnight fast of at least ten hours (Treatment dose = 300 mg). *Treatment B:* Day 1: Three Tramadol HCl Extended Release 100 mg Tablets with 240 mL of ambient temperature water following an overnight fast of at least ten hours (Treatment dose = 300 mg).			

Test Articles:
Treatment A (Test):
Tramadol HCl 300 mg Extended Release Tablets
Manufacturer: Biovail Corporation, Steinbach, Manitoba
Lot #: 02J126; Expiry Date: 07/03

Treatment B (Reference):
Tramadol HCl 100 mg Extended Release Tablets
Manufacturer: Biovail Corporation, Steinbach, Manitoba
Lot #: 02H218; Expiry Date: 07/03

Sample Collection and Handling:
For each Study Period: 0.0 hour (pre-dose), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0, 24.0, 30.0, 36.0, and 48.0 hours post-0.0 hour drug administration

Approximately 270 mL of blood was collected over the two study periods, including the amount for pre-study test and post-study clinical blood tests.

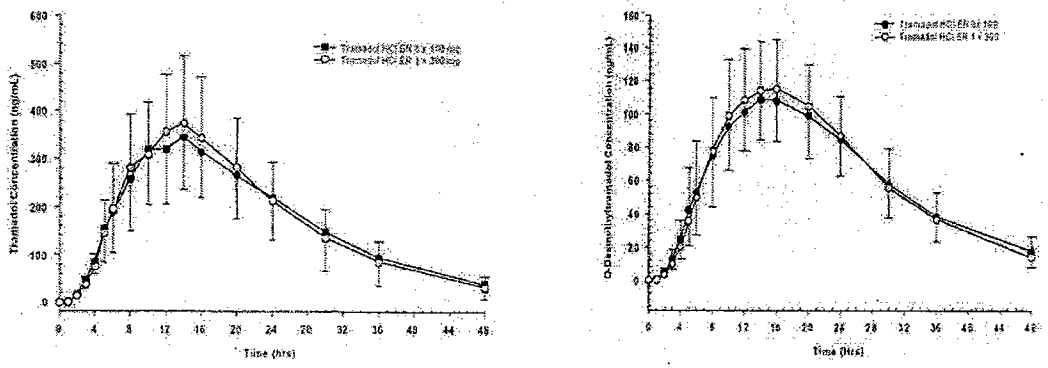
The blood samples were stored in an ice bath prior to centrifugation and were centrifuged as soon as possible under refrigerated conditions [redacted] The collected plasma from each blood collection tube was aliquotted into labeled, duplicate, polypropylene culture tubes, and stored frozen at minus (-) 25°C ± 10°C until assayed.

Sample Analysis: All plasma samples were delivered to the analytical facility (Bioanalytical Lab of BCR) after the completion of the clinical portion of the study for the analysis of tramadol, O-desmethyltramadol (Ml) and O, N-di-desmethyltramadol (M5), using a suitably validated and sensitive assay method. Full validation of the method, including precision, accuracy and reproducibility is included in the analytical report (T11-08a, Appendix 6 of the study report), along with a statement regarding the stability of the frozen samples. The analytical facility was blinded regarding the dosage regimen.

Pharmacokinetic and Statistical Analysis: Descriptive statistics were performed on the plasma concentrations of tramadol, and its metabolites O-desmethyltramadol (Ml) and O, N-di-desmethyltramadol (M5) at each sampling and for all the PK parameters outlined in the protocol.

Analysis of variance (ANOVA) was performed on the pharmacokinetic parameters and log-transformed AUC0-t, AUC0-inf and Cmax. Based on the pair-wise comparisons of the log-transformed AUC0-t, AUC0-inf and Cmax data, the intra-subject coefficient of variation (CV), the relative ratios of the geometric means (Treatment A/Treatment B), and the 90% geometric confidence intervals (CI) were determined.

Pharmacokinetic Results:
PK Profiles
The mean plasma concentration-time profiles of tramadol and its metabolite M1 following Tramadol ER (1 x 300 mg and 3 x 100mg) administration under fasting conditions are shown in Figures 1a and 1b. *(Reviewer's Note: PK profile for M5 is not shown.)*



a. Tramadol b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations After Single Dosing With 1 x 300-mg Versus 3 x 100-mg Tramadol HCl ER Tablets Under Fasting Conditions.

The pharmacokinetic parameters (mean ± SD) for tramadol, O-desmethyltramadol (M1), and O, N-di-desmethyltramadol (M5) are summarized in Tables 2-4.

Table 2. Pharmacokinetic Parameters for Tramadol.

Pharmacokinetic Parameters	Tramadol HCl Extended Release 300 mg Tablets (A) (n = 23) (Mean ± SD)	Tramadol HCl Extended Release 100 mg Tablets (B) (n = 23) (Mean ± SD)
AUC_{0-t} (ng·hr/mL)	8099.63 ± 2657.50	8145.75 ± 2832.14
AUC_{0-inf} (ng·hr/mL)	8710.51 ± 3154.58	8568.98 ± 3174.70
C_{max} (ng/mL)	379.69 ± 110.39	401.20 ± 140.94
T_{max} (hr)	13.22 ± 3.00	13.39 ± 3.04
$t_{1/2}$ (hr)	9.08 ± 2.81	8.31 ± 1.93
K_{el} (hr^{-1})	8.29E-02 ± 2.34E-02	8.73E-02 ± 1.79E-02
MRT (hr)	22.00 ± 4.46	20.92 ± 2.66

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

Pharmacokinetic Parameters	Tramadol HCl Extended Release 300 mg Tablets (A) (n = 23) (Mean ± SD)	Tramadol HCl Extended Release 100 mg Tablets (B) (n = 23) (Mean ± SD)
AUC_{0-t} (ng·hr/mL)	2855.06 ± 808.04	2884.60 ± 735.04
AUC_{0-inf} (ng·hr/mL)	3163.61 ± 922.32 *	3087.39 ± 788.30
C_{max} (ng/mL)	117.65 ± 37.50	124.87 ± 32.22
T_{max} (hr)	14.96 ± 3.90	14.70 ± 2.61
$t_{1/2}$ (hr)	10.39 ± 2.81 †	9.30 ± 2.07
K_{el} (hr^{-1})	7.16E-02 ± 1.94E-02 †	7.77E-02 ± 1.53E-02
MRT (hr)	24.67 ± 4.31 *	23.46 ± 2.99

* n=21

† n=22

Reviewer's Note: When AUC(0-t)/AUC(0-inf) < 80%, the respective AUC(0-inf) and MRT were excluded from the statistical analysis.

Table 4. Pharmacokinetic Parameters for O, N-di-desmethyltramadol (M5).

Pharmacokinetic Parameters	Tramadol HCl Extended Release 300 mg Tablets (A) (n = 23) (Mean ± SD)	Tramadol HCl Extended Release 100 mg Tablets (B) (n = 23) (Mean ± SD)
AUC_{0-t} (ng·hr/mL)	1016.71 ± 278.16	1065.19 ± 298.67
AUC_{0-inf} (ng·hr/mL)	1103.13 ± 334.97 *	1167.40 ± 337.75 ‡
C_{max} (ng/mL)	38.52 ± 10.97	42.62 ± 12.94
T_{max} (hr)	16.96 ± 5.25	17.57 ± 4.26
$t_{1/2}$ (hr)	11.80 ± 4.19 †	10.33 ± 2.50 ‡
K_{el} (hr^{-1})	6.50E-02 ± 2.02E-02 †	7.08E-02 ± 1.60E-02 ‡
MRT (hr)	25.00 ± 3.56 *	25.87 ± 3.67 ‡

* n=16
† n=20
‡ n=22

Relative Bioavailability

The relative bioavailability analysis results for AUC_{0-t}, AUC_{0-inf} and C_{max}, transformed using the natural logarithm, are summarized in Table 5.

Table 5. Relative Bioavailability Analysis for Tramadol, M1, and M5 Following Tramadol HCl ER 1 x 300 mg Tablet (A) versus Tramadol HCl ER 3 x 100 mg Tablet (B) Administration.

Parameters	Tramadol		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	97.48% - 104.84%	101.10%	7.11%
AUC_{0-inf}	99.18% - 106.93%	102.98%	7.35%
C_{max}	91.34% - 106.74%	98.74%	15.22%

Parameters	O-Desmethyltramadol			O-N-di-Desmethyltramadol		
	90% C.I.	Ratio of Means	Intra-Subject CV	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	94.81% - 102.52%	98.59%	7.65%	93.19% - 101.17%	97.09%	8.03%
AUC_{0-inf}	96.13% - 105.81%	100.85%	8.97%	92.63% - 102.55%	97.46%	8.10%
C_{max}	86.69% - 99.16%	92.72%	13.12%	86.02% - 98.41%	92.01%	13.14%

Discussion and Conclusions:

This study compared the rate and extent of absorption of one Tramadol HCl 300 mg Extended Release Tablet relative to that of 3 x 100 mg Tramadol ER tablets under fasting conditions. The relative bioavailability of the tramadol from two treatments (Treatment A vs. Treatment B) was assessed by a comparison of AUC_{0-t}, AUC_{0-inf} and C_{max} after a single dose administration. The

ratios of test (A)-to-reference (B) on the mean data for the three parameters between the two treatments were within 80.00% - 125.00% range. Similar results were observed for M1 and M5. Therefore, the 100 mg and 300 mg Tramadol HCl ER tablets are dosage strength equivalent.

Appendix for Study 2696. Demographic Information.

Table A1. Demographic Data for All Subjects.

Subject No.	Race	Gender	Age (years)	Height (m)	Weight (kg)	BMI (kg/m^2)
01	Caucasian	Male	29	1.88	91	25.75
~~*02~~	~~Caucasian~~	~~Female~~	~~44~~	~~1.63~~	~~62~~	~~23.34~~
03	Caucasian	Male	35	1.78	79	24.93
~~*04~~	~~Caucasian~~	~~Female~~	~~19~~	~~1.65~~	~~61~~	~~22.41~~
05	Caucasian	Male	23	1.78	80	25.25
~~*06~~	~~Caucasian~~	~~Female~~	~~39~~	~~1.63~~	~~68~~	~~25.59~~
07	Black	Male	22	1.78	74	23.36
08	Caucasian	Female	44	1.75	74	24.16
09	Caucasian	Male	20	1.85	83	24.25
10	Caucasian	Female	41	1.63	69	25.97
11	Caucasian	Male	44	1.75	75	24.49
12	Caucasian	Female	26	1.60	57	22.27
13	Black	Male	31	1.85	75	21.91
14	Caucasian	Female	25	1.73	77	25.73
15	Caucasian	Male	23	1.73	71	23.72
16	Asian	Female	27	1.68	58	20.55
17	Asian	Male	44	1.80	80	24.69
18	Caucasian	Female	25	1.63	54	20.32
19	Caucasian	Male	44	1.80	80	24.69
20	Caucasian	Female	28	1.68	60	21.26
21	Asian	Male	28	1.73	67	22.39
22	Black	Female	43	1.63	67	25.22
23	Black	Male	30	1.80	74	22.84
24	Caucasian	Female	37	1.83	69	20.60
25	Caucasian	Male	26	1.80	81	25.00
26	Caucasian	Female	34	1.80	73	22.53

Mean (All subjects)	32	1.74	72	23.59
S.D. (±)	9	0.08	9	1.74
Range: Minimum	19	1.60	54	20.32
Maximum	44	1.88	91	25.97
Mean (Completing subjects*)	32	1.75	73	23.56
S.D. (±)	8	0.08	9	1.79
Range: Minimum	20	1.60	54	20.32
Maximum	44	1.88	91	25.97

* Subjects #02, #04, and #06 did not complete the study. Subject #06 was dismissed during the confinement period of Period I due to adverse events. Subject #04 withdrew during the washout

period of Period I due to adverse events. Subject #02 was dismissed during the washout period of Period I due to adverse events.

Table A2. Demographic Characteristics for Subjects Who Completed the Study.

	N	%
Age (y)		
20-44	23	100
Race		
Caucasian	16	69.6
African American	4	17.4
Asian	3	13.0
Sex		
Male	13	56.5
Female	10	43.5

4.2.5 Study #2287-2 (B99-426PK-TRAP03): A Three-Way, Single-Dose, Open-Label, Fasting Comparative Bioavailability Study of the Scale Up and Pilot Formulations of Tramadlol Hydrochloride Extended-Release Tablets (3x100 mg o.d.) under Different Study Conditions (Morning, Evening) in Normal Healthy Non-Smoking Male and Female Volunteers

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Study Period: February 8, 2000 to February 25, 2000
Period I: February 8, 2000
Period II: February 15, 2000
Period III: February 22, 2000

Sample Analysis Period: March 6, 2000 to May 1, 2000

Principle Investigator: Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.

Study Center: Biovail Contract Research (BCR) – 460 Comstock Road, Toronto, ON, M1L 4S4 Canada – 689 Warden Avenue, Units 1 & 2, Toronto, ON, M1L 4R6 Canada

Analytical Site: Bioanalytical Lab of BCR

Objectives: To compare the effect of two study conditions (morning and night time dosing) on the scaled-up formulation of Tramadol HCl Extended Release Tablets (Regimens A and C). The second object is to compare the bioavailability of the scaled-up formulation to a pilot formulation, Tramadol HCl Extended Release Tablets (Regimen B) under the morning study condition.

Reviewer's Note: Only the first objective (i.e., AM vs. PM dosing with scale-up formulation) has been reviewed in detail. Because only scale-up formulations were used in pivotal PK and clinical trials, the relative bioavailability between scale-up and pilot formulations has not been reviewed in detail.

Study Design: The study was performed as a randomized, open-label, analytically blinded, single-dose, three-way, crossover study in thirty (30) normal, healthy, non-smoking male and female subjects under fasting conditions (24 plus 6 alternatives). Twenty-six (26) subjects (15 males and 11 females) completed the study. Please refer to Tables A1 and A2 in the Appendix for demographic information.

Subjects were randomized to Sequences 1 to 6 (Table 1). There was a 6-day washout period between each treatment.

Table 1. Study Design.

	Period I	Period II	Period III
Sequence 1	A	B	C
Sequence 2	A	C	B
Sequence 3	B	A	C
Sequence 4	B	C	A
Sequence 5	C	A	B
Sequence 6	C	B	A

Treatment A:
Day 1: Three Tramadol HCl Extended Release 100 mg Tablet (scale-up formulation) with 240 mL of water following an overnight fast (Treatment dose = 300 mg).

Treatment B:
Day 1: Three Tramadol HCl Extended Release 100 mg Tablets (pilot formulation) with 240 mL of water following an overnight fast (Treatment dose = 300 mg).

Treatment C:
Day 1: Three Tramadol HCl Extended Release 100 mg Tablets (scale-up formulation) with 240 mL of water dosed at 10 pm, 4 hours after an evening meal. Blood draws through the night. (Treatment dose = 300 mg).

Test Articles:
Treatments A and C:
Tramadol HCl 100 mg Extended Release Tablets
Manufacturer: [redacted] For: Bioavail Corporation International
[redacted] Lot #: 000103; Manufacturing Date: 1/27/00

Treatment B:
Tramadol HCl 100 mg Extended Release Tablets
Manufacturer: [redacted] For: Bioavail Corporation International
Lot #: 2162; Manufacturing Date: 12/99

Sample Collection and Handling:
For each Study Period: 0.0 hour (pre-dose), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0, 30.0, 36.0, and 48.0 hours post-0.0 hour drug administration

Approximately 360 mL of blood was collected over the three study periods, including the amount for pre-study test and post-study clinical blood tests.

The blood samples were stored in an ice bath prior to centrifugation and were centrifuged as soon as possible under refrigerated conditions within 15 minutes of venipuncture. The collected plasma from each blood collection tube was aliquotted into labeled, duplicate, polypropylene culture tubes, and stored frozen at minus (-) 15°C or colder until assayed.

Sample Analysis: All plasma samples were delivered to the analytical facility (Bioanalytical Lab of BCR) after the completion of the clinical portion of the study for the analysis of tramadol, O-desmethyltramadol (Ml) and O, N-di-desmethyltramadol (M5), using a suitably validated and sensitive LC/MS/MS assay method (T11-00). This method is valid from the range of 2.00 ng/mL to 1023.75 ng/mL for tramadol, 0.99 ng/mL to 506.51 ng/mL for M1, and 0.97 ng/mL to 496.64 ng/mL for M5. The analytical facility was blinded regarding the dosage regimen.

Pharmacokinetic and Statistical Analysis: The analytical determination, PK and statistical analysis were conducted on 24 evaluable subjects that completed the study according to the protocol (Samples for Subjects#29 and #30 were not analyzed). Descriptive statistics were performed on the plasma concentrations of tramadol, and its metabolites O-desmethyltramadol (Ml) and O, N-di- desmethyltramadol (M5) at each sampling and for all the PK parameters outlined in the protocol.

Analysis of variance (ANOVA) was performed on the pharmacokinetic parameters and log-transformed AUC0-t, AUC0-inf and Cmax. Based on the pair-wise comparisons of the log-transformed AUC0-t, AUC0-inf and Cmax data, the intra-subject coefficient of variation (CV), the relative ratios of the geometric means (Treatment C/Treatment A), and the 90% geometric confidence intervals (CI) were determined.

Pharmacokinetic Results:

PK Profiles

The mean plasma concentration-time profiles of tramadol and its metabolite M1 following Tramadol ER (3 x 100mg) administration dosing at AM (Treatment A) and PM (Treatment C) under fasting conditions are shown in Figures 1a and 1b. *(Reviewer's Note: PK profile for M5 is not shown.)*

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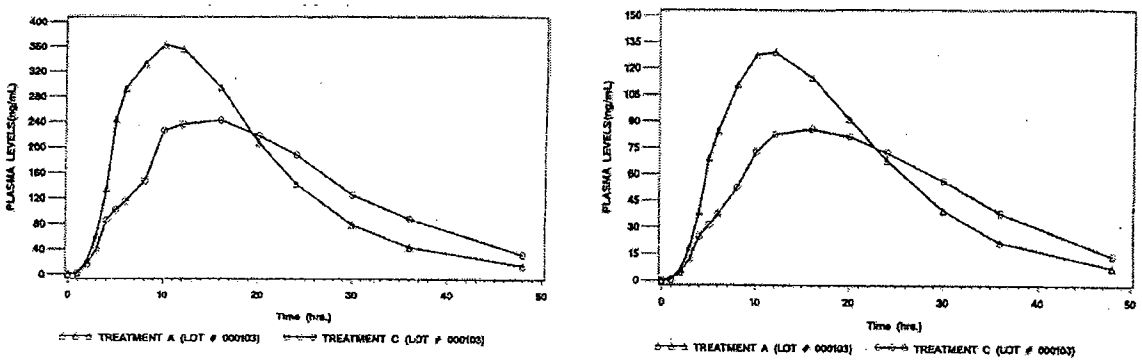

a. Tramadol b. M1

Figure 1. Mean Plasma Tramadol (a) and M1 (b) Concentrations After Single Dosing With 3 x 100-mg Tramadol HCl ER Tablets Dosing at AM (Treatment A, triagle) and PM (Treatment C, circle) Under Fasting Conditions.

The pharmacokinetic parameters (mean ± SD) for tramadol, O-desmethyltramadol (M1), and O, N-di-desmethyltramadol (M5) under different treatments are summarized in Tables 2-4.

Table 2. Pharmacokinetic Parameters for Tramadol.

Parameter	BIOVAIL (A) (AM) 3 x 100 mg Mean ± SD	BIOVAIL (B) (AM) 3 x 100 mg Mean ± SD	BIOVAIL (C) (PM) 3 x 100 mg Mean ± SD
AUC (0 - t) (ng.hr/mL)	6999.85 ± 2523.33	7111.29 ± 2221.38	6368.53 ± 2083.52
AUC (0 - inf) (ng.hr/mL)	7163.94 ± 2632.97	7526.01 ± 2338.85	6763.02 ± 2414.54
C_{max} (ng/mL)	378.00 ± 115.15	377.81 ± 102.14	270.19 ± 89.19
T_{max} (hours)	10.43 ± 2.63	10.58 ± 1.61	15.50 ± 5.28
$t_{1/2}$ (hours)	6.85 ± 1.56	7.43 ± 1.76	8.50 ± 2.50
K_{el} ($hour^{-1}$)	0.106 ± 0.025	0.099 ± 0.025	0.090 ± 0.034

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

Parameter	BIOVAIL (A) (AM) 3 x 100 mg Mean ± SD	BIOVAIL (B) (AM) 3 x 100 mg Mean ± SD	BIOVAIL (C) (PM) 3 x 100 mg Mean ± SD
AUC (0 - t) (ng.hr/mL)	2750.55 ± 876.34	2788.84 ± 937.28	2409.39 ± 716.84
AUC (0 - inf) (ng.hr/mL)	2836.41 ± 886.25	2964.68 ± 989.78	2607.44 ± 790.09
C_{max} (ng/mL)	136.00 ± 49.58	131.96 ± 53.85	94.41 ± 30.90
T_{max} (hours)	12.68 ± 3.25	13.08 ± 2.64	16.84 ± 6.50
$t_{1/2}$ (hours)	7.37 ± 1.61	8.06 ± 1.90	8.91 ± 1.85
K_{el} ($hour^{-1}$)	0.098 ± 0.020	0.091 ± 0.022	0.082 ± 0.020

Table 4. Pharmacokinetic Parameters for O, N-di-desmethyltramadol (M5).

Parameter	BIOVAIL (A) (AM) 3 x 100 mg Mean ± SD	BIOVAIL (B) (AM) 3 x 100 mg Mean ± SD	BIOVAIL (C) (PM) 3 x 100 mg Mean ± SD
AUC (0 - t) (ng.hr/mL)	1148.17 ± 388.90	1148.96 ± 357.64	1013.10 ± 376.39
AUC (0 - inf) (ng.hr/mL)	1222.43 ± 409.45	1276.57 ± 419.54	1180.01 ± 458.87
C_{max} (ng/mL)	50.46 ± 17.63	49.15 ± 15.93	38.04 ± 14.34
T_{max} (hours)	13.75 ± 3.30	15.67 ± 3.27	20.08 ± 4.74
$t_{1/2}$ (hours)	9.12 ± 3.09	10.00 ± 3.59	11.60 ± 4.25
K_{el} ($hour^{-1}$)	0.083 ± 0.022	0.076 ± 0.022	0.067 ± 0.025

Relative Bioavailability

The relative bioavailability analysis (PM/AM) results for AUC_{0-t}, AUC_{0-inf} and C_{max}, transformed using the natural logarithm, are summarized in Table 5.

Table 5. Relative Bioavailability Analysis (PM/AM) for Tramadol, M1, and M5 Following Tramadol HCl ER 1 x 300 mg Tablet (PM, Test) versus Tramadol HCl ER 3 x 100 mg Tablet (AM, Reference) Administration.

Tramadol

	AUC (0 - t)	AUC (0 - infinity)	C_{max}
90% Geometric C.I.[4]	84% - 96%	87% - 101%	65% - 77%
Ratio of Means[5]	90%	94 %	71 %
CV[6]	13.51%	13.79 %	16.85 %

M1

	AUC (0 - t)	AUC (0 - infinity)	C_{max}
90% Geometric C.I.[4]	82% - 92%	85% - 96%	63% - 74%
Ratio of Means[5]	87%	90 %	69 %
CV[6]	11.76%	12.24 %	15.38 %

M5

	AUC (0 - t)	AUC (0 - infinity)	C_{max}
90% Geometric C.I.[4]	80% - 91%	86% - 99%	70% - 79%
Ratio of Means[5]	86%	92 %	74 %
CV[6]	13.39%	13.89 %	12.13 %

[4] 90% Geometric Confidence Interval using log-transformed data and Biovail (A) as the reference, calculated based on two-way C vs. A comparison.

[5] Calculated using geometric means according to the formula: $e^{(C-A)}$ x 100%, calculated based on two-way C vs. A comparison.

[6] Intra-subject coefficient of variation for log-transformed pharmacokinetic parameter, calculated based on two-way C vs. A comparison.

Discussion and Conclusions:

This study compared dosing in the morning (Treatment A) vs. dosing in the evening (Treatment C) with the tablets from the scaled-up batch. Evening administration of the ER formulation

resulted in a significant reduction and delay in the rate of drug absorption but did not reduce the total amount absorbed. Compared to morning dosing, C_{max} and $AUC_{0\text{-}inf}$ of tramadol decreased 29% and 6%, respectively after evening administration of the tablet. T_{max} increased by 5 hr (15 hr PM vs. 10 hr AM). The 90% geometric confidence intervals based on the evening-to-morning ratio of geometric means for tramadol $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ were within 80% to 125%. However, the results for C_{max} were outside the 80% to 125% limit (<80%). The same qualitative similarities and differences between the dosing conditions were observed for the M1 and M5 metabolites as well. The differences in the profiles may be related to a slowing in gastrointestinal transit during the night compared with the daytime. This diurnal effect in drug absorption may have implications in the pharmacodynamic effect and should be included in the labeling.

Appendix for Study 2287-2. Demographic Information.

Table A1. Demographic Data for All Subjects.

SUBJECT NO.	SUBJECT INITIALS	RACE	GENDER	AGE (years)	HEIGHT (inches)	WEIGHT (pounds)	SMOKER	FRAME	SERUM CREATININE (umol/L)
01		White	Male	40	69	200	No	Large	117
02		White	Male	39	72	189	No	Medium	88
03		White	Male	35	73	180	No	Medium	89
04		White	Male	35	71	207	No	Large	115
05		White	Male	30	75	173	No	Medium	88
06		White	Male	25	74	200	No	Medium	104
07		White	Male	42	68	145	No	Medium	90
08		White	Male	19	74	193	No	Medium	85
09		White	Male	36	72	212	No	Large	89
10		White	Male	38	71	158	No	Medium	94
11		White	Male	43	72	190	No	Large	92
12		Black	Male	25	70	185	No	Medium	83
13		White	Male	27	74	189	No	Medium	102
14		White	Male	35	67	155	No	Medium	83
15		White	Male	24	69	157	No	Medium	83
16		Mulatto	Female	28	65	126	No	Medium	61
17		Black	Female	20	63	166	No	Large	55
18		White	Female	30	67	182	No	Large	51
19		White	Female	39	67	185	No	Large	70
20		White	Female	44	67	153	No	Large	56
21		White	Female	32	68	126	No	Medium	68
22		White	Female	37	66	151	No	Medium	73
23		White	Female	28	67	123	No	Medium	67
24		White	Female	19	67	131	No	Medium	65
25		White	Female	29	63	118	No	Medium	59
26		White	Female	43	65	166	No	Large	83
27		Hispanic	Female	41	61	121	No	Medium	58
28		White	Female	21	65	166	No	Large	75
29		White	Female	28	64	129	No	Medium	52
30		White	Female	39	66	125	No	Medium	70
			MEAN	32	68	163			
			S.D.(±)	7.7	3.7	28.4			

Subjects #18, #21, #26, and #28 did not complete the study. Subject #18 withdrew prior to Period II due to personal reasons; Subject #21 was dismissed during Period II due to adverse events; and Subject #26 withdrew prior to Period III and Subject #28 withdrew during Period III, both due to personal reasons.

Table A2. Demographic Characteristics for Subjects Who Completed the Study and Whose Data were Analyzed.

	N	%
Age (y)		
19-44	24	100
Race		
Caucasian	20	83.3
African American	2	8.3
Hispanic	1	4.2
Mulatto	1	4.2
Sex		
Male	15	62.5
Female	9	37.5

4.2.6 Study #109316 (B02-589PK-P03P1): Steady State Pharmacokinetics of Tramadol HCL Extended-Release Tablets in Healthy Individuals and Patients with Mild and Moderate Renal Failure

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Study # B02-589PK-P03P1

Study Title:	Steady State Pharmacokinetics of Tramadol HCL Extended-Release Tablets in Healthy Individuals and Patients with Mild and Moderate Renal Failure
Objectives:	To estimate and to compare plasma and urine pharmacokinetic parameters of tramadol and 2 of its metabolites (M1 and M5) in healthy volunteers and in patients with mild or moderate renal impairment. • To delineate the steady-state pharmacokinetics of Tramadol HCl Extended-Release Tablets, 100 mg in mild and moderate renal failure patients compared to healthy volunteers with normal renal function. • To assess the safety of single and multiple doses of Tramadol HCl Extended Release tablets, 100 mg in patients with mild and moderate chronic renal failure.
Study Design:	Open-label, multiple-dose, parallel study
Treatment:	All subjects received a single oral dose of one Tramadol HCl Extended Release Tablet (Lot #:02C139 by Bioavail Corporation, Canada), 100 mg with 240 mL of water in the morning for 6 consecutive days, Following an 10-hour overnight fast
PK Sampling	Blood Samples: 10m per sample on Day 1, 3, 4, 5 at 0 hr (pre-dose) and on Day 6 at 0 hr (pre-dose) 2, 3, 4, 6, 8, 10, 12, 14, 18, and 24 hours post-dose. Urine Samples: On day 1 at 0 hr (pre-dose) and on Day 6, at 0 hr (pre-dose) and 0-2, 2-4, 408, 8-12, 12-24 hr post dose.
PK Parameters and Statistical Analysis:	AUCtau, Cmax, Tmax, Cmin, Cavg, Fluctuation, CLr, Metabolite/Parent ratio (AUC tau). Descriptive statistics and ANOVA using SAS
Study Population:	The study population consisted of 18 completers (15 M and 3 F): 6 healthy, 6

	mild renal failure (MiRF) and 6 with moderate renal failure (MoRF). (Applicant stated that sample size was agreed upon by FDA (fax dated June 25th, 2002). Subject 206 was excluded from the final statistical analysis as the subject's plasma concentration values were below BLQ for all analytes on Days 5 and 6 suggesting a lack of compliance to the treatment.

Population Description (sample size)	**Creatinine Clearance (mL/min) mean (SD)/[range]**	**Mean (SD) Age (yrs) [range]**	**Mean Weight (lbs) [range]**	**Height (inches) [range]**	***Sex/Race**
#Normal renal function (n=6)	110.50 (28.42)/ [91.0-167.0]	55.8 (1.2) [55-58]	171.8 (23.3) [134-194]	68.6 (4.2) [64-73]	6M/4C&2AA
Mild renal impairment (n = 5)	53.00 (2.97)/ [50.0-56.0]	68.3 (6.9) [61-79]	181.3 (42.9) [120.2-238.0]	66.1 (4.7) [58-72]	5M &1F/3C & 3AA
Moderate renal impairment (n=6)	41.17 (7.65)/ [31.0-49.0]	54.2 (10.3) [41-70]	174 (55.1) [127.2-244.0]	68.6 (4.3) [62-73]	4M &2F/6AA

*M=male, F= female, C=Caucasian, AA= African American
Guidance Definition: Normal => 80 mL/min, Mild = 50-80 ml/min, Moderate 30-50 mL/min, Severe renal impairment < 30 mL/min, ESRD requiring dialysis

Analytical Methods:	A validated LC/MS/MS assay method was used to determine the concentrations of tramadol and its metabolites-desmethyltramadol (M1) and O, N-di-desmethyltramadol (M5) in plasma and urine.		
Compound	Tramadol	O-Desmethyltramadol (M1)	O,N-di-desmethyltramadol (M5)
Internal Standard (IS)	Diltiazem	Diltiazem	Diltiazem
Matrix	**Plasma**	**Plasma**	**Plasma**
Accuracy (%) *Within–Day* *Between-Day*			
Precision (CV %) *Within-day* *Between-Day*			
Standard curve range	2.00 to 1024.42 ng/mL Mean r = 0.999 (N = 5)	1.00 to 512.31 Mean r = 0.998 (N = 5)	1.00 to 512.16 Mean r = 0.999 (N = 5)
Sensitivity (LOQ)			
Selectivity	No interfering peaks @ retention time of tramadol	No interfering peaks @ retention time of M1	No interfering peaks @ retention time of M5
Mean Recovery (%CV)			
Stability	degradation @ -25°C for 115 days and, < degradation after 3 freeze-thaw cycles	degradation @ -25°C for 115 days and, % degradation after 3 freeze-thaw cycles	degradation @ -25°C for 115 days and, degradation after 3 freeze-thaw cycles
Conclusions	Method validation acceptable	Method validation acceptable	Method validation acceptable

Method	LC/MS/MS	LC/MS/MS	LC/MS/MS
Compound	Tramadol	O-Desmethyltramadol (M1)	O, N-di-desmethyltramadol (M5)
Internal Standard (IS)	Not stated	Not stated	Not stated
Matrix	**Urine**	**Urine**	**Urine**

Accuracy (%) ***Within–Day*** ***Between-Day***	[redacted]	[redacted]	[redacted]
Precision (CV %) ***Within-day*** ***Between-Day***	[redacted]	[redacted]	[redacted]
Standard curve range	0.195 to 49.996 ng/mL Mean r = 0.998 (N = 5)	0.049 to 12.503 Mean r = 0.998 (N = 5)	0.049 to 12.503 Mean r = 0.996 (N = 5)
Sensitivity (LOQ)	[redacted]	[redacted]	[redacted]
Selectivity	No interfering peaks @ retention time of tramadol	No interfering peaks @ retention time of M1	No interfering peaks @ retention time of M5
Mean Recovery % (%CV)	[redacted]	[redacted]	[redacted]
Stability	[redacted] degradation @ room temperature, at -25 °C ± 10 °C and -70 °C for 154 days and after 3 freeze thaw cycles @-70 °C ± 10 °C.	[redacted] degradation @ room temperature -70 °C and after 3 freeze thaw cycles @-70 °C ± 10 °C	[redacted] degradation @ room temperature, at-25 °C ± 10 °C and -70 °C for 154 days and after 3 freeze thaw cycles @ -70 °C ± 10 °C.
Conclusions	Method validation acceptable	Method validation acceptable	Method validation acceptable

Results:

Plasma Concentrations

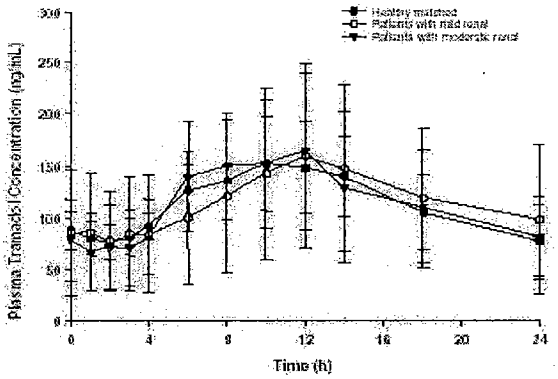

Figure 36 Mean Plasma Tramadol Concentrations in Patients With Mild or Moderate Renal Impairment and Healthy Subjects During QD Dosing With Tramadol HCl ER

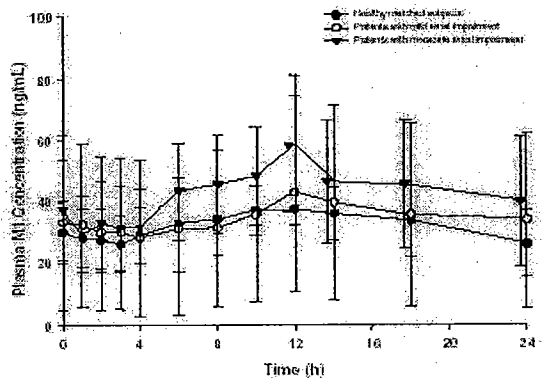

Figure 37 Mean Plasma M1 Concentrations in Patients With Mild or Moderate Renal Impairment and Healthy Subjects During QD Dosing With Tramadol HCl ER

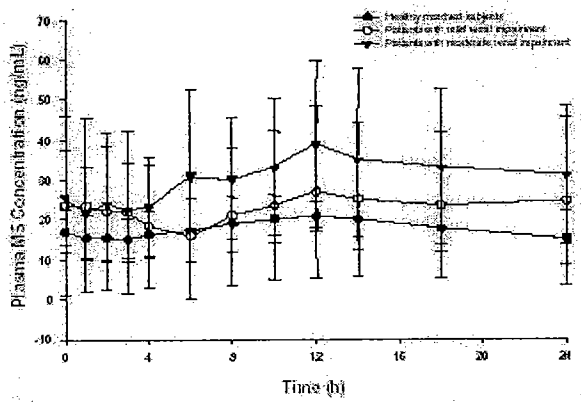

Figure 38 Mean Plasma M5 Concentrations in Patients With Mild or Moderate Renal Impairment and Healthy Subjects During QD Dosing With Tramadol HCl ER

Reviewer's comments: Although the scales of the graphs above look very compressed they do indicate that renal impairment increases the plasma concentrations of the M1 and M5 metabolites. The effects of renal impairment on tramadol are difficult to interpret from the graph but the individual data does suggest that there some increase in plasma concentrations in the moderately impaired patients however, this is not consistent in all patients as reflected by the high variability associated with the data.

Tramadol

The PK parameters (AUCtau, Cmax, Cmin and Cavg) all appeared to be higher in the Mild RF group, however this was not observed in the Moderate RF group. The parameters for the Moderate RF group were similar to those of the healthy volunteers. There was no statistical difference ($p > 0.5$) for tramadol Cmax, AUCtau, Cmin, Cavg, degree of fluctuation or CLr between the 3 groups. There was no significant correlation ($p > 0.05$ and r values were 0.1030 and 0.1581) between Cmax and AUCtau and creatinine clearance (CLcr). The amount of unchanged tramadol excreted and the renal clearance of tramadol decreased in patients with the

moderate renal impairment. The trend was not statistically significant (p=0.1435). Tramadol renal clearance did not significantly correlate with creatinine clearance (p > 0.05 and r=0.3279).

M1 metabolite

The PK parameters (AUCtau, Cmax, and Cavg) all appeared to increase with the severity of the renal impairment. (HV < MiRF< MoRF). There was no statistical difference (p > 0.05) for O-Desmethyltramadol Cmax, Tmax, AUCtau, Cmin, and Cavg between the 3 groups. There was no significant correlation (p> 0.05 and r =0.3243 and 0.2173) between Cmax or AUCtau and creatinine clearance (CLcr).

The amount of unchanged O-Desmethyltramadol excreted and its renal clearance decreased by 50% in patients with mild or moderate renal impairment. The trend was statistically significant (p=0.0057). In addition, O-Desmethyltramadol renal clearance showed a significant correlation with creatinine clearance (p=0.0018 and r = 0.6992).

M5 metabolite

The PK parameters (AUCtau, Cmax, and Cavg) all appeared to increase with the severity of the renal impairment. (HV < MiRF< MoRF). There was no statistical difference (p > 0.05) for O-N-di-Desmethyltramadol Cmax, Tmax, AUCtau, Cmin, and Cavg between the 3 groups. There was no significant correlation between Cmax or AUCtau and creatinine clearance (CLcr).

The amount of unchanged O-N-di-Desmethyltramadol excreted decreased in patients with renal impairment. Similarly, the renal clearance of O-N-di-Desmethyltramadol decreased with the decrease of the renal function. This difference was statistically significant (p < 0.001). O-N-di-Desmethyltramadol renal clearance significantly correlated with creatinine clearance (r = 0.8024, p = 0.001).

Table 9D – p-values for the Pharmacokinetic Parameters for Tramadol, O-desmethyltramadol (M1) and O,N-di-desmethyltramadol (M5)

Parameter	Tramadol	O-Desmethyltramadol (M1)	O, N-Didesmethyltramadol (M5)
AUC_τ	0.4770	0.7951	0.4667
C_{max}	0.7142	0.4993	0.3188
C_{min}	0.2618	0.9965	0.7219
C_{av}	0.4770	0.7951	0.4669
T_{max}	0.1653	0.4305	0.5328
Fluctuation	0.2038	N/AP	N/AP
CL_r	0.1435	0.0057	<0.001
M/P ratio	N/AP	0.4963	0.1953

Reviewer's comments

The MiRF patients and the MoRF patients presented an overall higher systemic exposure to tramadol and its 2 metabolites. For both metabolites the metabolic ratio increased with the severity of the renal impairment.

Urinary clearance of tramadol and its 2 metabolites appeared to decrease in patients with renal failure. This difference was statistically significant for M1 and M5. The applicant concluded that despite the lack of significance of these observations, for tramadol dosage adjustment may be needed when administering Tramadol ER to renally impaired patients. The question is what would the dosage adjustment be based on?

4.2.7 Study #B02-590PK-P03P1: Steady State Stereospecific Pharmacokinetics of Tramadol HCL Extended-Release Tablets in Patients with Mild and Moderate Hepatic Impairment

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Study #: B02-590PK-P03P1

Study Title:	Steady State Stereospecific Pharmacokinetics of Tramadol HCL Extended-Release Tablets in Patients with Mild and Moderate Hepatic Impairment
Objectives:	To delinate the stereospecific pharmacokinetics of tramadol HCl extended-release tablets, patients with mild and moderate hepatic insufficiency and to compare to those in healthy volunteers under steady-state, fasting conditions.
Study Design:	Open-label, multiple-dose, parallel study
Treatment:	All subjects received a single oral dose of one Tramadol HCl Extended Release Tablet (Lot #:02C139 by Bioavail Corporation, Canada), 100 mg with 240 mL of water in the morning for 6 consecutive days, following an 10-hour overnight fast
PK Sampling	7 mL/sample of blood was collected as follows: Days 1, 3, 4, 5: 0 hr (pre-dose)- and Day 6: 0 (pre-dose), 1, 2, 3, 4, 6, 8, 10, 12, 14, 18, 24 h.
PK Parameters and Statistical Analysis:	AUCtau, Cmax, Tmax, Cmin, Cavg, Fluctuation, CLr, Metabolite/Parent ratio (AUC tau). Descriptive statistics and ANOVA using SAS. The primary comparison was to determine if pharmacokinetic differences existed between the healthy matched subjects and mild and moderate hepatic impaired patients.
Study Population:	The study population consisted of 18 completers (16 M and 2 F): 6 age and weight matched healthy, 6 mild hepatic impairment and 6 with moderate hepatic impairment. (Number agreed upon with FDA in fax dated June 25th, 2002).

Population Description (sample size)	**Child-Pugh score**	**Mean (SD) Age (yrs) [range]**	**Mean Weight (Kg) [range]**	**Height (inches) [range]**	**Sex/Race** M=male, F= female, C=Caucasian, H= Hispanic
Healthy Subjects (n=6)	Not Applicable	50.5 (6.6) [41-61]	80.9 (7.9) [69.4-92.5]	171 (10.8) [152-183]	5M &1F/5H & 1C
Mild Hepatic impairment (n = 6)	5-6	53 (5.3) [49-63]	84.9 (14.7) [71.2-107.9]	171.2 (9.6) [168-183]	5M & 1F/5C&1H
Moderate Hepatic impairment (n=6)	7-9	52.7 (3.3) [49-57]	84.7 (15.8) [65.3-104.8]	171.5 (8.5) [160-183]	6M /4C & 2H

Assay Methods:	An enantiospecific validated LC/MS/MS method equipped with a chiral column assay was used to determine the concentrations of (+/-) tramadol and its metabolite-(+/-) desmethyltramadol (M1) in plasma. The assay method was developed and validated

	(effective on September 23rd, 2002) for a range of 10 to 400ng/mL for each tramadol and M1 enantiomer. However, the quantitation range was not appropriate for the study samples. A number of study samples were BLQ (8 for tramadol, many for M1), and only limited PK data analysis was feasible with the reported values. Consequently, the method was revalidated (effective February, 2003) to accommodate a lower concentration range. A report of the re-validated method is reported in the table below:			
Compound	(+) Tramadol	(-) Tramadol	(+) O-desmethyltramadol	(-) O-desmethyltramadol
Internal Standard (IS)	(+) Tramadol – D6	(-) Tramadol – D6	(+)M1 – D3	(+) M1 – D3
Accuracy (%) *Within-Day* *Between-Day*	[redacted]			
Precision (CV %) *Within-day* *Between-Day*	[redacted]			
Standard curve range	5 to 200 ng/mL (r^2 = 0.9999, N=3)	5 to 200 ng/mL (r^2 = 0.9999, N=3)	1 to 40 ng/mL (r^2 = 0.9997, N=3)	1 to 40 ng/mL (r^2 = 0.9998, N=3)
Sensitivity (LOQ)	[redacted]			
Selectivity	No significant interferences were observed at the retention times of tramadol, (+/-), M1 (+/-), or the internal standards.			
Mean Recovery	[redacted]			
Stability	4 Freeze thaw cycles, 70 hrs storage, 8 week storage [redacted] degradation.	4 Freeze thaw cycles, 70 hrs storage [redacted] degradation.	4 Freeze thaw cycles, 70 hrs storage < [redacted] degradation.	4 Freeze thaw cycles, 70 hrs storage [redacted] %.degradation
Conclusions	Method validation is acceptable. Validation data shows that method is reproducible for its intended use. Although samples were stored for about 6 months before they could be analyzed again using the re-validated method, a comparison of the plasma concentrations obtained before re-validation and after re-validation were within +/- 20 % of each other. This means the values obtained with the revalidation were probably ~ 20 % less than what may have been obtained with the original samples.			

Results:

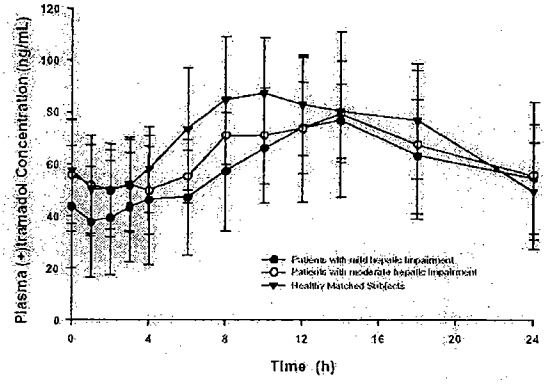

Figure 39 Mean Plasma (+)Tramadol Concentration-Time Profile for Patients With Mild or Moderate Liver Disease and in Healthy Subjects During QD Dosing With Tramadol HCl ER

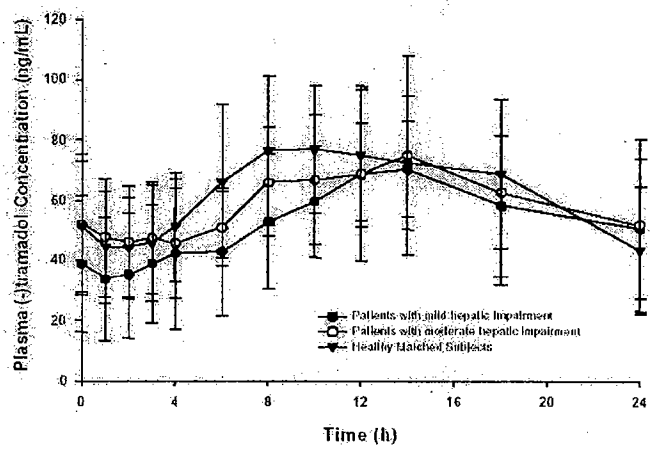

Figure 40 **Mean Plasma (-)Tramadol Concentration-Time Profile for Patients With Mild or Moderate Liver Disease and In Healthy Subjects During QD Dosing With Tramadol HCl ER**

Reviewer's comments: Mean exposure of both enantiomers of tramadol is somewhat lower in the patients with mild and moderate hepatic impairment compared to the healthy subjects

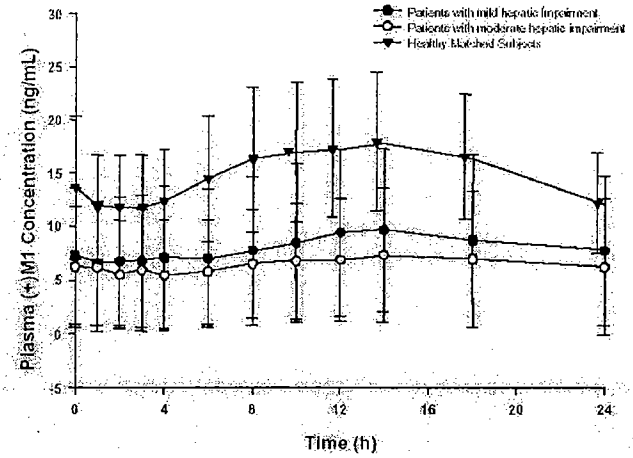

Figure 41 **Mean Plasma (+)M1 Concentration-Time Profile for Patients With Mild or Moderate Liver Disease and In Healthy Subjects During QD Dosing With Tramadol HCl ER**

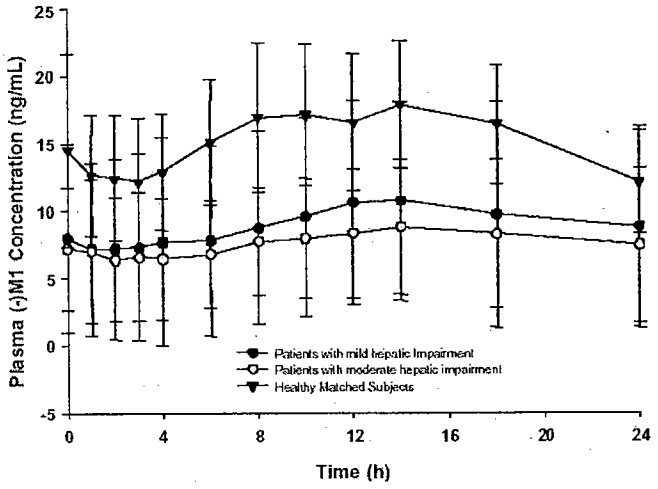

Figure 42 Mean Plasma (-)M1 Concentration-Time Profile for Patients With Mild or Moderate Liver Disease and in Healthy Subjects During QD Dosing With Tramadol HCl ER

Reviewer's comments: Mean exposure of both enantiomers of M1 is lower (~ 50%) in patients with mild and moderate hepatic impairment compared to healthy subjects. The patients with moderate hepatic impairment had a lower exposure.

PK parameters

Table 15. Metabolite:Parent Ratio for (+) and (-) enantiomers of tramadol and O-desmethyltramadol in mild and moderately impaired hepatic patients and in healthy matched subjects.

Subject (Mild)	AUC, (ng ·hr/mL) (+) Tramadol	(+) M1	(M/P) Ratio	Subject (Moderate)	AUC, (ng ·hr/mL) (+) Tramadol	(+) M1	(M/P) Ratio	Subject (Healthy)	AUC, (ng ·hr/mL) (+) Tramadol	(+) M1	(M/P) Ratio
101	1140.89	19.62	0.018	201	2352.10			301	1809.90	429.25	0.251
102	1238.00			202	1082.05	187.05	0.163	302	2349.65	497.90	0.224
103	1374.95	205.42	0.156	203	918.40	70.39	0.081	303	1413.95	304.90	0.250
104	2258.15	458.70	0.214	204	1906.30	360.45	0.200	304	996.70	326.50	0.340
105	1059.40	242.80	0.242	205	1538.75	60.87	0.042	305	1862.75	121.62	0.068
106	1393.55	245.92	0.188	206	1436.35	268.39	0.189	306	1736.30	467.75	0.279
Mean	1405.49	234.09	0.164		1539.33	187.03	0.139		1697.98	361.65	0.237
SD	435.33	156.21	0.087		529.17	126.89	0.072		457.15	135.50	0.093
CV (%)	30.89	66.73	53.36		34.38	67.85	52.05		26.93	37.47	39.24

Subject (Mild)	AUC, (ng ·hr/mL) (-) Tramadol	(-) M1	(M/P) Ratio	Subject (Moderate)	AUC, (ng ·hr/mL) (-) Tramadol	(-) M1	(M/P) Ratio	Subject (Healthy)	AUC, (ng ·hr/mL) (-) Tramadol	(-) M1	(M/P) Ratio
101	101	1125.34	54.66	0.051	201	2339.35	105.40	0.048	301	1738.75	379.10
102	102	1209.75	47.17	0.041	202	1039.85	216.29	0.222	302	2319.95	455.85
103	103	1300.15	230.13	0.179	203	792.85	78.98	0.105	303	1391.80	259.94
104	104	2179.05	538.10	0.251	204	1814.40	378.70	0.220	304	769.90	334.21
105	105	993.05	219.79	0.234	205	1535.05	91.60	0.063	305	1372.25	252.15
106	106	963.15	219.84	0.243	206	1085.65	227.20	0.221	306	1524.70	519.66
Mean	1292.41	216.73	0.168		1434.36	183.52	0.147		1519.56	356.82	0.275
SD	453.14	178.31	0.093		576.29	115.35	0.084		567.69	106.84	0.110
CV (%)	35.06	82.27	55.50		40.18	62.86	57.12		33.41	29.13	39.90

(M/P) ratio = Metabolite/Parent Ratio

(+)Tramadol Pharmacokinetic Analysis

Pharmacokinetic Parameter	Geometric Least Squares Mean Ratio	p-value
Healthy Subjects Vs. Mild Hepatic Impaired Patients		
AUC_t	0.83	0.4855
C_{max}	0.89	0.6383
T_{max}	1.23	0.4614
C_{min}	0.66	0.3266
C_{ave}	0.83	0.4855
MRT	1.05	0.2161
%Fluctuation	1.39	0.4146
Healthy Subjects Vs. Moderate Hepatic Impaired Patients		
AUC_t	0.89	0.7456
C_{max}	0.93	0.8573
T_{max}	1.09	0.8863
C_{min}	0.95	0.9626
C_{ave}	0.89	0.7456
MRT	1.01	0.9457
%Fluctuation	1.02	0.9967

(-)Tramadol Pharmacokinetic Analysis

Pharmacokinetic Parameter	Geometric Least Squares Mean Ratio	p-value
Healthy Subjects Vs. Mild Hepatic Impaired Patients		
AUC_t	0.86	0.6880
C_{max}	0.92	0.8399
T_{max}	1.30	0.2844
C_{min}	0.68	0.3742
C_{ave}	0.86	0.6880
MRT	1.06	0.2294
%Fluctuation	1.42	0.3594
Healthy Subjects Vs. Moderate Hepatic Impaired Patients		
AUC_t	0.93	0.9130
C_{max}	0.98	0.9681
T_{max}	1.09	0.8748
C_{min}	1.00	1.0000
C_{ave}	0.93	0.9130
MRT	1.01	0.9450
%Fluctuation	1.03	0.9922

(+)O-desmethyl tramadol Pharmacokinetic Analysis

Pharmacokinetic Parameter	Geometric Least Squares Mean Ratio	p-value
Healthy Subjects Vs. Mild Hepatic Impaired Patients		
AUC_t	0.49	0.3243
C_{max}	0.56	0.3987
T_{max}	1.38	0.2726
C_{min}	0.88	0.9255
C_{ave}	0.49	0.3243
MRT	1.09	0.3407
%Fluctuation	2.05	0.3603
Healthy Subjects Vs. Moderate Hepatic Impaired Patients		
AUC_t	0.45	0.2605
C_{max}	0.45	0.2011
T_{max}	1.10	0.8434
C_{min}	0.51	0.1550
C_{ave}	0.45	0.2605
MRT	0.99	0.9845
%Fluctuation	0.69	0.9022

Pharmacokinetic Parameter	Geometric Least Squares Mean Ratio	p-value
Healthy Subjects Vs. Mild Hepatic Impaired Patients		
AUC_t	0.44	0.0941
C_{max}	0.49	0.1215
T_{max}	1.45	0.1770
C_{min}	0.54	0.2646
C_{ave}	0.44	0.0941
MRT	1.08	0.2325
%Fluctuation	2.01	0.2713
Healthy Subjects Vs. Moderate Hepatic Impaired Patients		
AUC_t	0.44	0.0926
C_{max}	0.45	0.0781
T_{max}	1.39	0.2636
C_{min}	0.47	0.1295
C_{ave}	0.44	0.0926
MRT	1.01	0.9561
%Fluctuation	0.95	0.9966

Applicant's Conclusions:

- Overall extended release tramadol hydrochloride tablets were well tolerated as a single daily dose of 100 mg for 6 days when administered under fasting conditions; no new or unexpected adverse events were reported.

- The objective of this study was to delineate the stereospecific pharmacokinetics of tramadol HCl extended release tablets in patients with mild and moderate hepatic insufficiency and compare to those in healthy volunteers. Based upon the data from 18 completing subjects, the results for (+) and (-)tramadol and its metabolite (+) and (-)O-desmethyltramadol indicate that the pharmacokinetics of tramadol are unaltered in mild and moderate hepatic impairment. In patients with hepatic cirrhosis, the plasma concentration and elimination half-life of tramadol were reported to have increased by a factor of 2 to 3 compared to patients with normal hepatic function. Contrary to this assumption, the present study did not show any difference in the stereoselective pharmacokinetics of tramadol and M1 between hepatic patients and normal volunteers. The reason for a lack of difference of the pharmacokinetic parameters between the 3 groups is unclear. It could be that there were confounding effects of the disease progression in the hepatic patients and the concomitant medications they were taking, and this led to the observation of similar results in the 3 groups. A comparison of the metabolite to parent ratio for the enantiomers of tramadol and M1 showed a trend (healthy>mild hepatic>moderate hepatic), however, there was no statistically significant difference between the three groups.

Reviewer's comments: In hepatically impaired patients one would have expected a decrease in metabolizing enzymes to result in higher levels of tramadol and lower levels of M1 and consequently lower metabolite to parent ratio values in hepatically impaired patients compared to healthy subjects. However, what was observed in this study was lower exposure and lower metabolite/plasma ratio in hepatically impaired patients of tramadol and M1 (more pronounced) compared to healthy volunteers. The lower exposure obtained in the hepatically impaired population does not imply a safety concern that requires a dosage adjustment in the mild or moderate he1patically impaired patient population. A comparison of the metabolite to parent ratio for the enantiomers of tramadol and M1 showed a trend (healthy>mild hepatic>moderate hepatic).

4.2.8 Study #2584 (B02-591PK-P03P1): Influence of CYP 2D6 Inhibition on Pharamcokinetics of Tramadol HCL Extended Release 100 mg Tablets in Normal Healthy Non-smoking Male and Female Subjects

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Study #: 2584 (B02-591PK-P03P1)

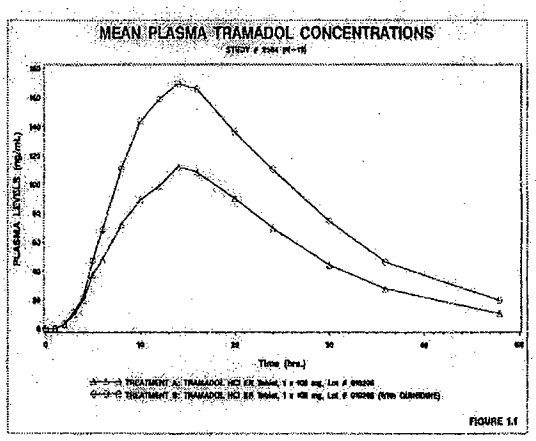
Study Title:	Influence of CYP 2D6 Inhibition on Pharamcokinetics of Tramadol HCL Extended Release 100 mg Tablets in Normal Healthy Non-smoking Male and Female Subjects
Objectives:	To evaluate the effect of CYP 2D6 inhibition on the pharmacokinetics of Tramadol Hydrochloride 100 mg ER Tablets under single-dose, fasting conditions. Quinidine sulfate was used as the CYP 2D6 inhibitor.
Study Design:	Two-way, open-label, single-dose design with a one (1) week washout period between study periods
Investigational Drugs:	Tramadol HCl Extended Release Tablet (Lot #:010206 by [redacted]) Quinidine Sulfate Tablets 200 mg (Lot # 46942 by [redacted]
Treatment:	*Treatment A: Period I, Day 1:* One Tramadol HCL 100 mg ER tablet (starting at 08:00)with 240 mL of ambient temperature water following an overnight fast of at least 10 hours *Treatment B: Period II, Day 1:* One Quinidine sulfate tablet 200 mg (starting at 18:00) with 240 mL of ambient temperature water following a fast of at least two hours *Period II, Day 2:* One Quinidine sulfate tablet 200 mg (starting at 06:00) with 240 mL of ambient temperature water following an overnight fast of at least eight hours. Subjects continued to fast for an additional two and a half (2.5) hours until dosing for the test drug. One Tramadol HCL 100 mg ER tablet (starting at 08:30) with 240 mL of ambient temperature water was then administered. The subjects continued to fast for an additional 4 hours following the test drug administration.
PK Sampling	During each study period, seventeen blood samples (7 mL each) were collected as follows:

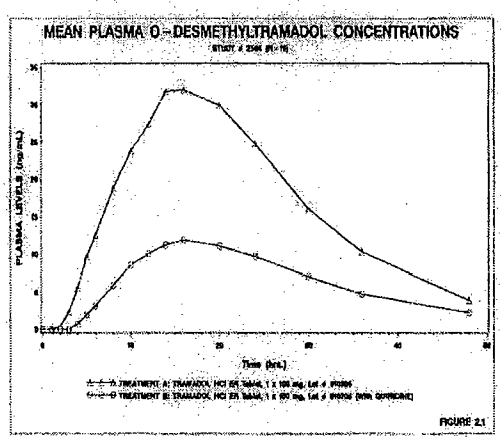
	Period I, Day 1 and Period II, Day 1: 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36 and 48 hours post drug-administration.
PK Parameters and Statistical Analysis:	AUCtau, Cmax, Tmax, Cmin, Cavg, Fluctuation, CLr, Metabolite/Parent ratio (AUC tau). Descriptive statistics and ANOVA using SAS. The primary comparison was to determine if pharmacokinetic differences existed between the healthy matched subjects and mild and moderate hepatic impaired patients.
Study Population:	24 subjects were enrolled, 19 competed the study, while 5 subjects completed only one period. The study population demographics was as follows: *Race:* 17 C, 3 Asian, 4 Black *Gender:*14 M, 10 F *Weight*: mean = 70 (9), range = 55-86 kg *Age*: mean =31 (8), range = 22- 48 years old *Height*: mean =171 (9), range = 152-185 cm 4 subjects were dismissed and 1 was withdrawn. #02 was dismissed during the confinement period I due to AEs, # 23 withdrew voluntarily during period I washout (W/O), # 16 dismissed during period I washout due to an AE, # 10 dismissed during W/O period II due to an AE, # 22 dismissed during W/O period II due to an AE.
Safety	The subjects were dismissed due to the following AEs: #02, pallor, dizziness, headache, nausea and sweating, #16, low blood pressure, # 10 and # 22, prolonged QTC. The relationship of these AEs to the study drugs are currently being reviewed by the medical officer.
Assay Methods:	A report of the validated LC with tandem MS assay method used to determine tramadol and its two metabolites (M1 and M5) in human plasma is reproduced in the table below:

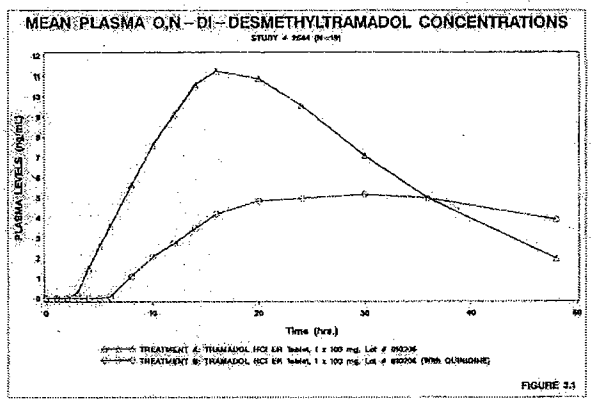
Compound	Tramadol	O-Desmethyltramadol	O, N-di--Desmethyltramadol
Internal Standard (IS)	Metoprolol	Metoprolol	Metoprolol
Accuracy (%) ***Within-Day*** ***Between-Day***	[redacted]		
Precision (CV %) ***Within-day*** ***Between-Day***	[redacted]		
Standard curve range	2.02 to 1031.74 ng/mL (r = 0.9990, N=3)	1.00 to 511.95 ng/mL (r = 0.9992, N=3)	0.97 to 496.64 ng/mL (r = 0.9982, N=3)
Sensitivity (LOQ)	[redacted]		
Mean Recovery (CV%)	[redacted]	[redacted]	[redacted]
Selectivity	No interferences observed at retention times of interest for tramadol, M1 and M5		
Stability	3 Freeze thaw cycles, [redacted] degradation. Stability in plasma @ -25 °C for 115 days [redacted] degradation.	3 Freeze thaw cycles, < [redacted] degradation. Stability in plasma @ -25 °C for 115 days % degradation.	3 Freeze thaw cycles, [redacted] degradation. Stability in plasma @ -25 °C for 115 days [redacted] degradation.
Conclusions	Method validation demonstrates reproducibility, accuracy, sensitivity and selectivity for intended use and is acceptable.		

Results:

Plasma Concentrations







Pharmacokinetic Parameters

The AUCs of tramadol were 50 to 60 % higher (2576.22 versus 4227.24 ng.hr/mL) after tramadol co-administration with quinidine as compared to tramadol alone. The increased AUC was related to a 41 decrease (729.68 versus 429.94 mL/min) in the clearance of tramadol during treatment with quinidine. In addition the elimination half-life of tramadol was prolonged from 7.6 to 9.3 hours. As a consequence of this decreased metabolic rate of tramadol during treatment with quinidine, the plasma concentrations of the two metabolites of tramadol (M1 and M5) were lower and the approximately 50 to 60 % lower AUCs is a reflection of the decreased formation rate of these metabolites as compared to the treatment with tramadol alone.

Table 9F – Pharmacokinetic Parameters for O,N-di-Desmethyltramadol (M5)

Pharmacokinetic Parameter	Tramadol HCl 100 mg ER Tablets (A) (n=19) (mean ±SD)	Tramadol HCl 100 mg ER Tablets with Quinidine Sulfate Tablets 200mg (B) (n=19) (mean ±SD)
AUC_{0-t} (ng·hr/mL)	294.50 ± 117.80	173.94 ± 64.13
AUC_{0-inf} (ng·hr/mL)	324.95 ± 144.23	331.64 ± 149.96
C_{max} (ng/mL)	12.24 ± 4.51	5.59 ± 1.89
T_{max} (hours)	17.37 ± 5.08	28.95 ± 8.85
$t_{1/2}$ (hours)	9.80 ± 2.68	33.89 ± 10.58
K_{el} (hour^{-1})	$7.54 \times 10^{-2} \pm 1.91 \times 10^{-2}$	$2.25 \times 10^{-2} \pm 7.89 \times 10^{-3}$
MRT (hours)	25.30 ± 5.09	61.96 ± 14.99
Cl (mL/min)	6003.53 ± 2296.18	7479.30 ± 7444.59
Vd (L)	4876.88 ± 1760.02	18418.35 ± 10187.90
M/P Ratio (AUC_{0-inf})	0.1552 ± 0.0589	0.1131 ± 0.0619

Table 9I – Estimated 90% CI, Ratio of Means, and p-Values for O,N-di-desmethyltramadol (M5) following administration of Tramadol HCl 100 mg ER Tablets (A) or a combination of Tramadol HCl 100 mg ER Tablets and Quinidine Sulfate Tablets 200 mg (B)

Parameter	O,N-di-desmethyltramadol		
	90% C.I.	Ratio of Means	P-value
AUC_{0-t}	49.10% - 70.15%	58.70%	<0.0001
AUC_{0-inf}	70.12% - 132.45%	96.27%	0.8320
C_{max}	39.19% - 53.17%	45.65%	<0.0001
$T_{1/2}$	N/AP	N/AP	0.0001

Reviewer's Comments: The AUCinf, MRT, T1/2, CL and VD data in table 9Fand AUC inf in table 9I for treatment B should be interpreted with great caution as it may be inaccurate due to an imbalance in data (N=8 for treatment B versus N = 17 for treatment A). This is because Kel could only be calculated in 8 subjects. The values obtained look erroneous e.g. AUC inf suggests similar exposure while AUC t suggest lower exposure in the presence of quinidine. This is also reflected in the 90 % CI obtained for AUCinf suggesting higher metabolite exposure while AUC inf suggests lower exposure. For this data set one should rely only on AUCt and Cmax.

Reviewer's Overall Comments
As per applicant's conclusions data from this study demonstrated that quinidine inhibits the metabolism of tramadol resulting in higher exposure of tramadol and a lower exposure of the active metabolite (M1) and an inactive metabolite (M5). From the regulatory perspective these findings could suggest a safety concern for tramadol and an efficacy concern for the active metabolite however, since the effects are opposite to each and both tramadol and M1 are active it is hard to predict the clinical consequences.

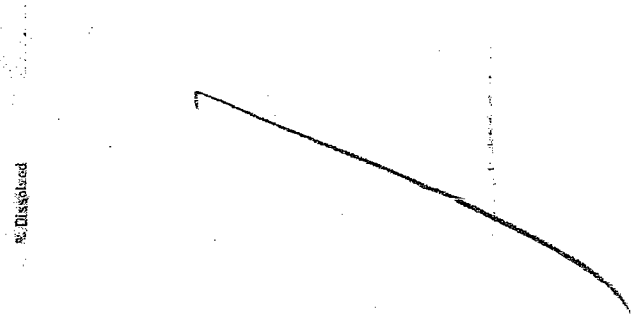
4.2.9 Dissolution Study

Drug Release Methods

In vitro dissolution was determined in accordance with USP General Chapter <724> Drug Release using Apparatus 1 (at a speed of with UV detection. The drug release limits were evaluated in accordance with the acceptance criteria specified in the Extended-Release Articles - General Drug Release Standard. Evaluation of the dissolution profiles for the final selected formulation included assessments of the effects of dissolution media and tablet strength. Representative mean dissolution profiles in , pH buffer, water, and pH

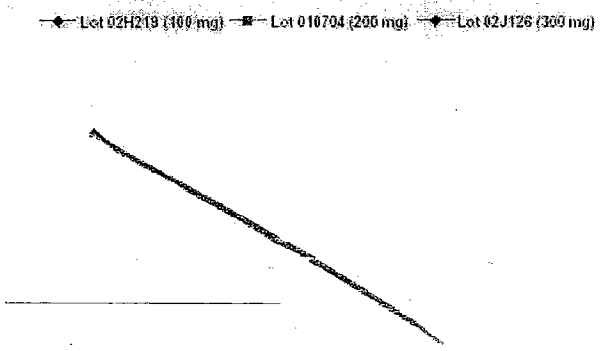
— buffer for the Tramadol HCl ER 100-mg tablets (Lot 02C139) used in Study B03-619PK-P03P1 (*in vitro-in vivo* correlation study) are shown below in Figure 52.

Figure 52. Representative Dissolution profiles for Tramadol HCL ER Tablets, 100 mg (Lot 02C139) in Different Dissolution Media



This batch has the same qualitative composition as the proposed commercial formulation. Dissolution in —— provided for 100% drug release over a 16-hour period. In addition, the average profiles showed little or no dependence on the pH or composition of the dissolution media. This finding suggests that *in vivo* drug release should be independent of the location of the extended-release tablet in the gastrointestinal tract and unaffected by the intra-luminal environment. Both factors should contribute to greater consistency in the performance of the oral dosage form. Representative dissolution profiles for Tramadol HCl ER tablets at dosage strengths of 100 mg (Lot 02H218), 200 mg (Lot 010704) and 300 mg (Lot 02J126) in the proposed dissolution media of —— are shown below in Figure 53.

Figure 53. Representative Dissolution profiles for Tramadol HCL ER Tablets, 100 mg, 200 mg and 300 mg in —— (Proposed Commercial Formulations)



These data show that the percentage of drug release from the different strengths of the extended-release is essentially independent of dose over the total duration of release. The individual values used to calculate the mean profiles shown in Figure 53 are provided in Table 30.

1 Page(s) Withheld

0 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

The data in this table illustrate the consistency in the *in vitro* performance of the dosage forms both within a batch and between batches of different strengths of the Tramadol HCl ER tablets. The similarity of the dissolution profiles between the different strengths was assessed by performing an f2 test on the dissolution results of 100-mg, 200-mg and 300-mg strengths. The results of this test indicate that the dissolution profiles, expressed as a percent of label claim, for the 3 strengths are similar because the f2 values were > 50. The f2 value for the comparison between 100-mg and 200-mg strengths was 72, and the f2 value for the comparison between 100-mg and 300-mg strengths was 88. The f2 value for the comparison between 200-mg and 300-mg strengths was 76.

Reviewer's Comments:
The proposed method is okay although the sponsor could have also evaluated different speeds and provided a rationale for choosing the acid over the other media. The in vitro release specifications are wider than the traditional 10% range around the mean dissolution profiles and are not acceptable on the based on dissolution results of the batches used in the bioequivalence and pivotal clinical studies. They cannot be justified based on the IVIVC because this was not found to be acceptable by Dr. Patrick Marroum who reviewed of the Study Report 2003-14. A new IVIVC analysis report (Report RA612005) will be reviewed in the next review cycle. The dissolution specification may be further revised based on the review of IVIVC results.

4.5 Synopses of Studies that not Reviewed

Study #2549 (B01-570PK-TRAP03)

SYNOPSIS

Name of Sponsor Company: BIOVAIL CORPORATION c/o BIOVAIL TECHNOLOGIES LTD.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:*	***For National Authority Use Only***
Name of Finished Product: Tramadol HCl 100 mg Extended Release Tablets	*Page:*	
Name of Active Ingredient: Tramadol hydrocholoride		

Title of Study:

A Two-Way, Crossover, Open-Label, Single-Dose, Fasting, Dosage Strength Equivalency Study Of Two Strengths (200 mg And 100 mg) Of Tramadol HCl Extended Release Tablets Given Once Daily In Normal Healthy Non-Smoking Male And Female Subjects

Protocol No.: 2549 (B01-570PK-TRAP03)

Investigators:

Principal Investigator: Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.

Sub-Investigators:

Study Center:

Biovail Contract Research
- 460 Comstock Road, Toronto, ON, M1L 4S4 Canada
- 689 Warden Avenue, Units 1 & 2, Toronto, ON, M1L 4R6 Canada

Publication (reference):

NONE

Studied period:	*Phase of development:*
December 11, 2001 – December 21, 2001	Phase I – dosage strength equivalency

Objectives:

The objective of this study is to investigate the dosage strength equivalency of Biovail Corporation's test product Tramadol HCl 100 mg Extended Release Tablets and Tramadol HCl 200 mg Extended Release Tablets under fasting conditions.

Analytical Procedure:

A suitably validated and sensitive assay method was employed for the analysis of tramadol and its metabolites, O-desmethyltramadol (M1) and O, N-di-desmethyltramadol (M5), in plasma samples. Full validation of the method, including precision, accuracy and reproducibility is included in the final report, along with a statement regarding the stability of the frozen samples. The analytical facility was blinded regarding the dosage regimen.

Number of subjects (planned and analyzed):

Twenty-four (24) male and female subjects were planned to be entered into the study. There were twenty-four (24) subjects dosed in period I, twenty-three (23) of which completed the study. Pharmacokinetic and statistical analyses were performed on twenty-three (23) subjects that completed the study.

Main criteria for inclusion:

Normal, healthy, non-smoking male and female subjects.

Test product, lot number and mode of administration:

Tramadol HCl 100 mg Extended Release Tablets, [redacted] (potency value = [redacted] of label claim), administered orally with 240 mL of ambient temperature water following an overnight fast of at least ten (10) hours.

Reference therapy, lot number and mode of administration:

Tramadol HCl 200 mg Extended Release Tablets, [redacted] (potency value = [redacted] of label claim), administered orally with 240 mL of ambient temperature water following an overnight fast of at least ten (10) hours.

Treatment Periods:

Period I : December 12, 2001

Period II: December 19, 2001

Criteria for evaluation:

Pharmacokinetics:

The following pharmacokinetic parameters for tramadol, O-desmethyltramadol (M1) and O, N-di-desmethyltramadol (M5) were calculated by standard non-compartmental methods: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el}, $t_{½}$, M/P ratio and MRT.

Safety:

The incidences of all adverse events were tabulated by treatment group and subject number. Absolute values for vital signs, ECGs, laboratory parameters and physical examination were also documented and values outside the normal range were flagged. Shifts (normal to abnormal) from baseline assessment to final assessment were tabulated.

Statistical methods:

Using GLM procedures in SAS, analysis of variance (ANOVA) were performed on Ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and on untransformed T_{max}, K_{el} and $t_{½}$ at the significance level of 0.05. The intra-subject coefficient of variation (CV), ratio of means (Treatment A/Treatment B) based on the geometric means from the ANOVA, and the 90% geometric confidence interval were calculated for the natural log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}.

SUMMARY CONCLUSIONS:

SUMMARY OF PHARMACOKINETIC RESULTS: Tramadol

Pharmacokinetic Parameters	Tramadol (A) 2 x 100 mg (n=23)	Tramadol (B) 1 x 200 mg (n=23)
AUC_{0-t} (ng.hr/mL)	5439.35 ± 2378.71	5575.08 ± 2687.32
AUC_{0-inf} (ng.hr/mL)	5682.37 ± 2576.07	5785.50 ± 2833.64
C_{max} (ng/mL)	261.35 ± 104.90	271.02 ± 128.34
T_{max} (hour)	13.22 ± 3.45	14.01 ± 3.87
$t_{½}$ (hour)	7.55 ± 1.64	7.35 ± 1.44
K_{el} ($hour^{-1}$)	0.096 ± 0.023	0.097 ± 0.017
MRT (hours)	20.46 ± 2.92	20.29 ± 3.07

	Tramadol (A) 2 x 100 mg vs. Tramadol (B) 1 x 200 mg		
	AUC_{0-t}	AUC_{0-inf}	C_{max}
90% C.I.	95.54% - 103.59%	96.04% - 103.74%	91.68% - 108.44%
Ratio of Means	99.48%	99.82%	99.71%
Intra-Subject CV	7.96%	7.59%	16.52%

SUMMARY OF SAFETY RESULTS:

No serious adverse events were reported. No subjects were dismissed due to adverse events. Overall, Tramadol HCl 100 mg Extended Release Tablets were well tolerated as a single-dose of 2 x 100 mg and Tramadol HCl 200 mg Extended Release Tablets were well tolerated as a single-dose of 1 x 200 mg, administered under fasting conditions, and no significant safety issues were raised.

CONCLUSION:

The objective of this study was to compare the rate and extent of absorption of the Tramadol HCl 100 mg Extended Release Tablets (2 x 100 mg), relative to Tramadol HCl 100 mg Extended Release Tablets (1 x 200 mg), administered under fasting conditions.

Based on twenty-three (23) completing subjects, the pharmacokinetics from the two (2) treatment groups were assessed. The pharmacokinetic parameters were similar between the two (2) formulations. The relative bioavailability of the two (2) formulations was evaluated by a comparison of AUC_{0-t}, AUC_{0-inf} and C_{max}, after a single dose under fasting conditions. The ANOVAs for AUC_{0-t}, AUC_{0-inf} and C_{max} indicated that the 90% geometric confidence intervals on the mean data for the three (3) parameters were within 80.00% - 125.00% range.

Therefore, the two (2) treatments are bioequivalent according to the FDA criteria for bioequivalence study under single dose fasting conditions. The Biovail Corporations's unique products, Tramadol HCl 100 mg Extended Release Tablets (2 x 100 mg) and Tramadol HCl 200 mg Extended Release Tablets (1 x 200 mg) demonstrated strength equivalence. Overall, tramadol was well tolerated as a single dose of 200 mg, and no significant safety issues were raised.

Report Issue Date:

March 14, 2002

This study was performed in compliance with Good Clinical Practice (GCP).

4.5.2 Study #109327 (B03-629PK-P01P1)

Synopsis

Name of Sponsor Company: Biovail Corporation c/o Biovail Technologies, Ltd.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only***
Name of Finished Product: Tramadol HCl Extended Release 300 mg Tablets		
Name of Active Ingredient: Tramadol		

Title of Study:

A Single Period, Two-Way Crossover, Open-Label, Multiple-Dose, Food-Effect Study of Tramadol Hydrochloride Extended Release 300 mg Tablets in Normal Healthy, Non-Smoking Male and Female Subjects

Protocol No.: 109327 (B03-629PK-P03P1)

Publication (reference):

NONE

Phase of development:

Phase I

Objectives:

The objective of this study was to determine the effect of food on the bioavailability of tramadol from Tramadol HCl Extended Release 300 mg Tablets under steady state conditions.

Test Products/Investigational Products, lot numbers and mode of administration:

All subjects received the following treatments from Day 1 to Day 9:

Titration Phase 1 – Days 1 to 4:

One Tramadol HCl Extended Release 100 mg Tablet, Bulk Printed Tablet Lot # 02H218, administered orally at 0.0 hour daily with 240 mL of ambient temperature water following an overnight fast of at least ten hours (Treatment dose = 100 mg/day).

Titration Phase 2 – Days 5 to 9:

Two Tramadol HCl Extended Release 100 mg Tablets, Bulk Printed Tablet Lot # 02H218, administered orally at 0.0 hour daily with 240 mL of ambient temperature water following an overnight fast of at least ten hours (Treatment dose = 200 mg/day).

Test Products/Investigational Products, lot numbers and mode of administration (Cont'd):

Treatment Phase – Day 10 to Day 23:

Subjects followed one of two different treatment sequences according to the randomization scheme.

Subjects received either Treatment A from Day 10 to Day 16 followed by Treatment B from Day 17 to Day 23 or Treatment B from Day 10 to Day 16 followed by Treatment A from Day 17 to Day 23.

Treatment A:

One Tramadol HCl Extended Release 300 mg Tablet, Bulk Printed Tablet Lot # 02J126, administered orally at 0.0 hour daily with 240 mL of ambient temperature water following an overnight fast of ten hours (Treatment dose = 300 mg/day).

Treatment B:

One Tramadol HCl Extended Release 300 mg Tablet, Bulk Printed Tablet Lot # 02J126, administered orally at 0.0 hour daily with 240 mL of ambient temperature water 30 minutes after the start of the high fat content meal (Treatment dose = 300 mg/day).

Analytical Procedure:

A validated and sensitive assay method (LC-MS/MS) was employed for the analysis of tramadol and its metabolites, O-desmethyltramadol (M1) and O,N-di-desmethyltramadol (M5), in plasma samples.

Evaluation of the assay was carried out by the construction of an [redacted] calibration curve (excluding zero concentration) covering the range of [redacted] ng/mL (in human plasma) for Tramadol, [redacted] (in human plasma) for *O*-Desmethyltramadol, and [redacted] (in human plasma) for *O,N*-di-Desmethyltramadol.

The lower limit of quantitation (LOQ) was [redacted] for tramadol. The limit of quantitation (LOQ) was [redacted] for O-desmethyltramadol (M1) and for O, N-di-Desmethyltramadol (M5). The analytical facility was blinded regarding the randomization code and treatment plan.

Number of subjects (planned and analyzed):

Thirty were planned to be entered into the study. There were thirty subjects dosed, 29 of whom completed the study. Initial pharmacokinetic and statistical analyses were performed on all of the 29 subjects who completed the study. Final pharmacokinetic and statistical analyses were performed on 27 subjects, since data for Subjects #04 and #28 were removed due to suspicion of non-compliance to study treatment (as shown by low plasma concentrations).

Criteria for evaluation:

Pharmacokinetics:

The following pharmacokinetic parameters for tramadol, O-desmethyltramadol (M1) and O,N-di-desmethyltramadol (M5) were calculated by standard non-compartmental methods: AUC_τ, C_{max}, C_{min}, T_{max} and percent fluctuation (% Fluct).

Pre-drug (0.0 hour) levels were used to determine whether steady state was achieved for each treatment based on linear regression analysis.

Descriptive statistics was provided and analysis of variance (ANOVA) was performed on all pharmacokinetic parameters.

Statistical methods:

Bioavailability comparison based on C_{max} and AUC_τ was carried out to compare Treatment B (Fed) / Treatment A (Fasting) for tramadol, O-desmethyltramadol (M1) and O, N-di-Desmethyltramadol (M5). The ratio of geometric means and the corresponding 90% geometric confidence interval was computed based on log transformed C_{max} and AUC_τ.

SUMMARY CONCLUSIONS:

SUMMARY OF PHARMACOKINETIC RESULTS: TRAMADOL

Pharmacokinetic Parameters	*Tramadol HCl Extended Release 300 mg Tablets (Fasting) (A) n = 27 Mean ± SD*	*Tramadol HCl Extended Release 300 mg Tablets (Fed) (B) n = 27 Mean ± SD*
AUC_τ (ng.hr/mL)	11349.24 ± 3142.99	9907.58 ± 3754.67
C_{max} (ng/mL)	611.30 ± 165.36	576.97 ± 228.19
C_{min} (ng/mL)	362.17 ± 111.00	321.90 ± 143.30
T_{max} (hr)	11.56 ± 3.34 12.00†	10.59 ± 4.55 10.00†
Fluctuation (%)	53.24 ± 20.13	63.72 ± 29.85

†This is the median value

	Tramadol HCl Extended Release 300 mg Tablets (Fed) (B) vs. Tramadol HCl Extended Release 300 mg Tablets (Fasting) (A)		
	90% Confidence Interval	Ratio of Means	Intra-Subject CV
AUC_τ	76.26% to 94.40%	84.84%	22.94%
C_{max}	84.08% to 99.99%	91.69%	18.63%
C_{min}	70.80% to 97.33%	83.01%	34.20%

SUMMARY CONCLUSIONS:

SUMMARY OF PHARMACOKINETIC RESULTS: N- DESMETHYLTRAMADOL (M1)

Pharmacokinetic Parameters	*Tramadol HCl Extended Release 300 mg Tablets (Fasting) (A) n = 27 Mean ± SD*	*Tramadol HCl Extended Release 300 mg Tablets (Fed) (B) n = 27 Mean ± SD*
AUC_τ (ng.hr/mL)	2608.07 ± 694.05	2250.60 ± 830.77
C_{max} (ng/mL)	133.36 ± 38.09	120.55 ± 44.61
C_{min} (ng/mL)	93.14 ± 22.25	78.54 ± 32.17
T_{max} (hr)	12.93 ± 3.52 12.00†	12.07 ± 5.12 12.00†
Fluctuation (%)	35.17 ± 16.03	47.20 ± 23.68*

*n = 26

† This is the median value

	Tramadol HCl Extended Release 300 mg Tablets (Fed) (B) vs. Tramadol HCl Extended Release 300 mg Tablets (Fasting) (A)		
	90% Confidence Interval	Ratio of Means	Intra-Subject CV
AUC_τ	76.53% to 91.95%	83.88%	19.73%
C_{max}	82.34% to 95.12%	88.50%	15.50%
C_{min}	69.62% to 90.53%	79.39%	28.23%

SUMMARY CONCLUSIONS:

SUMMARY OF PHARMACOKINETIC RESULTS: O, N-di -DESMETHYLTRAMADOL (M5)

Pharmacokinetic Parameters	*Tramadol HCl Extended Release 300 mg Tablets (Fasting) (A) n = 27 Mean ± SD*	*Tramadol HCl Extended Release 300 mg Tablets (Fed) (B) n = 27 Mean ± SD*
AUC_τ (ng.hr/mL)	1317.61 ± 566.37	1152.33 ± 554.15
C_{max} (ng/mL)	65.87 ± 27.87	59.15 ± 26.68
C_{min} (ng/mL)	50.11 ± 22.39	43.44 ± 23.51
T_{max} (hr)	15.15 ± 4.60 16.00†	13.44 ± 5.34 16.00†
Fluctuation (%)	29.91 ± 14.50*	39.19 ± 23.99**

*n = 26; **n = 25

†This is the median value

	Tramadol HCl Extended Release 300 mg Tablets (Fed) (B) vs. Tramadol HCl Extended Release 300 mg Tablets (Fasting) (A)		
	90% Confidence Interval	Ratio of Means	Intra-Subject CV
AUC_τ	74.53% to 95.27%	84.26%	26.38%
C_{max}	78.70% to 96.62%	87.20%	22.04%
C_{min}	69.27% to 93.52%	80.49%	32.25%

CONCLUSION:

The objective of this study was to determine the effect of food on the bioavailability of Tramadol HCl Extended Release 300 mg Tablets under steady-state conditions.

In presence of food, the exposure to tramadol was significantly reduced as shown by a decrease AUC_τ. The peak tramadol concentrations were similar under fed and fasted conditions. Similar to tramadol, a decrease in exposure to O-desmethyltramadol (M1) and O,N -di-desmethyltramadol (M5) was observed under fed conditions compared to fasted.

The 90% geometric confidence intervals on the relative mean data for AUC_τ and C_{max} were outside the 80.00% - 125.00% limits. However, this is unlikely to be clinically significant.

Report Issue Date:

November 11, 2003

This study was performed in compliance with Good Clinical Practice (GCP).

4.4 OCPB 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	21-692	Brand Name	Ralivia ER™
OCPB Division (I, II, III)	DPE III (HFD-880)	Generic Name	Tramadol Hydrochloride
Medical Division	DAAODP (HFD-550)	Drug Class	Centrally Acting Analgesic
OCPB Reviewer	Lei Zhang, Ph.D. (Primary) Abimbola Adebowale , Ph.D.	Indication(s)	Management of moderate to moderately severe pain in adults
OCPB Team Leader	Dennis Bashaw, Pharm. D.	Dosage Form	Extended Release Tablets, 100, 200, and 300 mg
		Dosing Regimen	Start at a dose of 100 mg QD and titrated up if required by 100 mg increments every 5 days as necessary. Not to exceed ~~~ /day.
Date of Submission	12/31/2003	Route of Administration	Oral
Estimated Due Date of OCPB Review	9/30/2004	Sponsor	Bioavil laboratories, Inc.
PDUFA Due Date	10/31/2004	Priority Classification	New Formulation (5-S)
Division Due Date			IND 59,023 505 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			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	1		1. Study #2552 (B01-569PK-TRAP03) (100, 200 and 400 mg, multi dose)
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		1. Study #2584 (B02-591PK-P03P1) (effect of CYP2D6 inhibition with Quinidine)
In-vivo effects of primary drug:				

In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		1. Study #109316 (B02-589PK-P03P1) (mild, moderate renal failure and normal, multi dose)
hepatic impairment:	X	1		1. Study B02-590PK-P03P1 (mild and moderate hepatic impairment, multi dose)
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:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	4		1. Study #2551 (B01-567PK-TRAP03) (200 mg vs. Ultram single/multi dose) Pilot: 2. Study B99-401PK-TRAP03 (3 formulation of 100 mg vs. Ultram, single dose) 3. Study #99103 (B99-416PK-TRAP03) (prototype 2x100 mg vs. Ultram QID, multi dose) 4. Study #2282 (B99-424PK-TRAP03) (2 formulations of prototype 3x100 mg vs. Ultram TID, multi dose)
Bioequivalence studies -				
traditional design; single / multi dose:	X	5		1. Study #2287-2 (B99-426PK-TRAP03) (scale-up vs. pilot formulation, 100 mg, single dose) 2. Study #2549 (B01-570PK-TRAP03) (2x100 mg vs. 200 mg, single dose) 3. Study #2696 (B03-623PK-P03P1) (3x100 mg vs. 300 mg, single dose) Pilot: 4. Study #99105 (B99-415PK-TRAP03) (2 formulations of 100 mg, single dose, fast/fed) 5. Study #2375 (B00-471PK-TRAP03) (2x100 mg vs. 200 mg, single dose)
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		1. Study #2550 (B01-568PK-TRAP03) (200 mg, single dose) 2. Study #109327 (B03-629PK-P03P1) (300 mg, multi dose)

Dissolution:	X			Apparatus 1 [redacted] at a speed of [redacted] with UV detection
(IVIVC):	X	2		1. Study #2677 (B03-619PK-P03P1) Pilot: 2. Study #2553 (B01-571PK-TRAP03) Report 2003-14
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		17		

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	
Comments sent to firm?		
QBR questions (key issues to be considered)	• What is PK profile of 100, 200 and 300 mg ER tablets? Is PK dose proportional? • What is steady state PK of the highest dose strength tablet (300 mg)? • How does exposure of the ER tablets compare to Ultram at steady state for both tarmadol and O-desmethylated M1 metabolite at equivalent doses? • Is there a food effect (done with 300 mg tablet)? • Does PK of the new ER formulation support the proposed indication?	
Other comments or information not included above	This is a 505 b(2) application. The sponsor did not conduct the bioequivalence study 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. Historically, the sponsor developed the 300 mg tablet at late stage. They have steady state PK information for 300 mg tablet that could be compared to steady state PK of 200 mg tablet. Therefore, additional BE study with 300 mg tablet is not necessary.	
Primary reviewer Signature and Date	Lei Zhang, 2/24/2004	
Secondary reviewer Signature and Date	Dennis Bashaw, 2/24/2004	

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

/s/

Lei Zhang
10/19/04 05:30:31 PM
BIOPHARMACEUTICS

Dennis Bashaw
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