CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-693

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Tramadol HCl Orally Disintegrating Tablets
PRODUCT (Proposed Brand Name):	Ralivia Flashdose
DOSAGE FORM:	Orally Disintegrating Tablets
DOSAGE STRENGTH:	50 mg
NDA:	21- 693
PROPOSED INDICATIONS:	Moderate to moderately severe pain
NDA TYPE:	505(b)(2)
SUBMISSION DATE:	March 10, 2004
SPONSOR:	Biovail
REVIEWER:	Tapash K. Ghosh, Ph.D.
TEAM LEADER:	Edward D. Bashaw, PharmD.
OCPB DIVISION:	DPE III, HFD 880
OND DIVISION:	HFD 550

EXECUTIVE SUMMARY

Tramadol HCl is a centrally acting analgesic. Biovail Laboratories, Inc. (Biovail) submitted NDA 21-693 as a 505(b)(2) application for Ralivia™ FlashDose®, the proposed tradename for tramadol HCl orally disintegrating tablet (ODT). It is intended for daily dosing at up to 4 to 6 times a day, not to exceed 400 mg per day, for the management of moderate to moderately severe pain in adults. The conventional tablet form of tramadol HCl was approved in the United States on March 3, 1995 with the tradename of Ultram® (NDA 20-281) for the management of moderate to moderately severe pain in adults. In addition, there are currently 14 generic versions of Ultram® that were approved in 2002 in the US for the same indication. If approved, Ralivia™ FlashDose® will be the first ODT not only for tramadol but also for any other prescription analgesic drug. As a 505 (b) (2) application, the sponsor is referring to the existing information on the basic pharmacokinetics, metabolism, and pharmacodynamic behavior of tramadol that has been published in the literature and is included in the approved NDA and labeling for Ultram®.

The clinical pharmacology and biopharmaceutics development program for Ralivia FlashDose consisted of 5 definitive studies and 1 supportive (pilot) study. This program was designed to address only the performance of the ODT formulation and to compare this performance with the approved reference product. In this review, 3 definitive studies which are considered pertinent to labeling have been reviewed.

The results from single-dose BA/BE studies showed that equivalent amounts of drug were absorbed after dosing with the Ralivia FlashDose 50 mg and Ultram® 50 mg tablets. The plasma concentration time profiles for tramadol and its M1 and M5 metabolites tracked each other. The results also showed that administering Ralivia FlashDose with food had no effect on the total amount of tramadol drug absorbed. However, time to peak exposure (t_{max}) following administration of Ralivia FlashDose after food was delayed by about 30 minutes compared to administration under fasting condition.

Recommendation:

The Clinical Pharmacology and Biopharmaceutics section of NDA 21-683 is acceptable with the suggested labeling changes and dissolution specification as described below.

***In-vitro* Dissolution Specification:**

Because of a potential for conusion, the sponsor is advised to change the way in which they express their in vitro drug release specification to "Q = [redacted] at 30 minutes" rather than using a "not less than" nomenclature.

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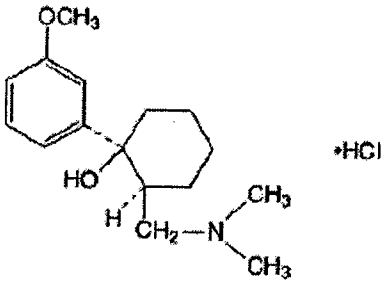
GENERAL ATTRIBUTES

Trade name: Ralivia™ FlashDose® (50 mg)
Generic name: Tramadol HCl
Chemical name: (±) *cis* -2- [(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride
Chemical Structure:



Dosage Form Description

Ralivia FlashDose tablets, 50 mg, are white to off-white round tablets with a dimple on both sides and debossed with a "B" on one side, "50" on the other side.

The composition of the pilot and final formulation batches and the studies in which they were used are provided in the following Table.

Name of Ingredient	Unit Formula (mg/tab)	% Formula	Unit Formula (mg/tab)	% Formula	Function
	Lot # D0Z124 (TRA 9903700036/50)		Lot # PR03175R		
Tramadol HCl	50.00	[redacted]	50.00	[redacted]	Active Ingredient
[redacted]					
(Ethylcellulose [redacted]					
[redacted] (Copovidone)					
[redacted]					
(Silicon Dioxide)					
[redacted]					
Mannitol [redacted]					
[redacted] (Crospovidone)					
[redacted] Aspartame)					
Mint Rootbeer Flavor					
[redacted]					
[redacted]					
Magnesium Stearate					
[redacted]					
[redacted]					
Unit Mass					
[redacted]					

Clinical Pharmacology and Biopharmaceutics: The clinical pharmacology and biopharmaceutics development program for Ralivia FlashDose consisted of 5 definitive studies and 1 supportive (pilot) study. This program was designed to address only the

performance of the ODT formulation and to compare this performance with the approved reference product. In this review, 3 definitive studies which are considered pertinent to labeling have been reviewed (See attached review of the individual studies).

Influence of Intrinsic and Extrinsic Factors

Intrinsic Factors: The effects of age, gender, and race on the pharmacokinetic behavior of Tramadol HCl ODT was evaluated by analyzing data across studies. The findings in these evaluations are discussed briefly below.

Effect of Age: Data for 151 subjects (19 – 64 years) who received Tramadol HCl ODT and 103 subjects who received Ultram® (19 – 61 years) were included in the analysis. The regression analysis showed that there were no formulation specific age-related changes in the pharmacokinetics of tramadol from the Tramadol HCl ODT formulation, and that the distribution of AUC values by age was similar for Tramadol HCl ODT and Ultram®. The correlation coefficient (R^2) for the least squares fit of the data were 0.0058 and 0.0206 for Tramadol HCl ODT and Ultram®, respectively.

Effect of Gender: Data for 104 males and 43 females who received single doses of Tramadol HCl ODT were included in the analysis. There was no difference in the tramadol pharmacokinetics between male and female subjects in these studies.

Effect of Race: Data were obtained in 107 Caucasian subjects, 33 Black subjects, and 8 Asian subjects. Due to the small sample size for Asian population, conclusions cannot be drawn about the pharmacokinetics of tramadol in this population, but the values observed in this group were not noticeably different from those in the population as a whole. There was no difference in tramadol pharmacokinetics between Caucasian and Black subjects.

Extrinsic Factors: The effects of body weight on the pharmacokinetic behavior of Tramadol HCl ODT was evaluated by analyzing data across studies. Single-dose data were generated in 151 subjects who received Tramadol HCl ODT and 103 subjects who received Ultram® tablets. There was a very weak downward trend in the AUC values with increasing body weight; the correlation coefficient (R^2) values were 0.0421 and 0.0911 for Tramadol HCl ODT and Ultram®, respectively.

All of the studies in the current development program utilized non-smoking subjects; therefore, the effect of smoking on the pharmacokinetics of tramadol from the Tramadol HCl ODT could not be evaluated.

ANALYTICAL METHODOLOGY

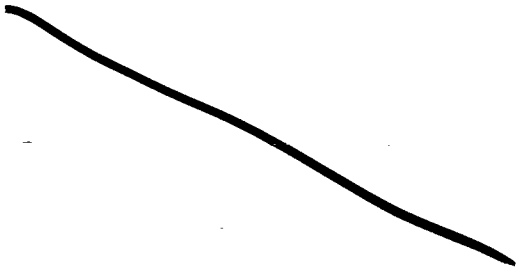
An LC-MS/MS analytical method has been developed to assay tramadol and its M1 and M5 metabolites in biological fluids. The same basic assay was used throughout the development plan and consistent performance was achieved from study to study. The essential steps in the method are the following:

[redacted] a high performance liquid chromatograph (HPLC) with a tandem mass spectrometry (LC-MS/MS) detection system. [redacted] chromatography [redacted] quantified by mass spectrometry. Validation activities addressed the following performance-related aspects for the various plasma and urine assays: linearity, limit of detection, intra-run accuracy and precision, inter-run accuracy and precision, recovery, freeze-thaw stability, in-process stability of human plasma, autosampler stability, dilution integrity and long-term stability in human plasma and human urine. The results of the validation indicate that the analytical methods performed in a consistent manner between analytical runs and between studies. The lower limits of quantification of the assay, as described below, were sufficiently low to allow the pharmacokinetics of the drug and its M1 and M5 metabolites to be fully characterized after single dosing of the Tramadol HCl ODT 50-mg tablets.

Type of Biological Fluid	Sensitivity of Method (Range)	Specificity
Plasma	2.001 ng/mL	Tramadol
[redacted]		
Plasma	2.001 ng/mL	[redacted]

Drug Release Methods

In vitro dissolution was determined in accordance with USP General Chapter <724> Drug Release using Apparatus 2 (paddle) at a speed of 50 rpm with UV detection. Evaluation of the dissolution profiles for the pivotal formulation included assessments of the effects of dissolution media. Representative mean dissolution profiles in 0.1 N HCl, pH 4.5 buffer, water, and pH 6.8 buffer for the Ralivia FlashDose 50-mg tablets (Lot 26140203) used in stability studies are shown in the following Figure.



Time (min)

This batch has the same qualitative composition as the pivotal biobatch (proposed commercial formulation). Dissolution in all 4 media tested provided for almost [redacted] drug release over a 1-hour period. In addition, the average profiles showed little or no dependence on the pH or composition of the dissolution media. A summary of the method and proposed specifications is provided in the following Table.

(1)	Apparatus Type:	USP Apparatus #2 (Paddles)
(2)	Stirring Speed:	50 rpm
(3)	Medium:	500 mL of 0.1 N HCl
(4)	Temperature:	37°C ± 0.5°C
(5)	Sample Size:	Single tablet per vessel
(6)	Sampling Times:	5, 10, 20, 30, 45 and 60 minutes
(7)	Brief Description of Drug Release Analytical Method:	Withdraw an aliquot of the dissolution medium at each sampling point and determine the absorbance at a wavelength of 271 nm using a suitable UV spectrophotometer. Calculate the percent Tramadol hydrochloride dissolved, applying a volume correction.
(8)	Drug Release Specification (proposed for Ralivia FlashDose Tablets, 50 mg):	Meets USP requirements for drug release with the following criteria: *Not less than [redacted] dissolved (Q) in 30 minutes*

Comments: *The sponsor's language for dissolution specification "NLT [redacted] (Q) at 30 mins" is not clear. It transpires that NLT and Q are same. The in vitro dissolution profiles showed that more than [redacted] dissolved in 30 minutes in all medias. While we agree with Q = [redacted] at 30 minutes, the actual interpretation will be "Not less than [redacted] dissolved (Q = [redacted]) in 30 minutes. Therefore, the sponsor is suggested to change their in vitro drug release specification to "Q = [redacted] at 30 minutes".*

In vivo **Disintegration Time:** The *in vivo* disintegration time of Ralivia FlashDose was measured in 3 studies (Studies 2794, 2795, and 2821, respectively). The mean *in vivo* disintegration times in these studies were 20.6 ± 12.7 seconds, 23.7 ± 15.2 seconds and

16.5 ± 11.1 seconds respectively. Out of 120 *in vivo* disintegration time data reported in this study, 2 data were above 60 secs with the highest being 69 secs.

Comments on the *In-vivo* Disintegration Time:

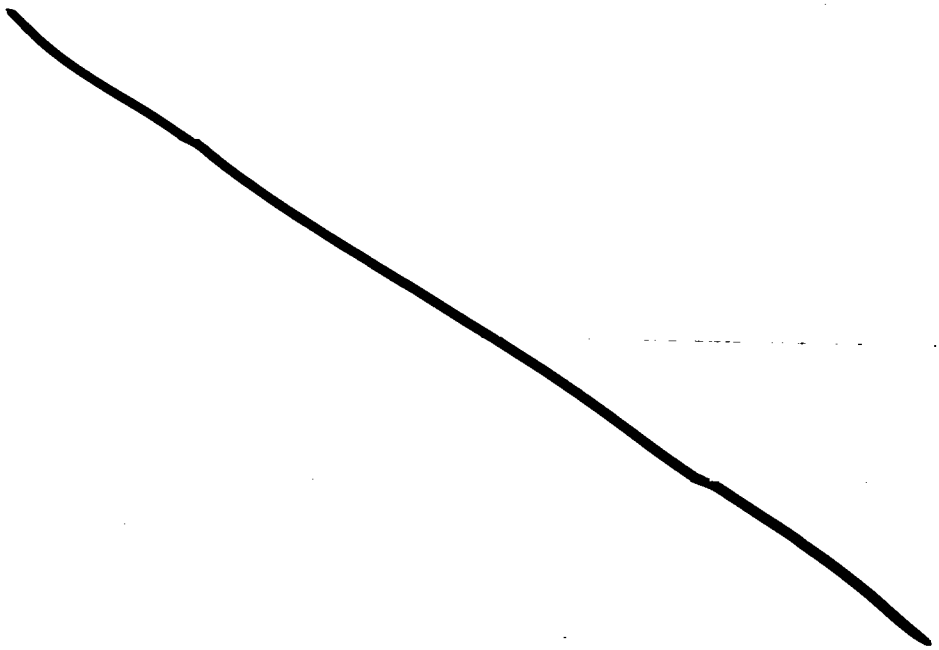
The Center for Drug Evaluation and Research (CDER) defines in the Orange Book an ODT as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue." However, no specific cut-off disintegration time has been established yet.

***In vitro* Disintegration Time Spec:** Disintegration in 60 seconds.

CPB LABELING:

The following text should be inserted into the labeling, as appropriate. ABC indicates suggested inclusion.

CLINICAL PHARMACOLOGY



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Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation III

Team Leader: Edward D. Bashaw, Pharm.D.

Appendix

Sponsor's Proposed Label

Appears This Way
On Original

10 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

Individual Studies

NDA: 21-693/Study 2686 **Study Dates: Sep '03 – Oct '03**

A Three-way Crossover, Open-label, Single-dose, fasting, Comparative Bioavailability Study of Tramadol HCl 50 mg Flashtab (Administered With and Without Water) Versus Ultram 50 mg Tablets in Healthy male Volunteers

Study Design: A total of 19 healthy male subjects (11 Caucasians, one Asian and seven Blacks) with the following demographics completed this study.

Mean Age: 32 years (range 19 – 43 years); mean height: 1.79 m (range 1.60 – 1.91 m); mean weight: 79 kg (range 61 – 97 kg).

A crossover study design with a one-week washout between study periods was used to evaluate bioavailability. Blood samples for tramadol, O-desmethyltramadol (M1), and O, N-di-desmethyltramadol (M5) metabolite were determined by a validated LC-MS/MS technique.

Treatment A: Following an overnight fast of at least 10 hours, one Tramadol HCl 50 mg Flashtab® Tablet (Lot # PR03175R) was placed on the tongue and was sucked for at least 2 minutes until completely dissolved. The subject's mouth was then checked to ensure that the drug had completely dissolved. If the drug had not completely dissolved, the subject was instructed to suck on the Flashtab® until it completely dissolved. Subjects were instructed not to swallow or chew any portion of the Flashtab®. No water was provided. The actual dosing time was recorded when the Flashtab® was placed on the subject's tongue.

Treatment B: Following an overnight fast of at least 10 hours, one Tramadol HCl 50 mg Flashtab® Tablet (Lot # PR03175R) was placed on the tongue and was sucked for at least 2 minutes until completely dissolved. The subject's mouth was then checked to ensure that the drug had completely dissolved. If the drug had not completely dissolved, the subject was instructed to suck on the Flashtab® until it completely dissolved. Subjects were instructed not to swallow or chew any portion of the Flashtab®. The subject was then given 240 ml of ambient temperature water one minute after the complete disintegration of the tablets in the mouth that was ingested within one minute. The actual dosing time was recorded when the Flashtab® was placed on the subject's tongue.

Treatment C: One Ultram® 50 mg Tablet (Lot # 92P0432E) was administered orally with 240 ml of ambient temperature water following an overnight fast of at least 10 hours.

Results: The mean plasma concentration-time profiles for tramadol following ODT and the IR reference are shown in Figure 1. Similar profiles were also observed for its metabolites M1 and M5. Plasma profiles of all three analytes attributable to tramadol HCl ODT and the IR reference appear superimposable.

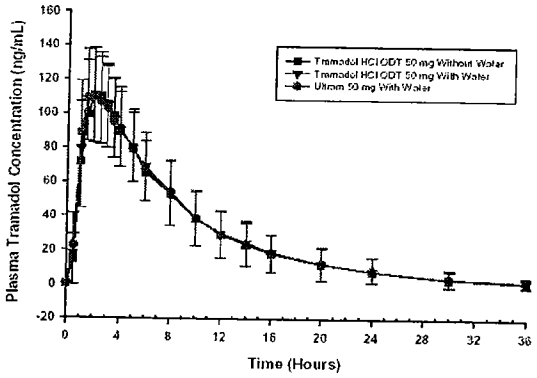

Figure 1: Mean Plasma Tramadol Concentrations After Single Dosing With Tramadol HCl ODT Tablets (1 x 50 mg) With and Without Water Versus Ultram® (1 x 50 mg) Tablets

The pharmacokinetic parameters derived from the plasma concentration data for tramadol and metabolites are summarized in Table 1 whereas the outcome of the statistical analysis of the pharmacokinetic parameter from this study is summarized in Table 2 respectively.

Table 1: Pharmacokinetic Parameter Values for Tramadol and Metabolites After Oral Dosing With Pivotal Ralivia FlashDose Tablets and Ultram® Tablets in 19 Healthy Male Subjects

Pharmacokinetic Parameters	*Tramadol HCl 50 mg ODT (Without water) (n=19) (mean ±SD)*	*Tramadol HCl 50 mg ODT (With Water) (n=19) (mean ±SD)*	*Ultram© 50 mg Tablets (n=19) (mean ±SD)*
	Tramadol		
AUC_{0-t} (ng·hr/mL)	1001.30 ± 385.26	1038.12 ± 410.91	1003.52 ± 383.00
$AUC_{0-\infty}$ (ng·hr/mL)	1031.14 ± 407.07	1067.87 ± 429.88	1037.27 ± 413.49
C_{max} (ng/mL)	115.66 ± 27.49	112.80 ± 27.31	122.02 ± 26.32
T_{max} (hour)	2.16 ± 0.53 2.00*	2.11 ± 0.52 2.00*	1.97 ± 0.70 1.50*
$t_{½}$ (hour)	5.73 ± 1.14	5.79 ± 1.21	5.64 ± 1.21
MRT (hour)	8.79 ± 1.92	8.76 ± 1.68	8.53 ± 1.88
	O-Desmethyltramadol (M1)		
AUC_{0-t} (ng·hr/mL)	368.81 ± 110.15	373.63 ± 104.11	384.77 ± 114.50
$AUC_{0-\infty}$ (ng·hr/mL)	384.46 ± 110.28	390.42 ± 104.24	399.98 ± 114.97
C_{max} (ng/mL)	32.26 ± 11.89	31.99 ± 10.61	33.78 ± 12.80
T_{max} (hour)	3.16 ± 0.91 3.00*	3.24 ± 1.47 3.00*	2.84 ± 1.04 2.50*
$t_{½}$ (hour)	6.64 ± 1.44	6.59 ± 1.22	6.52 ± 1.23
MRT (hour)	11.38 ± 2.65	11.16 ± 2.31	11.05 ± 2.40
M/P[a] Ratio	0.4466 ± 0.1874	0.4451 ± 0.1924	0.4614 ± 0.1968
	O,N-Didesmethyltramadol (M5)		
AUC_{0-t} (ng·hr/mL)	116.17 ± 48.33	121.46 ± 51.02	120.98 ± 44.92
$AUC_{0-\infty}$ (ng·hr/mL)	135.76 ± 43.39†	142.15 ± 49.65‡	142.51 ± 42.42‡
C_{max} (ng/mL)	9.68 ± 3.57	9.75 ± 3.36	10.34 ± 4.10
T_{max} (hour)	3.40 ± 2.00 3.00*	3.90 ± 3.35 3.00*	3.45 ± 2.32 3.00*
$t_{½}$ (hour)	6.91 ± 2.85†	6.81 ± 2.02‡	7.03 ± 2.18‡
MRT (hour)	11.97 ± 4.43	11.85 ± 3.91	11.97 ± 4.32
M/P[a] Ratio	0.1580 ± 0.0482†	0.1618 ± 0.0476‡	0.1633 ± 0.0535‡

[a] Metabolite/Parent Ratio = (AUC_{∞} M5/Mol. Wt. of M5)/(AUC_{∞} Tramadol/Mol. Wt. of Tramadol).

Mol. Wt. of M5 : [redacted]

Mol. Wt of Tramadol = [redacted]

*This is the median value.

Table 2: Key Statistical Results of Tramadol and Metabolites for the Comparison of 1 x 50-mg Tramadol HCl ODT Tablets and 1 x 50-mg Ultram® Tablets in 19 Healthy Male Subjects

	Tramadol HCl 50 mg ODT (Without water) vs. Ultram® 50 mg Tablets			*Tramadol HCl 50 mg ODT (With water) vs Ultram® 50 mg Tablets*			*Tramadol HCl 50 mg ODT (With water) vs. Tramadol HCl 50 mg ODT (Without water)*		
	90% C.I.	Ratio of Means	Intra-Subject CV	90% C.I.	Ratio of Means	Intra-Subject CV	90% C.I.	Ratio of Means	Intra-Subject CV
					Tramadol				
AUC_{0t}	95.17% - 103.70%	99.34%	7.75%	98.00% - 106.79%	102.30%	7.75%	98.64% - 107.49%	102.97%	7.75%
$AUC_{0\infty}$	95.05% - 103.41%	99.14%	7.61%	97.80% - 106.41%	102.02%	7.61%	98.65% - 107.33%	102.90%	7.61%
C_{max}	89.52% - 99.97%	94.60%	9.97%	87.27% - 97.46%	92.22%	9.97%	92.25% - 103.02%	97.49%	9.97%
					O-Desmethyltramadol (M1)				
AUC_{0t}	91.66% - 99.70%	95.64%	7.66%	93.75% - 102.06%	97.82%	7.66%	98.03% - 106.71%	102.28%	7.66%
$AUC_{0\infty}$	92.12% - 100.16%	96.05%	7.55%	94.21% - 102.43%	98.24%	7.55%	98.08% - 106.64%	102.27%	7.55%
C_{max}	92.09% - 100.82%	96.35%	8.17%	92.45% - 101.21%	96.73%	8.17%	95.95% - 105.05%	100.39%	8.17%
					O,N-Didesmethyltramadol (M5)				
AUC_{0t}	90.26% - 99.65%	94.84%	8.93%	95.00% - 104.88%	99.82%	8.93%	100.17% - 110.59%	105.25%	8.93%
$AUC_{0\infty}$	92.10% - 100.75%	96.33%	7.65%	95.35% - 104.59%	99.86%	7.65%	99.06% - 109.49%	103.67%	7.65%
C_{max}	89.90% - 99.35%	94.51%	9.02%	91.13% - 100.70%	95.79%	9.02%	96.42% - 106.55%	101.36%	9.02%

Discussion:

Bioavailability (exposure, rate and extent) of a drug may be affected when the ODT is swallowed intact with water versus allowing it to disintegrate in the oral cavity followed by swallowing the slurry. One of the objectives of this study was to support the labeling language for this product as proposed in the Dosage and Administration section [redacted]

Overall, keeping in mind that tramadol undergoes first-metabolism, as the product when given without water (Treatment A) showed BE with Ultram, the product will be expected to be BE also with Ultram when given with water. Therefore, even though the sponsor's design of treatment B did not exactly reflect the design of administering the

product with water, the sponsor may still be given the claim of *"Tablet may be taken with or without water."* Therefore, the labeling language should be changed according to reflect the study design which is the basis for such a claim. Also, based on the data it may be concluded that time to peak exposure (Tmax) following administration of RALIVIA FLASHDOSE may be delayed by about 30 minutes compared to immediate release forms of tramadol.

Comments:

It would have been more useful to see what would happen if the ODT was swallowed whole with water. In absence of that, Treatment B did not add any value to the overall outcome of the study. Also, chewing and/or breaking the tablet should not change the pharmacokinetic outcome of the ODT. Unless the tablets are scored, only the effect of splitting, as it relates to administered dose, is unknown.

NDA: 21-693/Study 2794 **Study Dates: Oct '03 – Nov '03**

A Two-way Crossover, Open-label, Single-dose, fasting, Comparative Bioavailability Study of Tramadol HCl 50 mg Flashtab Versus Ultram 50 mg Tablets in Normal Healthy Non-smoking Male and Female Subjects

Study Design: A total of 36 healthy subjects (21 males, 15 females, 26 Caucasians, 10 Blacks) with the following demographics completed this study. [*Mean Age: 40 years (range 19 – 64 years); mean height: 1.69 m (range 1.51 – 1.88 m); mean weight: 73 kg (range 55 – 93 kg).*]

A crossover study design with a one-week washout between study periods was used to evaluate bioavailability. Blood samples for tramadol, O-desmethyltramadol (M1), and O,N-di-desmethyltramadol (M5) metabolites were determined by a validated LC-MS/MS technique.

Treatment A: Following an overnight fast of at least 10 hours, one Tramadol HCl 50 mg Flashtab® Tablet (Lot # PR03175R) was placed on the tongue and was sucked for at least 2 minutes until completely dissolved. The subject's mouth was then checked to ensure that the drug had completely dissolved. If the drug had not completely dissolved, the subject was instructed to suck on the Flashtab® until it completely dissolved. Subjects were instructed not to swallow or chew any portion of the Flashtab®. No water was provided at least for 1 hour after dosing. Subjects being dosed were provided with stop watches and instructed to start the timer when the tablet was placed on the tongue and stop it once the tablet had disintegrated. The difference between start and stop times was recorded as *in-vivo* disintegration time of the ODT.
Treatment B: One Ultram® 50 mg Tablet (Lot # 3EG016) was administered orally with 240 ml of ambient temperature water following an overnight fast of at least 10 hours.

Results: The mean plasma concentration-time profiles for tramadol following ODT and Ultram are shown in Figure 1. Similar profiles were also observed for its metabolites M1 and M5. Plasma profiles of all three analytes attributable to tramadol HCl ODT and the IR reference appear superimposable.

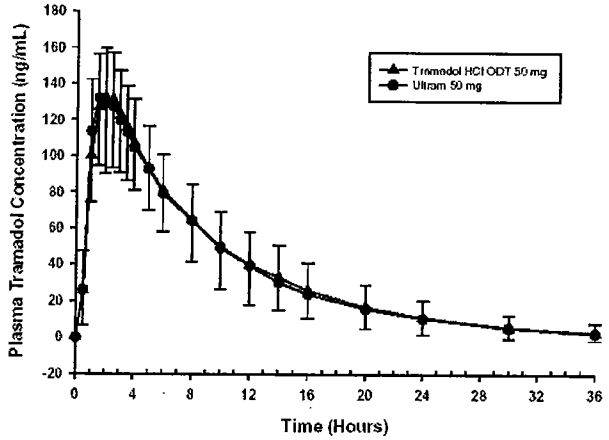

Figure 1: Mean Plasma Tramadol Concentrations After Single Dosing With Tramadol HCl ODT Tablets (1 x 50 mg) Without Water Versus Ultram® (1 x 50 mg) Tablets

The pharmacokinetic parameters derived from the plasma concentration data for tramadol and metabolites are summarized in Table 1 whereas the outcome of the statistical analysis of the pharmacokinetic parameter from this study is summarized in Table 2 respectively.

Table 1: Pharmacokinetic Parameter Values for Tramadol After Oral Dosing With Pivotal Tramadol HCl ODT Tablets and Ultram® Tablets in 36 Healthy Male and Female Subjects

Pharmacokinetic Parameters	*Tramadol HCl 50 mg ODT (Fasting) (n=36) (mean ±SD)*	*Ultram® 50 mg (Fasting) (n=36) (mean ±SD)*
	Tramadol	
AUC_{0-t} (ng·hr/mL)	1284.24 ± 459.47	1257.27 ± 448.17
$AUC_{0-\infty}$ (ng·hr/mL)	1332.76 ± 525.87	1298.26 ± 489.96
C_{max} (ng/mL)	143.12 ± 26.45	142.19 ± 32.74
T_{max} (hour)	1.98 ± 0.66 2.00*	1.75 ± 0.63 1.50*
$t_{½}$ (hour)	6.20 ± 1.51	6.11 ± 1.32
MRT	9.45 ± 2.24	9.18 ± 1.96
	O-Desmethyltramadol (M1)	
AUC_{0-t} (ng·hr/mL)	436.47 ± 118.68	425.39 ± 114.42
$AUC_{0-\infty}$ (ng·hr/mL)	455.46 ± 120.90	443.24 ± 115.56
C_{max} (ng/mL)	35.80 ± 12.41	34.97 ± 12.36
T_{max} (hour)	3.19 ± 0.98 3.00*	2.88 ± 1.06 2.50*
$t_{½}$ (hour)	6.85 ± 1.44	6.87 ± 1.59
MRT	11.91 ± 2.48	11.70 ± 2.57
M/P[a] ratio	0.4023 ± 0.1525	0.4025 ± 0.1552
	O,N-Didesmethyltramadol (M5)	
AUC_{0-t} (ng·hr/mL)	174.43 ± 61.89	170.65 ± 63.88
$AUC_{0-\infty}$ (ng·hr/mL)	194.80 ± 58.36†	190.42 ± 58.98†
C_{max} (ng/mL)	13.02 ± 4.31	12.59 ± 3.67
T_{max} (hour)	3.92 ± 2.30 3.50*	3.75 ± 3.04 2.50*
$t_{½}$ (hour)	7.36 ± 1.93†	7.18 ± 1.85†
MRT	12.94 ± 3.67†	12.60 ± 3.35†
M/P[a] ratio	0.1797 ± 0.0544†	0.1793 ± 0.0578†

*This is the median value.

[a] Metabolite/Parent Ratio = ($AUC_{0-\infty, M5}$/Mol. Wt. of M5)/($AUC_{0-\infty, Tramadol}$/Mol. Wt. of Tramadol).

Mol. Wt. of M5 = [redacted]

Mol. Wt. of Tramadol = [redacted]

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Table 2: Key Statistical Results of Tramadol for the Comparison of a Single Dose of 50-mg Tramadol HCl ODT Tablets and 50-mg Ultram® Tablets in 36 Healthy Male and Female Subjects

Statistical Analysis	*Tramadol HCl 50 mg ODT Tablets vs. Ultram® 50 mg*		
(ANOVA)	*90% Confidence Interval*	*Ratio of Means*	*Intra Subject CV*
	Tramadol		
AUC_{0-t}	98.74% – 105.73%	102.17%	8.58%
$AUC_{0-\infty}$	98.85% – 106.06%	102.39%	8.84%
C_{max}	96.81% – 105.99%	101.29%	11.37%
	O-Desmethyltramadol (M1)		
AUC_{0-t}	99.26% - 106.21%	102.68%	8.50%
$AUC_{0-\infty}$	99.21% - 106.12%	102.61%	8.44%
C_{max}	99.26% - 105.70%	102.43%	7.89%
	O,N-Didesmethyltramadol (M5)		
AUC_{0-t}	98.87% - 106.43%	102.58%	9.10%
$AUC_{0-\infty}$	99.37% - 106.59%	102.92%	8.67%
C_{max}	96.23% - 107.34%	101.63%	13.49%

In this study, the *in vivo* disintegration time of Tramadol ODT was also measured. The *in vivo* disintegration time was 20.6 ± 12.7 seconds with a range of 4 to 68 seconds.

Discussion: Based on these results, bioequivalence between the two treatments (Tramadol HCl 50 mg ODT Tablets without water versus Ultram® 50 mg Tablets) was established as shown in study 2686. One of the differences between this study and study 2686 was inclusion of both male and females subjects in this study as opposed to only male subjects in study 2686. However, no gender analysis was performed on the data. Gender analysis, however, had been performed on pooled data from all the studies.

NDA: 21-693/Study 2821 **Study Dates: Dec '03 – Jan '04**

A Two-way Crossover, Open-label, Single-dose, Food-effect, Bioavailability Study of Tramadol HCl 50 mg Flashtab (Administered Without and With Food) in Normal Healthy Non-smoking Male and Female Subjects

Study Design:

A total of 24 healthy subjects (13 males, 11 females, 17 Caucasians, 4 Asians and 13 Blacks) with the following demographics were enrolled and 22 of them completed this study.

Mean Age: 35 years (range 19 – 52 years); mean height: 1.71 m (range 1.57 – 1.92 m); mean weight: 73 kg (range 52 – 97 kg).

The following crossover bioavailability study design was used. There was a one-week washout between study periods. Blood samples for tramadol, O-desmethyltramadol (M1), and O,N-di- desmethyltramadol (M5) metabolites were determined by a validated LC-MS/MS technique.

Treatment A (With Food): Following an overnight fast of at least 10 hours, subjects recievd a FDA-recommended standardized high fat meal, which was completely consumed within 30 minutes. Thirty minutes after the start of the high fat meal, one Tramadol HCl 50 mg Flashtab® Tablet (Lot # PR03175R) was placed on the tongue until it completely disintegrated and then swallowed with saliva. The subject's mouth was then checked to ensure that the drug had completely dissolved. Subjects were instructed not to swallow or chew any portion of the Flashtab®. No water was provided at least for 1 hour after dosing. Subjects being dosed were provided with Stop Watches and instructed to start the timer when the tablet was placed on the tongue and stop it once the tablet had disintegrated. The difference between start and stop times was recorded as *in-vivo* disintegration time of the ODT.

Treatment B (Without Food): Following an overnight fast of at least 10 hours, one Tramadol HCl 50 mg Flashtab® Tablet (Lot # PR03175R) was placed on the tongue until it completely disintegrated and then swallowed with saliva. The subject's mouth was then checked to ensure that the drug had completely dissolved. Subjects were instructed not to swallow or chew any portion of the Flashtab®. No water was provided at least for 1 hour after dosing. Subjects being dosed were provided with stop watches and instructed to start the timer when the tablet was placed on the tongue and stop it once the tablet had disintegrated. The difference between start and stop times was recorded as *in-vivo* disintegration time of the ODT.

Results: The mean plasma concentration-time profiles for tramadol ODT under fed and fasting conditions are shown in Figure 1. Similar profiles were also observed for its metabolites M1 and M5.

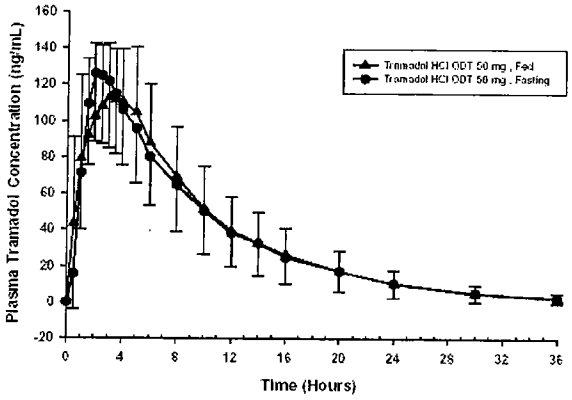


Figure 1: Mean Plasma Tramadol Concentrations After Single Dosing With Tramadol HCl ODT Tablets (1 x 50 mg) Under Fasting and Fed Conditions

The pharmacokinetic parameters derived from the plasma concentration data for tramadol and metabolites are summarized in Table 1 whereas the outcome of the statistical analysis of the pharmacokinetic parameter from this study is summarized in Table 2 respectively.

Table 1: Pharmacokinetic Parameter Values for Tramadol and Key Statistical Results for the Comparison for a Single Dose of 1 x 50-mg Tramadol HCl ODT Tablets Administered with Food and Under Fasting Conditions in 21 Subjects (12 males and 9 Females)

Pharmacokinetic Parameters	*Tramadol HCl 50 mg ODT* ***(Fed)*** *(n=21)* *(mean ±SD)*	*Tramadol HCl 50 mg ODT* ***(Fasting)*** *(n=21)* *(mean ±SD)*
	Tramadol	
AUC_{0-t} (ng·hr/mL)	1295.09 ± 441.70	1269.45 ± 487.99
$AUC_{0-\infty}$ (ng·hr/mL)	1329.38 ± 455.45	1307.90 ± 507.72
C_{max} (ng/mL)	135.68 ± 36.48	139.73 ± 30.44
T_{max} (hour)	3.02 ± 1.41	2.41 ± 0.78
T_{max} (hour)*	3.00	2.00
$t_{½}$ (hour)	5.72 ± 1.15	5.98 ± 1.23
MRT	9.37 ± 2.09	9.54 ± 2.03
	O-Desmethyltramadol (M1)	
AUC_{0-t} (ng·hr/mL)	332.41 ± 146.79	338.47 ± 142.22
$AUC_{0-\infty}$ (ng·hr/mL)	346.68 ± 146.50	354.90 ± 142.47
C_{max} (ng/mL)	27.11 ± 13.56	30.00 ± 15.07
T_{max} (hour)	4.12 ± 1.40	3.12 ± 0.93
$t_{½}$ (hour)	6.29 ± 1.18	6.62 ± 1.20
MRT	11.59 ± 2.33	11.61 ± 2.37
M/P[a] ratio	0.3271 ± 0.2045	0.3533 ± 0.2324
	O,N-Didesmethyltramadol (M5)	
AUC_{0-t} (ng·hr/mL)	129.72 ± 62.10	146.08 ± 66.92
$AUC_{0-\infty}$ (ng·hr/mL)	146.87 ± 64.04	163.86 ± 72.74
C_{max} (ng/mL)	9.02 ± 3.60	10.70 ± 4.22
T_{max} (hour)	6.08 ± 2.64	5.36 ± 3.29
$t_{½}$ (hour)	8.29 ± 3.83	8.10 ± 3.13
MRT	15.20 ± 6.67	14.64 ± 5.83
M/P[b] ratio	0.1304 ± 0.0485	0.1497 ± 0.0543

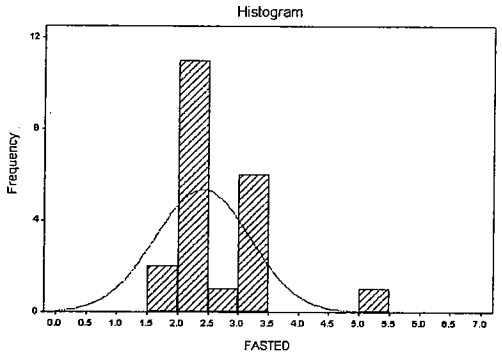
*This is the median value; [a]Metabolite/Parent Ratio = ($AUC_{0-\infty, M1}$/Mol. Wt of M1)/($AUC_{0-\infty, Tramadol}$/Mol. Wt of Tramadol)
[b]Metabolite/Parent Ratio = ($AUC_{0-\infty, M5}$/Mol. Wt of M5)/($AUC_{0-\infty, Tramadol}$/Mol. Wt of Tramadol)
Mol. Wt of M1 = [redacted] Mol. Wt of M5 = [redacted] Mol. Wt of Tramadol = [redacted]

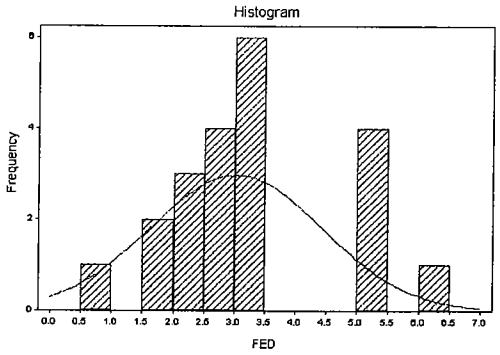
Table 2: Key Statistical Results for the Comparison of 1 x 50-mg Tramadol HCl ODT Tablets Administered with Food and Under Fasting Conditions in 21 Subjects (12 males and 9 Females)

Statistical Analysis (ANOVA)	*Tramadol HCl 50 mg ODT Tablets (Fed) vs. Tramadol HCl 50 mg ODT Tablets (Fasted)*		
	90% Confidence Interval	*Ratio of Means*	*Intra Subject CV*
	Tramadol		
AUC_{0-t}	98.10% – 108.90%	103.36%	9.68%
$AUC_{0-\infty}$	97.74% – 108.51%	102.98%	9.69%
C_{max}	89.14% - 106.13%	97.26%	16.18%
	O-Desmethyltramadol (M1)		
AUC_{0-t}	92.66% - 102.02%	97.23%	8.92%
$AUC_{0-\infty}$	92.46% - 101.44%	96.85%	8.59%
C_{max}	85.97% - 97.87%	91.73%	12.03%
	O,N-Didesmethyltramadol (M5)		
AUC_{0-t}	82.42% - 93.44%	87.76%	11.84%
$AUC_{0-\infty}$	85.09% - 94.91%	89.87%	10.13%
C_{max}	81.14% - 90.69%	85.78%	10.32%

In this study, the *in vivo* disintegration time of Tramadol ODT was also measured. The *in vivo* disintegration time was 16.5 ± 11.1 seconds with a range of 5 to 57 seconds.

Discussion: Based on the data it may be concluded that tramadol HCl ODT can be given to patients for management of moderate to moderately severe pain without regard to food. However, analysis of the individual t_{max} values under fasting and fed states revealed an obvious skew to the Fed data due to prolonged t_{max} observed in 5 subjects (see the following histograms). This explains a delay of t_{max} by about 30 minutes following administering tramadol HCl ODT after food compared to administering the same under fasting condition.





Comments: *Food did not affect the BA of the active drug in ODT as expected from lack of food effect observed with Ultram® (as per label). However, t_{max} was delayed by about 30 minutes when the ODT was administered after food.*

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-693	Brand Name	Ralivia Flashdose
OCPB Division (I, II, III)	III	Generic Name	Tramadol HCl
Medical Division	550	Drug Class	Analgesic
OCPB Reviewer	Tapash K. Ghosh	Indication(s)	Moderate to moderately severe pain
OCPB Team Leader	Edward D. Bashaw	Dosage Form	Orally Disintegrating Tablet
		Dosing Regimen	prn
Date of Submission	3/10/04	Route of Administration	Oral
Estimated Due Date of OCPB Review	11/10/04	Sponsor	Biovail
PDUFA Due Date	1/10/05	Priority Classification	3S
Division Due Date	12/10/04		

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			
HPK 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) -				
eers-				
single dose:	X	6		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X			
replicate design; single / multi dose:				
Food-drug interaction studies:	X			
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		6		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Is Tramadol ODT bioequivalent to IR Tramadol tablet?**	
Other comments or information not included above		
Primary reviewer Signature and Date	*Tapash Ghosh*	
Secondary reviewer Signature and Date	*Dennis Bashaw*	

CC: NDA XX-XXX, HFD-850(ELECTRONIC ENTRY OR LEE), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. MURPHY)

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/s/

Tapash Ghosh
12/12/04 10:03:27 AM
BIOPHARMACEUTICS

Dennis Bashaw
12/13/04 01:20:04 PM
BIOPHARMACEUTICS