

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-693**

**MEDICAL REVIEW**



**FDA Center for Drug Evaluation and Research**  
**Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products**  
**HFD-550, 9201 Corporate Blvd, Rockville MD 20850**                      **Tel:(301) 827-2040**

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DEPUTY DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

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DATE:            May 4, 2005

THROUGH:    Bob Rappaport, M.D., Division Director

DRUG:        Tramadol Hydrochloride Oral Disintegrating Tablet)

NDA:         21-693

SPONSOR:    Biovail Laboratories Inc.

INDICATION: Treatment of moderate to moderately severe pain

LETTER DATE: March 8, 2005

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Biovail Laboratories has submitted a complete response to an approvable action taken on January 11, 2005 for a 505(b)(2) application for tramadol hydrochloride oral disintegrating tablet (tramadol ODT). The outstanding deficiency was a failure to submit the blister and carton packaging for review. The reader is referred to the original action memo for details of the first cycle reviews.

The blister label and the carton label were reviewed by the review team and by the Division of Drug Marketing, Advertising and Communication (DDMAC) and the Office of Drug Safety, Division of Medication Errors and Technical Support (DMETS). The final tradename proposed by the sponsor, Ultram ODT, has not been formally submitted to the application and will not be reviewed prior to this action.

Bartholomew Ho, the chemistry reviewer, found the carton label acceptable. DMETS made several comments about the proposed blister label and carton label that were conveyed to the sponsor. For the blister label, it was pointed out that the strength is based on the active moiety, not the hydrochloride salt. As the dosage has the equivalent of 50 mg of tramadol, it should be clear that this is a 50 mg tablet. The established name should be at least one-half the size of the proprietary name and the  over the proprietary name could be deleted, leaving more room for the proprietary name, established name, and strength. The statement "Do not push table through" should be bolded. These comments

were also applicable to the carton labeling along with the request for a statement regarding whether the packaging utilizes child resistant closures and to relocate the net quantity farther from the product strength.

The sponsor has responded to these comments implementing the suggestions. In response to the final proposal, to add the "50 mg" below the established name, the sponsor has committed to implementing the change recommended.

Changes to the package insert were completed with the first review cycle. A line-by-line review found the currently submitted package insert to be accurate in representing the agreed upon language without differences.

The sponsor had initially requested a pediatric waiver. The nature of this formulation, that it disintegrates and then is swallowed rather than a whole tablet being swallowed may be useful in pediatric patients who have difficulty swallowing tablets. Therefore, a waiver will not be granted. To ensure that there are no unforeseen safety problems related to the new formulation, it was determined during the first cycle that a pediatric deferral of one year will be granted. Following a review of the postmarketing safety reports for the first year of marketing, pediatric studies will be required.

**Action recommended by the Division: Approval**

Sharon Hertz, M.D.  
Deputy Director  
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products  
Office of Drug Evaluation V, CDER, FDA

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DEPUTY DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

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DATE:            January 11, 2005

DRUG:           Ralivia Flashdose (Tramadol Hydrochloride Oral Disintegrating Tablet)

NDA:            21-693

SPONSOR:      Biovail Laboratories Inc.

INDICATION: Moderate to moderately severe pain

LETTER DATE: March 10, 2004

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Biovail Laboratories has submitted a 505(b)(2) application for tramadol hydrochloride oral disintegrating tablet (tramadol ODT) with the proposed proprietary name of Ralivia Flashdose. Tramadol HCl is a centrally acting synthetic opioid analgesic. The reference listed drug is Ultram, an immediate-release tramadol hydrochloride tablet approved March 3, 1995, is indicated for moderate to moderately severe pain. The sponsor has submitted six studies in support of this application that were intended to evaluate the pharmacokinetic characteristics of tramadol ODT and to demonstrate bioequivalence with the reference listed product. The sponsor is seeking the same indication as Ultram and is relying on prior findings of safety and efficacy. As such, no additional efficacy or safety studies were performed in support of this application. The sponsor is also referencing clinical pharmacology and nonclinical findings in the Ultram package insert and has not done any new studies other than those to characterize the clinical pharmacological properties of this new formulation. Carcinogenicity studies were performed by the sponsor for another application that has been referenced for this application. This data was reviewed by Dr. Conrad Chen and will be used to inform the package insert. The dosing is to be the same as Ultram, 50 mg every four to six hours as need, not to exceed 400 mg per day. Although questioned in the Team Leader Memo by Dr. Joel Schiffenbauer, the proposed indication is appropriate for this product as the sponsor has shown bioequivalence to the reference listed product, moderate to moderately severe pain are terms that are common and well understood in the clinical pain community, and this indication is well established in the regulatory environment of this Agency.

The chemistry, manufacturing, and controls review was performed by Bart Ho. Stability data was acceptable. No deficiencies were noted in regarding either the drug substance and drug product.

A total of six studies were performed in which 151 patients received tramadol ODT and 103 received Ultram. The clinical pharmacology and biopharmaceutics development program was reviewed by Dr. Tapash Ghosh. Dr. Ghosh describes three single-dose bioavailability/bioequivalence (BA/BE) studies considered pertinent to labeling. These studies which demonstrated that equivalent amounts of drug were absorbed after dosing with Tramadol ODT 50 mg tablets and Ultram 50 mg tablets, that the pharmacokinetic profiles for tramadol and its M1 and M5 metabolites were comparable for the two products, and that there was no food effect on the total amount of tramadol drug absorbed when tramadol ODT was administered with food. However, time to peak exposure ( $T_{max}$ ) following administration of tramadol ODT after food was delayed by about 30 minutes compared to administration under fasting condition. No effects of gender, age, and race were found in cross-study evaluations.

Safety was reviewed by Dr. Tatiana Oussova. There were no deaths or serious adverse events during the six studies. There were three subjects who discontinued study participation early, only one due to an adverse event, brief episodes of difficulty breathing 17 hours after the first dose of study drug. The adverse event profile was comparable to Ultram with no adverse events not previously identified.

The sponsor has requested a pediatric waiver. The nature of this formulation, that it disintegrates and then is swallowed, rather than a whole tablet swallowed may be useful in pediatric patients who have difficulty swallowing tablets. Therefore, a waiver will not be granted. To ensure that there are no unforeseen safety problems related to the new formulation, a pediatric deferral of one year will be granted. Following a review of the postmarketing safety reports for the first year of marketing, pediatric studies will be required.

Labeling reviews were obtained from the Division of Drug Marketing and Communication (DDMAC) and the Office of Drug Safety, Division of Medication Errors and Technical Support (DMETS) and a tradename review was also performed by DMETS. The DDMAC review recommended replacing the trade name in place of the generic name when discussing risk associated with use of the product and to add a comment that no studies have been conducted to determine if the onset of action is different for tramadol ODT than for Ultram. Additional recommendations for edits were incorporated into labeling negotiations. The DDMAC review also noted the name Ralivia is overly fanciful and implies that the medication will provide relief. The DMETS review found that the proprietary name Ralivia, proposed for two products, Ralivia ER and Ralivia Flashdose, is not recommended as when the two products are approved and marketed at different times, there is potential for the modifier to be omitted leading to confusion once the second product is approved and marketed. Concern was also raised for the potential of look-alike and sound-alike confusion between the name Ralivia and several already marketed products (Revia, Alinia, Kariva, Raptiva). The term flashdose refers to a technology

employing an orally disintegrating tablet which has been used in several other medications already on the market. Use of a modifier is not recommended in general, and in particular if there is a possibility that other products in the market place employ the same technology.

The Division requested amended language for the proposed package insert and agreement was reached with the sponsor. This is reflected in the package insert accompanying the action letter. A request was also made to submit an alternate proprietary name, and an alternate name was proposed by the sponsor, [REDACTED]. This proprietary name is not acceptable. The modifier is misleading, the tablet does not melt, it disintegrates and it still brings to mind the suggestion of a more rapid onset. The only acceptable modifier for this type of product is ODT for orally disintegrating tablet. There is also insufficient time for a proper review of [REDACTED] as a proprietary name.

Discussion took place how to reference the data from Ultram in the clinical pharmacology and clinical trial sections of the package insert. Agreement was reached to use the term orally swallowed immediate-release tramadol tablet.

The one deficiency of this application is that the blister label and carton label have not been submitted for review with the original application. The sponsor was requested during the review period to submit this material but as of January 11, 2025, this has not been submitted to the application.

I recommend an approvable action due to the deficiency of failure to submit the blister label and carton label.

**Action recommended by the Division: Approvable**

Sharon Hertz, M.D.  
Deputy Director  
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products  
Office of Drug Evaluation V, CDER, FDA

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# Clinical Review Cover Sheet

## Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Product (HFD-550)

<b>Application Type:</b>	<b>NDA 21-693</b>
<b>NDA Type:</b>	<b>505(b)(2)</b>
<b>Date of Submission:</b>	<b>March 10, 2004</b>
<b>Date received:</b>	<b>March 15, 2004</b>
<b>Review Date:</b>	<b>January 10, 2005</b>
<b>Drug Name:</b>	<b>Ralivia FlashDose</b>
<b>Generic Name:</b>	<b>Tramadol Hydrochloride Orally Disintegrating Tablets</b>
<b>Applicant:</b>	<b>Biovail Laboratories, Inc.</b>
<b>Pharmacologic category:</b>	<b>NSAID</b>
<b>Proposed Indication:</b>	<b>Moderate to moderately severe pain in adults</b>
<b>Dosage forms and route:</b>	<b>Orally disintegrating tablets Starting dose 50 mg once daily titrated as needed</b>
<b>Intended Population</b>	<b>Adults</b>
<b>Medical reviewer:</b>	<b>Joel Schiffenbauer</b>
<b>Project manager:</b>	<b>Kathleen Reedy</b>

NDA 21-693  
Ralivia Flashdose

## SUMMARY

Biovail Laboratories, Inc. (Biovail) submitted NDA 21-693 as a 505(b)(2) application for Ralivia FlashDose. This drug is an orally disintegrating formulation of tramadol hydrochloride (tramadol HCL) intended for dosing every four-to-six hours (up to a maximum of 400 mg/day) for the management of moderate to moderately severe pain in adults.

The immediate-release formulation of tramadol HCl was approved in the United States on March 3, 1995 with the trade name of Ultram (NDA 20-281) for the management of moderate to moderately severe pain in adults. As a 505 (b) (2) application, the sponsor is referencing the existing information on the 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 overall conclusions based on the outcome of the pharmacokinetic studies performed with Ralivia FlashDose are the following:

- Dosing with Ralivia FlashDose 50 mg delivers the same amount of drug to the systemic circulation as the approved reference product Ultram 50 mg tablets.
- 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. It is not known if this delay will affect the clinical efficacy of the drug. Because Ultram is used for acute as well as chronic pain indications, in the acute situation, time to onset of analgesia is a critical component.

A detailed review of the biopharmacology studies can be found in Dr. Tapash K. Ghosh's review.

The limited safety data available from this development program suggests that the safety profile of Ralivia Flashdose is consistent with known safety profile of Ultram. There were no deaths or SAEs reported in the trials. There were 3 subjects who dropped out prior to completing the trials, one with a positive drug screen, one due to personal reasons, and one with dyspnea. The common AE profile is similar to Ultram.

In terms of labeling, the sponsor should be requested to address the labeling issues raised by the DDMAC reviewer. Specifically, the use of the generic name tramadol should be replaced with Ralivia where appropriate (see review by Jialynn Wang, Pharm. D. for additional comments) In addition, the label should reflect the fact that use of food delays the time to peak exposure, although the clinical consequence of this is not known, since no efficacy studies were provided. A letter dated December 21,2004 was sent to the

sponsor with comments on the label. At the time of this review the sponsor had not yet responded to this letter.

The use of the name "Flashdose" implies a rapidity of action. This is clearly not the case, based on the PK studies, and because of this DMETS does not recommend the use of the name Flashdose. DMETS also does not recommend the use of the name Ralivia which implies that the medication will provide relief. Therefore, additional discussions with the sponsor will be necessary to address these concerns.

Comment: plies

The sponsor is requesting the same indication as Ultram which is "treats moderate to moderately severe pain." Recently the Division has not allowed this indication for new analgesics because of the difficulty in defining severity of pain. However, because Ultram has this indication, and because Ralivia is essentially bioequivalent to Ultram, it seems reasonable to grant Ralivia the same indication as Ultram. Furthermore, to consider changing indications might be confusing to the general public, as they would not understand which drug to use for different indications (even though the drugs are essentially the same).

## CONCLUSIONS

The safety profile of the immediate release formulation of Tramadol HCl (Ultram) is well known due to its long marketing history. Since this is a 505 (b) (2) application, the sponsor is referencing the existing information on the pharmacokinetics, metabolism, and pharmacodynamic behavior of tramadol. Ralivia FlashDose 50 mg is designed to deliver an equivalent amount of drug to the systemic circulation as the immediate-release Ultram 50 mg tablets. The clinical significance of the delay in peak exposure with food, is unknown, but should be reflected in the label.

### Recommendations:

The recommendation is for approval for Ralivia FlashDose 50 mg tablets for the management of moderate to moderately severe pain in adults (this product is essentially bioequivalent to the innovator product Ultram; Ralivia Flashdose should receive the same indication as for Ultram) pending labeling negotiations.

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Joel Schiffenbauer  
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# Clinical Review Cover Sheet

## Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Product (HFD-550)

<b>Application Type:</b>	<b>NDA 21-693</b>
<b>NDA Type:</b>	<b>505(b)(2)</b>
<b>Date of Submission:</b>	<b>March 10, 2004</b>
<b>Date received:</b>	<b>March 15, 2004</b>
<b>Review Date:</b>	<b>December 21, 2004</b>
<b>Drug Name:</b>	<b>Ralivia FlashDose</b>
<b>Generic Name:</b>	<b>Tramadol Hydrochloride Orally Disintegrating Tablets</b>
<b>Applicant:</b>	<b>Biovail Laboratories, Inc.</b>
<b>Pharmacologic category:</b>	<b>NSAID</b>
<b>Proposed Indication:</b>	<b>Moderate to moderately severe pain in adults</b>
<b>Dosage forms and route:</b>	<b>Orally disintegrating tablets Starting dose 50 mg once daily titrated as needed</b>
<b>Intended Population</b>	<b>Adults</b>
<b>Medical reviewer:</b>	<b>Tatiana Oussova, M.D., M.P.H.</b>
<b>Project manager:</b>	<b>Kathleen Reedy, RDH, MS</b>

NDA 21-693  
Ralivia Flashdose  
Safety Review

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# Integrated Review of Safety

## 1.0 Introduction

Biovail Laboratories, Inc. (Biovail) submitted NDA 21-693 as a 505(b)(2) application for Ralivia FlashDose. This drug is an orally **disintegrating** (not dissolving!) formulation of tramadol hydrochloride (tramadol HCL) intended for dosing every four-to-six hours (up to a maximum of 400 mg/day) for the management of moderate to moderately severe pain in adults.

The immediate-release formulation of tramadol HCl was approved in the United States on March 3, 1995 with the trade name of Ultram (NDA 20-281) for the management of moderate to moderately severe pain in adults. There are currently 14 generic versions of Ultram that are approved in the US for the same indication. If approved, Ralivia FlashDose will be the first orally disintegrating tablets (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 Ralivia FlashDose clinical program is comprised of 6 pharmacokinetic studies. The key elements in the development program were the following:

- Comparison with the approved (Ultram) immediate-release tablet formulation to establish compliance with the biopharmaceutic requirements for a 505(b)(2) submission (3 studies);
- Influence of food on the *in vivo* performance of Ralivia FlashDose (3 studies);
- Effect of administering Ralivia FlashDose tablets with or without water on the bioavailability of Ralivia FlashDose tablets (50 mg) after single dosing.

The overall conclusions based on the outcome of the pharmacokinetic studies performed with Ralivia FlashDose are the following:

- Dosing with Ralivia FlashDose 50 mg delivers the same amount of drug to the systemic circulation as the approved reference product Ultram 50 mg tablets. Therefore, Ralivia FlashDose 50 mg satisfies the bioavailability requirements for a 505(b)(2) submission.
- 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.

The detailed review of these studies can be found in Dr. Tapash K. Ghosh's review.

Since there were no clinical efficacy studies provided with this application, this review consists of the safety review only.

## **1.1 Methods and Findings**

The clinical safety data that are presented in the ISS include adverse events, vital signs (blood pressure, heart rate), laboratory measurements (blood chemistry, hematology, urinalysis), physical examination, and electrocardiogram (ECG).

The safety data from all the six Phase I single-dose studies were integrated and summarized descriptively; no statistical testing was performed. This information was used to assess the relative safety of Ralivia FlashDose compared to Ultram safety as provided in Ultram label.

The summary of adverse events on study drug included only treatment-emergent adverse events. A treatment-emergent adverse event was defined as one that occurred after the subject took the dose of study drug. This includes adverse events that were present before the first dose of study drug but which worsened in severity after the dosing with the study drug.

An adverse event was considered serious if it was fatal or life threatening; required inpatient hospitalization or prolongation of hospitalization; resulted in a persistent or significant disability/incapacity; or was a congenital anomaly/birth defect. Adverse events also were considered serious if, based on medical judgment, they jeopardized the patient and required medical or surgical intervention to prevent one of the above outcomes.

In summary, healthy volunteers dosed with Ralivia FlashDose 50 mg reported adverse events similar to those experienced by subjects who were administered Ultram. The most common events were gastrointestinal and central nervous system in nature. The incidence of adverse events was comparable between the study and the reference drug.

In this reviewer's opinion, based on the information provided with this NDA there is no reason to believe that Ralivia FlashDose adverse events profile would be different from that of approved Ultram in equivalent doses.

### **1.1.1 Deaths**

There were no deaths reported for any of the six Phase I studies.

### **1.1.2 Other Serious Adverse Events**

There were no serious adverse events reported for any of the six Phase I studies.

### **1.1.3 Dropouts and Other Significant Adverse Events**

Four of the six studies did not have any subject who prematurely discontinued. There were 3 subjects from two studies who dropped out prior to completing all the dosing

periods. The overall dropout rate is 1.9% (3/151). Subject 17, from Study 2687, was dropped because of a positive drug screen test prior to Period 2 dosing. Subject 3 from Study 2821 withdrew due to personal reasons and Subject 20, from the same study, prematurely discontinued due to an adverse event (dyspnea).

### 1.1.3.1 Adverse Events Associated with Dropouts

Subject 20 (Study 2821), a 43 year-old, White, female was dosed with Ralivia FlashDose 50 mg under fasted condition, without water on the morning of January 10, 2004. As per study protocol, the subject stayed in the study site facility for 24 hours after dosing. The subject reported to the study site staff that she experienced four episodes of difficulty of breathing on January 11, 2004 (between 1:00 – 4:00 am), approximately 17 hours after dosing. The episodes resolved spontaneously and were mild in intensity. No action was taken. The subject was discharged on January 11, 2004. She called the study site personnel on January 13, 2004 to report that she had another episode of difficulty of breathing on the night of January 11, 2004. The event was mild in intensity and resolved spontaneously. She informed the site personnel that she had decided to withdraw from the study. The subject returned to the site on January 18, 2004 for the post-study procedures.

### 1.1.3.2 Other Significant Adverse Events

There were no other significant adverse events

### 1.1.4 Common Adverse Events

The incidence of adverse events reported  $\geq 2\%$  by any subgroup is presented by overall descending frequency in Table 1.

**Table 1. Incidence of Adverse Events Reported in  $\geq 2\%$  of Subjects: Ralivia FlashDose Phase I Studies**

MedDRA Preferred Term	Ralivia FlashDose					Ultram <sup>®</sup>		
	Fasted, w/water (N=54) n (%)	Fasted, w/water (N=91) n (%)	Fed, w/water (N=24) n (%)	Fed, w/water (N=58) n (%)	All subjects (N=151) n (%)	Fasted, w/water (N=67) n (%)	Fed, w/water (N=33) n (%)	All subjects (N=103) n (%)
Subjects with at least 1 adverse event (excluding abnormal laboratory parameters)	6 (11)	14 (15)	1 (4)	11 (19)	28 (19)	8 (12)	5 (14)	13 (13)
Dizziness	2 (4)	8 (9)	0 (0)	2 (3)	12 (8)	6 (9)	2 (6)	8 (8)
Nausea	2 (4)	6 (7)	1 (4)	1 (2)	9 (6)	3 (4)	2 (6)	5 (5)
Headache	0 (0)	3 (3)	1 (4)	2 (3)	6 (4)	0 (0)	0 (0)	0 (0)
Vomiting	1 (2)	3 (3)	1 (4)	1 (2)	6 (4)	1 (1)	0 (0)	1 (<1)
Pallor	1 (2)	3 (3)	0 (0)	0 (0)	3 (2)	1 (1)	0 (0)	1 (<1)
Fatigue	1 (2)	1 (1)	0 (0)	0 (0)	2 (1)	0 (0)	1 (3)	1 (<1)
Herpes simplex	0 (0)	0 (0)	0 (0)	2 (3)	2 (1)	0 (0)	0 (0)	0 (0)
Hypoaesthesia	1 (2)	0 (0)	0 (0)	1 (2)	2 (1)	0 (0)	0 (0)	0 (0)
Somnolence	1 (2)	0 (0)	0 (0)	1 (2)	2 (1)	0 (0)	0 (0)	0 (0)
Feeling cold	1 (2)	1 (1)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
Abdominal pain upper	1 (2)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Loose stools	1 (2)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Stomach discomfort	1 (2)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Catheter site ecchymosis	0 (0)	0 (0)	0 (0)	1 (2)	1 (<1)	0 (0)	1 (3)	1 (<1)
Arthralgia	1 (2)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Pain in extremity	0 (0)	0 (0)	0 (0)	1 (2)	1 (<1)	0 (0)	0 (0)	0 (0)
Pollakiuria	0 (0)	0 (0)	0 (0)	1 (2)	1 (<1)	0 (0)	0 (0)	0 (0)
Erythema	1 (2)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)

Source data: ISS Table 4.1.1, ISS Listings 3 and 5.

The incidence rates of adverse events for subjects in the Ralivia FlashDose group were slightly higher compared to the Ultram group (19% vs. 13%). Most of the adverse events reported were consistent with those listed in the product monograph for Ultram. Dizziness, nausea, headache and vomiting were the three most frequently reported adverse events for the Ralivia FlashDose group. The fasted subgroups for the Ralivia FlashDose and Ultram have the highest incidences. A majority of the adverse events were mild in intensity. There was no treatment-emergent adverse event that was rated as severe.

Of the safety parameters of interest, only the adverse event and the vital signs data can be appropriately assigned to the different subgroups created because the information was collected continuously throughout the duration of the study.

The laboratory measurements and physical examination were taken at screening and at the end of the study, after all the crossovers were completed, so any abnormal change noted from screening can not be associated with a particular drug regimen or subgroup.

The ECG was performed only at screening. Potential subjects with a clinically significant abnormality were made to undergo another ECG and were allowed to join the study if the repeat ECG became normal or showed no clinically significant changes.

#### **1.1.4.1 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms**

The integrated adverse events for all studies are presented using the preferred term (PT) from the Medical Dictionary of Regulatory Activities (MedDRA). In the individual clinical reports, the adverse event data for Study 2613 was not coded in MedDRA, while Studies 2686 and 2687 were coded in MedDRA Version 6.0 and Studies 2794, 2795 and 2821 were coded in MedDRA Version 6.1. For consistency across the six studies, the integrated adverse event data were recoded to MedDRA Version 6.1. The conversion from MedDRA Version 6 to 6.1 affected only 1 adverse event term (verbatim term "vomiting" coded as "vomiting NOS" in MedDRA 6.0, now coded as "vomiting" in MedDRA 6.1).

Adverse events of all causalities, treatment-related adverse events, and adverse events leading to study medication discontinuation were listed by system organ class, MedDRA term, and the investigators' assessments of severity (mild, moderate, severe).

#### **1.1.4.2 Additional Analyses and Explorations**

There were six events that were reported to be treatment-related; the most common of which were dizziness, headache and nausea. The incidence of treatment-related adverse events from the Ralivia FlashDose group was comparable to that of the Ultram® group (10% vs. 7%).

The Ralivia FlashDose and the Ultram® fasted subgroups had the highest incidences. All the events were rated as mild in intensity, except for vomiting.

**Table 2.**  
**Incidence of Treatment-Related Adverse Events: Ralivia FlashDose Phase I Studies**

MedDRA Preferred Term	Ralivia FlashDose					Ultram®		
	fasted, w/water (N=54) n (%)	fasted, w/water (N=91) n (%)	fed, w/water (N=24) n (%)	fed, w/water (N=58) n (%)	All subjects (N=151) n (%)	fasted w/water (N=67) n (%)	fed w/water (N=36) n (%)	All subjects (N=103) n (%)
Subjects with at least 1 treatment-related adverse event	0 (0)	12 (13)	0 (0)	4 (7)	15 (10)	4 (6)	3 (8)	7 (7)
Dizziness	0 (0)	7 (8)	0 (0)	0 (0)	7 (5)	4 (6)	2 (6)	6 (6)
Headache	0 (0)	2 (2)	0 (0)	2 (3)	4 (3)	0 (0)	0 (0)	0 (0)
Nausea	0 (0)	5 (5)	0 (0)	0 (0)	5 (3)	2 (3)	2 (6)	4 (4)
Vomiting	0 (0)	2 (2)	0 (0)	1 (2)	3 (2)	2 (3)	1 (3)	3 (3)
Somnolence	0 (0)	0 (0)	0 (0)	1 (2)	1 (<1)	0 (0)	0 (0)	0 (0)
Hyperhidrosis	0 (0)	1 (1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)

Source data: ISS Table 4.2, ISS Listings 3 and 5

There were three subjects who experienced adverse events that occurred prior to dosing.

Subject 9 (Study 2613) had pallor, dizziness and rigors prior to Period 1 dosing. All the events were mild in intensity and resolved spontaneously. The subject completed the study.

Subject 15 (Study 2687) experienced dizziness and syncope prior to Period 1 dosing. The events occurred after the insertion of the catheter for blood extraction. The syncope was reported to be severe in intensity and lasted for 2 to 3 seconds. Both events resolved and the subject completed the study without any other adverse events.

Subject 14 (Study 2795) experienced nausea and dizziness prior to Period 1 dosing. The events were mild in intensity and resolved spontaneously. The subject completed the study.

### 1.1.5 Laboratory Findings

The abnormal laboratory parameters are summarized according to study. This separate table was created because **the post-study laboratory tests were conducted after the subjects had undergone all the crossovers for the different treatments**, hence, any change in the values observed cannot appropriately be reported under a particular drug regimen or subgroup.

**Table 3. Incidence of Abnormal Laboratory Parameters Reported as Adverse Events: Ralivia FlashDose Phase I Studies**

MedDRA Preferred Term	Study 2613 (N=12) n (%)	Study 2626 (N=19) n (%)	Study 2687 (N=24) n (%)	Study 2794 (N=36) n (%)	Study 2795 (N=36) n (%)	Study 2821 (N=24) n (%)	Total (N=151) n (%)
Subjects with at least 1 adverse event (including abnormal laboratory parameters)	7 (58)	8 (42)	4 (17)	18 (50)	12 (33)	14 (58)	63 (42)
Subjects with at least 1 abnormal laboratory finding	3 (25)	6 (32)	3 (13)	13 (36)	2 (6)	2 (8)	29 (19)
Blood creatinine increased	0 (0)	1 (5)	0 (0)	11 (31)	1 (3)	0 (0)	13 (9)
Alanine aminotransferase increased	2 (17)	2 (11)	0 (0)	0 (0)	0 (0)	0 (0)	4 (3)
Eosinophil count increased	0 (0)	1 (5)	1 (4)	1 (3)	0 (0)	0 (0)	3 (2)
Blood lactate dehydrogenase increased	0 (0)	0 (0)	0 (0)	0 (0)	2 (6)	0 (0)	2 (1)
Blood urine	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	1 (4)	2 (1)
Glucose urine	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	1 (4)	2 (1)
Aspartate aminotransferase increased	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Blood urea increased	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	1 (<1)
Lymphocyte count increased	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	1 (<1)
Neutrophil count decreased	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Platelet count decreased	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	1 (<1)
Platelet count increased	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	1 (<1)
Red blood cell count increased	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Urine ketone body present	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
White blood cells urine	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)

Source data: ISS Table 4.1.2, ISS Listing 5.

There were 35 (21 abnormal blood chemistry, 8 hematology and 6 urinalysis) results that were considered as adverse events. Thirty of these events (86%) occurred in the four studies where there was an Ultram treatment group. The most frequently reported abnormal laboratory findings were “*blood creatinine increased*” and “*alanine aminotransferase increased*”; both events are listed in the Ultram label.

### 1.1.5.1 Overview of Laboratory Testing in the Development Program

Blood chemistry, hematology and urine tests were conducted on all the subjects at screening and at the end of the study. The lists of subjects with abnormal laboratory values, at screening or post-study, based on the central laboratory’s reference ranges is provided with this submission (Appendix D, ISS Tables 7.3, 7.6, and 7.9).

#### Reviewer’s comments:

- *This reviewer noted a significant discrepancy in numbers of laboratory adverse events (such as increased creatinine values and increased ALT values) listed in Table 3 above (Sponsor’s Table 8) and Appendix D, Table 7.3. Of note, most of elevated values are not clinically significant.*
- *The Sponsor provided the following explanation for this: The principal investigator reviewed all the abnormal laboratory parameters and then evaluated the results to determine if they were clinically significant. The clinically significant ones were reported as adverse events. Hence, the ISS in-text Table 8 (Incidence of Abnormal Laboratory Parameters Reported*

as Adverse Events: Ralivia FlashDose Phase I Studies) included only those abnormal laboratory values that were categorized as adverse events by the principal investigator. Appendix D's Table 7.3 (Clinical Laboratory Tests – Blood Chemistry: Subjects with Abnormal Post-Study Laboratory Values [Safety Population]) listed all subjects with post-study abnormal laboratory values based on the central laboratory's reference ranges. Therefore, it was possible for the subject's laboratory value to be abnormal based on the reference range and not be considered as an adverse event because it was not deemed clinically significant.

- The Sponsor needs to be reminded that preferred method of analyzing laboratory adverse events is to include them all regardless of the investigator's assessment of their clinical significance

As noted above, any change in the values observed cannot appropriately be reported under a particular drug regimen.

All subjects with laboratory values that are categorized as adverse events were requested to return to the study site for a repeat testing.

**Reviewer's comment:**

- This reviewer noted that many subjects are missing their repeat testing values.

**1.1.6 Vital Signs**

Blood pressure (systolic and diastolic) and heart rate were measured with the subjects in sitting position at various time points during the study.

**Table 4.**  
**Vital Signs (Blood Pressure and Heart Rate): Ralivia FlashDose Phase I Studies**

Vital Sign Parameter	Ralivia FlashDose					Ultram		
	Fasted, w/water (N=54)	Fasted, w/water (N=91)	Fed, w/water (N=24)	Fed, w/water (N=58)	All subjects (N=151)	Fasted, w/water (N=67)	Fed, w/water (N=36)	All subjects (N=103)
pre-dose SBP, mmHg, mean (SD)	117 (8.6)	113 (8.6)	118 (8.6)	109 (6.2)	113 (7.6)	114 (9.0)	110 (7.3)	112 (8.7)
2 hour post-dose SBP, mmHg, mean (SD)	113 (7.6)	109 (8.5)	113 (8.6)	110 (7.0)	110 (7.4)	110 (9.3)	110 (7.8)	110 (8.8)
pre-dose DBP, mmHg, mean (SD)	76 (7.8)	74 (7.1)	74 (6.9)	71 (7.0)	73 (6.7)	75 (7.4)	73 (7.3)	74 (7.4)
2 hour post-dose DBP, mmHg, mean (SD)	76 (6.1)	73 (6.4)	75 (6.5)	72 (7.5)	73 (6.2)	74 (8.3)	72 (6.7)	73 (7.9)
pre-dose HR, beats per minute, mean (SD)	67 (5.9)	69 (7.3)	70 (5.5)	70 (8.0)	69 (6.9)	70 (7.5)	70 (8.1)	70 (7.7)
2 hour post-dose HR, beats per minute, mean (SD)	65 (6.6)	65 (5.6)	73 (8.1)	70 (8.2)	67 (7.0)	65 (5.4)	71 (7.5)	67 (6.8)

Source data: ISS Table 6.1, ISS Listing 7.

The mean systolic (SBP) and diastolic blood pressure (DBP) and the average heart rate (HR) at pre-dose and two hours post-dose for all the subgroups were within the normal

limits (BP = 100-140/60-90 mmHg; HR = 55-99 beats per minute) set by the study site. All the subgroups had comparable mean blood pressure and heart rate at pre-dose and at two hours post-dose.

There was one report (Subject 9, Study 2613) of hypotension (96/68 mmHg) after Period 2 dosing. The event was preceded by dizziness and occurred after a blood extraction. The condition resolved and the subject completed the study. There were no other reports of abnormal changes in blood pressure or heart rate.

#### **1.1.7 ECGs**

All the subjects underwent ECG at screening.

There were four subjects who had abnormal but not clinically significant ECG results at screening. These were Subjects 11, 12 (Study 2686), Subject 31 (Study 2794) and Subject 19 (Study 2821). Three subjects had abnormal and clinically significant findings on their initial ECG. A repeat ECG was performed on the three subjects after a few days. The second ECG showed normal findings for 2 subjects (Subject 11, Study 2795 and Subject 5, Study 2821) and abnormal but clinically insignificant changes for the third subject (Subject 34, Study 2794).

These seven subjects completed their respective studies and there were no abnormal ECG changes reported as adverse events.

#### **1.1.8 Special Safety Studies**

There were no special safety studies conducted.

#### **1.1.9 Withdrawal Phenomena/Abuse Potential**

No studies were done to assess these issues with Ralivia FlashDose. The Sponsor presented no additional abuse potential assessments for Ralivia Flashdose. A recommendation to schedule all tramadol products in the Controlled Substances Act (CSA) is under review within CSS, CDER and NIDA.

For additional information, please, see consultation on the Abuse Liability of Tramadol Products by Michael Klein, Ph.D. (HFD-009).

The applicable relevant statement in the Ultram label:

*Withdrawal symptoms may occur if Ultram is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication.*

The following statements appear in the Ultram label:

*Ultram may induce psychic and physical dependence of the morphine-type ( $\mu$ -opioid).*

*Ultram should not be used in opioid-dependent patients. Ultram has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids. Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug, are not limited to those patients with prior history of opioid dependence.*

#### **1.1.10 Human Reproduction and Pregnancy Data**

There is no information on drug exposure in pregnant women.

#### **1.1.11 Overdose Experience**

There is no information available for Ralivia FlashDose. Ultram label reflects symptoms of overdose exposure.

#### **1.1.12 Post-Marketing Experience**

Ralivia FlashDose has not been approved for marketing.

### **1.2 Adequacy of Patient Exposure and Safety Assessments**

As a (505)b(2) application, the Sponsor is not required to conduct clinical efficacy or safety studies for a new formulation if this formulation is bioequivalent to the original approved formulation. It is assumed that safety profile of the new formulation is no different from that of original approved formulation. The overall safety assessment of Ralivia FlashDose is based on several single dose studies. All tramadol safety database would be applicable to Ralivia FlashDose.

#### **1.2.1 Description of Clinical Data Sources (Populations Exposed and Extent of Exposure)**

##### **1.2.1.1 Primary Source Data (Development Program)**

The studies in the Ralivia FlashDose clinical development program are listed in Table 5.

**Table 5. List of Ralivia FlashDose Phase I Studies**

Report (Protocol) Number Start Date - Location		Investigator	Study Design	Treatment Group	Unit Dose (mg)	Regimen	Duration	Formulation	Participants				Age (YS) Mean(SD) Range	Gender (N) Male Female
Report Listings								ER	S	C	P			
<b>1.A Preliminary Study (Pilot)</b>														
<u>Study 2613</u> (B02-601PK-F03P1)		Tam	R, O, SD, CO, CB, IV	All Subjects									38.8 ± 9.7 20-51	
July 29, 2002				A = Ralivia FlashDose	50	1 x 50 mg, fasted, without water	Single Dose	EO2124	12	12	12	0		12/0
Item 11				B = Ralivia FlashDose	50	1 x 50 mg, fasted, with water	Single Dose	EO2124	12	12	12	0		
				C = Tramadol HCl IR (Ultram <sup>®</sup> )	50	1 x 50 mg, fasted, with water	Single Dose	92F0105	12	12	12	0		
<b>1.B Definitive Studies (Pivotal)</b>														
<u>Study 2638</u> (TR022019-002)		Tam	R, O, SD, CO, CB, IV	All Subjects									31.9 ± 6.1 19-43	15/0
September 30, 2003				A = Ralivia FlashDose	50	1 x 50 mg, fasted, without water	Single Dose	PR03175R	19	19	19	0		
Item 11				B = Ralivia FlashDose	50	1 x 50 mg, fasted, with water	Single Dose	PR03175R	19	19	19	0		
				C = Tramadol HCl IR (Ultram <sup>®</sup> )	50	1 x 50 mg, fasted, with water	Single Dose	92F0432E	10	19	19	0		
<u>Study 2687</u> (TR022019-003)		Tam	R, O, SD, CO, FE, IV	All Subjects									33.6 ± 8.1 22-50	24/0
October 4, 2003				A = Ralivia FlashDose	50	1 x 50 mg, fasted, with water	Single Dose	PR03175R	24	24	23	1		
Item 11				B = Ralivia FlashDose	50	1 x 50 mg, fed, with water	Single Dose	PR03175R	24	24	24	0		
<b>2. Additional Phase I Studies</b>														
<u>Study 2744</u> (B03-619PK-10015)		Tam	R, O, SD, CO, CB, IV	All Subjects									39.9 ± 11.5 19-64	21/15
October 31, 2003				A = Ralivia FlashDose	50	1 x 50 mg, fasted, without water	Single Dose	PR03175R	36	36	36	0		
Item 11				B = Tramadol HCl IR (Ultram <sup>®</sup> )	50	1 x 50 mg, fasted, with water	Single Dose	JE0016	36	36	36	0		
<u>Study 2795</u> (B03-650PK-10015)		Tam	R, O, SD, CO, CB, IV	All Subjects									35.4 ± 10.8 20-61	18/19
October 31, 2003				A = Ralivia FlashDose	50	1 x 50 mg, fed, without water	Single Dose	PR03175R	36	36	36	0		
Item 11				B = Tramadol HCl IR (Ultram <sup>®</sup> )	50	1 x 50 mg, fed, with water	Single Dose	JE0016	36	36	36	0		
<u>Study 2821</u> (B04-651PK-10015)		Tam	R, O, SD, CO, FE, IV	All Subjects									34.9 ± 9.6 19-52	13/11
January 10, 2004				A = Ralivia FlashDose	50	1 x 50 mg, fed, without water	Single Dose	PR03175R	24	24	22	2		
Item 11				B = Ralivia FlashDose	50	1 x 50 mg, fasted, without water	Single Dose	PR03175R	24	24	24	0		
Item 12														

**Study Design:** PK = Pharmacokinetic; CO = Crossover; CB = Comparative Bioavailability; FE = Food Effect; O = Open-Label; R = Randomized; SD = Single Dose; IV = Healthy Volunteers  
**Treatment Groups:** ODT = Orally Disintegrating Tablets; IR = Immediate Release  
**Participants:** ER = Enrolled and/or Randomized; S = Safety population in Integrated Summary; C = Completed; P = Prematurely Discontinued (Dropout)  
 Source data: Individual Study Reports.

Table 6 summarizes the disposition of the subjects who were randomized into the Phase I studies.

**Table 6.**  
Disposition of Subjects in the Ralivia FlashDose Phase I Studies

Disposition	Ralivia FlashDose					Ultram <sup>®</sup>		
	Fasted, w/water	Fasted, w/water	Fed, w/water	Fed, w/water	Total	Fasted, w/water	Fed, w/water	Total
Randomized/Enrolled	55	91	24	59	151	67	36	103
Completed	54	91	24	58	148	67	36	103
Premature Termination	1	0	0	2	3	0	0	0
Safety Population	54	91	24	58	151	67	36	103
Primary Reason for Discontinuation								
Adverse Event (PT: dyspnea)	0	0	0	1	1	0	0	0
Positive drug screen	1	0	0	0	1	0	0	0
Personal Reason	0	0	0	1	1	0	0	0

Source data: ISS Table 1.1, ISS Listings 1 and 2

A total of 151 male and female subjects were dosed at least once with the Ralivia FlashDose 50 mg, of whom 103 were also administered the reference drug, Ultram<sup>®</sup> 50 mg.

### 1.2.1.1.1 Demographics

**Table 7. Demographic Characteristics of Subjects in the Ralivia FlashDose Phase I Studies**

	Ralivia FlashDose					Ultram <sup>®</sup>		
	Fasted, w/water (N=54)	Fasted, w/water (N=91)	Fed, w/water (N=24)	Fed, w/water (N=59)	All subjects (N=151)	Fasted, w/water (N=67)	Fed, w/water (N=36)	All subjects (N=103)
Age in yrs								
Mean (SD)	32.9 (7.8)	33.1 (10.2)	33.6 (8.1)	35.1 (10.4)	35.6 (10.1)	36.6 (10.5)	35.4 (10.8)	36.2 (10.6)
Median	33.5	35.0	34.0	34.5	35.0	35.0	34.5	35.0
Range	19-51	19-64	22-50	19-61	19-64	19-64	20-61	19-64
Gender, n (%)								
Male	54 (100)	65 (71.4)	24 (100)	30 (51.7)	107 (70.9)	52 (77.6)	18 (50.0)	70 (68.0)
Female	0 (0)	26 (28.6)	0 (0)	28 (48.3)	44 (29.1)	15 (22.4)	18 (50.0)	33 (32.0)
Race, n (%)								
White	40 (74.1)	65 (71.4)	19 (79.2)	41 (70.7)	110 (72.8)	48 (71.6)	26 (72.2)	74 (71.8)
Black	11 (20.4)	20 (22.0)	4 (16.7)	12 (20.7)	33 (21.9)	17 (25.4)	9 (25.0)	26 (25.2)
Asian	3 (5.6)	6 (6.6)	1 (4.2)	6 (8.6)	8 (5.3)	2 (3.0)	1 (2.8)	3 (2.9)

Source data: ISS Table 2.1, ISS Listings 2 and 3.

All the subgroups were comparable in terms of age and race. The mean age across the subgroups ranged from 32.9 to 36.6 years and the majority of the subjects in all the groupings were White (70.7 to 79.2%).

Two of the Ralivia FlashDose subgroups, the fed, and the fasted administered water had all male subjects. The Ultram, fed, administered water and the Ralivia FlashDose, fed, without water subgroups had approximately equal number of males and females. The 2 other subgroups had comparable gender composition; between 71-78% males.

### 1.2.1.1.2 Extent of exposure (Dose/Duration)

A total of 151 male and female subjects were dosed at least once with the Ralivia FlashDose 50 mg, of whom 103 were also administered the reference drug, Ultram 50 mg.

One subject was counted twice because he participated in two Phase I studies (Subject 12, Study 2687; Subject 18, Study 2821). He completed both studies and he was included in the safety population for both trials.

**Table 8. Treatment Exposure: Ralivia FlashDose Phase I Studies**

Exposure to Treatment	Study 2613*	Study 2686*	Study 2687	Study 2794*	Study 2756*	Study 2821	Total
Total subject days of exposure	36	57	47	72	72	46	330
Days dosed (n)							
1	12	19	24	36	36	24	151
2	12	19	23	36	26	22	148
3	12	19	-	-	-	-	31

\* Included 1 day on 50 mg Ultram<sup>®</sup>.

### 1.2.1.1.3 Safety Literature Summary – Tramadol

In single-dose, randomized, placebo-controlled studies involving patients with acute postsurgical pain, common side effects included nausea, vomiting, headache and dizziness (Sunshine, 1994).

Tramadol causes a minor delay in colonic transit, but has no effect on upper gastrointestinal transit or gut smooth muscle tone (Wilder-Smith & Bettiga, 1997). Its intestinal action is mediated mainly peripherally through the enteric opioid and serotonergic systems (Bamigbade & Langford, 1998). It has no significant effect on the sphincter of Oddi or intrabiliary pressure, and has weak spasmolytic properties (Shipton, 2000). Constipation is thus reported to a lesser extent than with other opioids (Bamigbade & Langford, 1998).

Adverse events of tramadol from different routes of administration are comparable (Bamigbade & Langford, 1998). Data from short-term multiple dose studies show tramadol most commonly causes nausea, tiredness, vomiting, sweating, drowsiness and postural hypotension (Cossmann & Kohnen, 1995). Urinary retention occurs less commonly when compared to potent opioids (Bamigbade & Langford, 1998). An open Phase IV study using all the formulations of tramadol in 7198 patients with over 100 different pain indications showed adverse events in 16.8% of patients (68.9% were slight, 22.1% were severe) (Cossmann & Kohnen, 1987). The most common adverse events were: dizziness (5.3%), central nervous system effects/incoordination (7.1%); nausea (4.8%); autonomic system disorders (3.3%), dry mouth (2.2%) and sedation (2.4%) (Cossmann & Kohnen, 1987).

In a post-marketing surveillance of 7,710 patients with acute and chronic pain, treated with sustained-release tramadol, adverse effects occurred in 5.9% of patients, most

typically nausea and dizziness (Shipton, 2000). A more recent post-marketing surveillance study of sustained-release tramadol evaluated 3153 patients in acute and chronic pain (Nossol et al., 1998). Adverse events occurred in 6.5% of patients and included nausea (3.4%), dizziness (1.5%) and vomiting (1.1%).

Tramadol produces naloxone-reversible muscle rigidity at doses higher than the therapeutic dose (Ossowska & Wolfarth, 1994). The estimated incidence of anaphylactoid or anaphylactic reactions to tramadol is 1 in 700,000 (Fischer et al., 1991). In cardiovascular risk patients, tramadol seems to offer some advantages due to its minor cardiovascular and respiratory side-effects (Ellmauer et al., 1994).

The value of tramadol in pain states from ophthalmic origin has yet to be fully clinically established (Gaynes & Barkin, 1999).

In all areas of practice, the adverse event profile of tramadol, in a dose-response fashion, is a mixture of opioid (dyspepsia, nausea, vomiting, tiredness, drowsiness) and monoaminergic (headache, dizziness, sweating, dry mouth) effects (McQuay & Moore, 1998; Cossmann & Kohnen, 1997). Tramadol is associated with a low incidence of cardiac depression, and significantly less dizziness and drowsiness than morphine (Lehmann, 1997). Side effects predominate in one or other of the enantiomers and partly antagonize each other, reducing the severity of side-effects seen in the racemic mixture (Bamigbade & Langford, 1998). By comparison to other strong analgesics, the incidence of adverse events may be lower (Kupers et al., 1995; Cossmann & Kohnen, 1995; Cossmann & Kohnen, 1997). In children, the incidence of adverse events with tramadol is much less than in adults (Shipton, 2000). Tramadol has not been associated with clinically significant side effects such as respiratory depression, constipation, or sedation (Shipton, 1999). Tolerance and psychological dependence have not been a problem in the long-term (Bamigbade & Langford, 1998b). One of the more outstanding aspects of tramadol is the extremely low liability to produce clinically relevant respiratory depression, which is negligible in comparison with opioids used for postsurgical pain management (Radbruch et al., 1996; Lee et al., 1993; Tarkkila et al., 1998). Both tramadol and MI do, however, depress laryngeal activity (the cough reflex) (Bamigbade & Langford 1998).

The use of ondansetron fails to reduce the nausea associated with tramadol (Bromm et al., 1999). Concerning side effects, the rank order is (-) enantiomer > (+) enantiomer > racemate, proving the racemate to be superior in this respect (Shipton, 2000). Like opioids, **tramadol may induce seizures**, especially when used in the presence of proconvulsive drugs (such as monoamine oxidase inhibitors and the tricyclic and selective serotonin uptake inhibitor antidepressants) and it should be avoided in these cases and in epilepsy (Dayer et al., 1997; Bamigbade & Langford, 1998; Committee on Safety of Medicines/Medicines Control Agency, 1996; Bowdle, 1998). By increasing central nervous catecholamines, tramadol may cause convulsions in susceptible patients, and should be used with caution in patients with head injuries (Bamigbade & Langford, 1998). The reported rate of convulsions with tramadol by the Committee on Safety of Medicines in the United Kingdom is 1 in 7000, with most cases involving interaction

with proconvulsive agents or large IV tramadol doses (Budd & Langford, 1999; Committee on Safety of Medicines/ Medicines Control Agency, 1995).

Much of the toxicity in tramadol overdose appears attributable to the monoamine uptake inhibition rather than its opioid effects (Spiller et al., 1997). There is no risk of idiopathic convulsions with tramadol alone (Budd & Langford, 1999; Jick et al., 1998). Agitation, tachycardia, confusion and hypertension suggest a possible mild serotonin syndrome (Spiller et al., 1997). A serotonin syndrome may occur with the concomitant administration of tramadol with sertraline (Mason & Blackburn, 1997). In moderate overdose situations, cerebral depression, muscular spasms and opisthotonos without cardiovascular or respiratory depression can occur (Bamigbade & Langford, 1998). There has been failure to confirm the prolongation of the International Normalized Ratio (INR) due to the interaction of tramadol with coumarin anticoagulants (Boeijinga et al., 1998).

There is a low magnitude and frequency of withdrawal signs when daily treatment with tramadol is discontinued (Shipton, 2000). Tramadol fails to precipitate withdrawal in morphine-treated subjects or to attenuate withdrawal in morphine-deprived subjects (Shipton, 2000). It is hypothesized that minimal tolerance, reduced dependence and abuse liability occur because of a unique combination of pharmacological actions; namely, the low affinity and efficacy at the mu-opioid receptors, the slow onset of action and the blockade of noradrenaline reuptake (Shipton, 2000). The frequency of euphoria and dysphoria with tramadol are negligible (Bono & Cuffari, 1997). It thus has pharmacodynamic and pharmacokinetic properties that are unlikely to lead to dependence (Dayer et al., 1997). Epidemiological data, controlled clinical studies and post-marketing surveillance studies have all confirmed extremely low liability for the development of tolerance and dependence (Dayer et al., 1997; Shipton, 2000; Budd, 1994; Gibson, 1996). Tramadol neither produced morphine-like effects nor precipitated a withdrawal syndrome in volunteers on a methadone maintenance program, and is not an attractive substance for abuse or as an opioid substitute (Bamigbade & Langford, 1998; Cami et al., 1994). Clinical studies tend to demonstrate no significant precipitated withdrawal signs and minimal dose escalation (Bamigbade & Langford, 1998). In the United States, the abuse potential is less than 1 in 100,000 (Budd, 1999; Cicero et al, 1999).

## CONCLUSIONS

The safety profile of the immediate release formulation of Tramadol HCl (Ultram) is well known due to its long marketing history. Since this is 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 Sponsor conducted 6 pharmacokinetic studies of a single Ralivia FlashDose 50 mg dose in healthy volunteers. The safety results of Ralivia FlashDose 50 mg in those studies are consistent with the Ultram label.

The review of other safety parameters such as vital signs, laboratory measurements, physical examinations and electrocardiograms revealed no potential safety concerns. The most common side effects included nausea, vomiting, headache and dizziness.

Since there is a limited clinical experience with Ralivia FlashDose, the safety profile of Tramadol HCL would be applicable to Ralivia FlashDose.

Ralivia FlashDose 50 mg is designed to deliver an equivalent amount of drug to the systemic circulation as the immediate-release Ultram 50 mg tablets. The results 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. Though the clinical significance of this delay is unknown it should be reflected in the label.

This formulation is intended to be taken with or without water. To optimize patient tolerability, it is recommended that patients start on Ralivia FlashDose 50 mg QD and titrate as needed to achieve the desired therapeutic effect.

**Recommendations:**

This reviewer recommends an approval for Ralivia FlashDose 50 mg tablets for the management of moderate to moderately severe pain in adults pending labeling negotiations.

This review would be amended after the labeling negotiations are complete.

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/s/

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Tatiana Oussova  
1/5/05 11:32:19 AM  
MEDICAL OFFICER

Joel Schiffenbauer  
1/5/05 12:59:39 PM  
MEDICAL OFFICER  
I concur. Please also see TL review.