CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022370Orig1s000

PHARMACOLOGY REVIEW(S)

FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

SUPERVISOR'S SECONDARY REVIEW
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number:	**22-370**
Drug Substance:	**Tramadol extended release capsules**
PDUFA Goal Date:	15-Feb-2009
Sponsor:	**Cipher Pharmaceuticals**
Reviewer name:	R. Daniel Mellon, Ph.D., Pharmacology Toxicology Supervisor
Division name:	Division of Anesthesia, Analgesia, and Rheumatology Products
Review completion date:	16-Jan-2009
Recommendation:	**Approval**

I have read Dr. Asoke Mukherjee's review of the nonclinical pharmacology and toxicology sections of NDA 22-370 and agree with his conclusion that the NDA may be approved. I also concur with his recommendations for the nonclinical portions of the labeling.

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/s/

R. Daniel Mellon
1/16/2009 04:19:43 PM
PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-370**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**April 15, 2008**
PRODUCT:	**Tramadol Extended Release Capsules**
INTENDED CLINICAL POPULATION:	**Proposed indication: Management of Moderate to Moderately Severe Pain**
SPONSOR:	**Cipher Pharmaceuticals**
DOCUMENTS REVIEWED:	**Labeling**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170)**
PHARM/TOX REVIEWER:	**Asoke Mukherjee, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob A. Rappaport, M.D.**
PROJECT MANAGER:	**Kathleen Davies**

Date of review submission to Division File System (DFS): January 16, 2009

Executive Summary

Background: The original NDA (b) (4) for CIP-Tramadol ER capsules was reviewed on April 12, 2007 for the management of moderate to moderately severe pain indication. Due to the addition of a second referenced drug for this 505(b)(2) application, the complete response to the original action on NDA (b) (4) had to be submitted as a new application (NDA 22-370) for Tramadol ER capsules to the Division of Anesthesia, Analgesia and Rheumatology Products.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA (b) (4) are owned by Cipher Pharmaceuticals LTD or are data for which Cipher Pharmaceuticals LTD has obtained a written right of reference. Any information or data necessary for approval of NDA (b) (4) that Cipher Pharmaceuticals LTD does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Cipher Pharmaceuticals LTD does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA (b) (4).

The current application references both Ultram and Ultram ER NDAs which are held by Ortho-McNeil and Biovail Laboratories, respectively (NDAs 20-281 and 21-692).

There were no new non-clinical data were submitted to NDA 22-370, as this NDA cross references NDA (b) (4). Therefore, non-clinical recommendations for approvability of the product under NDA 22-370 would be same as that recommended for NDA (b) (4).

A. Recommendation on Approvability

This application may be approved from a nonclinical perspective for tramadol extended release capsules at 100, 200 and 300 mg once a day doses.

B. Recommendation for Nonclinical Studies

No recommendation is necessary.

C. Recommendations on Labeling:

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** *Teratogenic Effects: Pregnancy Category C*	**8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** *Teratogenic Effects: Pregnancy Category C* There are no adequate and well-	NOTE: Sponsor's proposed language was originally inserted into section 13. As per the Maternal Health Team's

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
	controlled studies in pregnant women. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during post-marketing reports with tramadol HCl immediate-release products. TRADENAME ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.	proposed labeling, this section is moved to the front of 8.1
(b) (4)	Tramadol was not teratogenic at oral dose levels up to 50 mg/kg/day (b) (4) 1.6-fold the MDHD) in rats and 100 mg/kg (approximately 6.5-fold MDHD) in rabbits during organogenesis. However, embryo-fetal lethality, reductions in fetal weight and skeletal ossification, and increased supernumerary ribs were observed at a maternal toxic dose of 140 mg/kg in mice (approximately 2.3-fold MDHD), 80 mg/kg in rats (2.6-fold MDHD) or 300 mg/kg in rabbits (approximately 19-fold MDHD).	(b) (4) All doses were adjusted to the maximum human daily dose of 300 mg/day.
Non-teratogenic Effects (b) (4)	**Non-teratogenic Effects** Tramadol caused a reduction in neonatal body weight at a dose of 50 mg/kg (1.6-fold MDHD) and reduced pup survival at an oral dose of 80 mg/kg (approximately 2.6-fold MDHD) when rats were treated during late gestation throughout lactation period.	Additional data from 50 mg/kg dose group is from labeling for NDA 20-281. As per the Maternal Health Team's proposed labeling, this section is moved to the front of 8.1
8.2 Labor and Delivery TRADENAME ER should not be used in pregnant women prior to or	**8.2 Labor and Delivery** TRADENAME ER should not be used in pregnant women prior to or	Sponsor's proposed labeling is basically verbatim from NDA 21-692 and 20-281. No changes are

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn *[see Drug Abuse and Dependence (9)]*. Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women treated with tramadol HCl during labor. The effect of TRADENAME ER, if any, on the later growth, development, and functional maturation of the child is unknown.	during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn *[see Drug Abuse and Dependence (9)]*. Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women treated with tramadol HCl during labor. The effect of TRADENAME ER, if any, on the later growth, development, and functional maturation of the child is unknown.	recommended.
8.3 Nursing Mothers TRADENAME ER is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. Following a single IV 100-mg dose of tramadol, the cumulative excretion in breast milk within sixteen hours postdose was 100 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.	**8.3 Nursing Mothers** TRADENAME ER is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. Following a single IV 100-mg dose of tramadol, the cumulative excretion in breast milk within sixteen hours postdose was 100 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.	Sponsor's proposed labeling is basically verbatim from NDA 21-692 and 20-281. No changes are recommended.
8.4 Pediatric Patients The safety and efficacy of TRADENAME ER in patients under 18 years of age have not been established. The use of TRADENAME ER in the pediatric population is not recommended.	**8.4 Pediatric Patients** The safety and efficacy of TRADENAME ER in patients under 18 years of age have not been established. The use of TRADENAME ER in the pediatric population is not recommended.	Sponsor's proposed labeling is verbatim from NDA 21-692. NDA 20-281 labeling is the same except that the age listed is 16 rather than 18.
13 NONCLINICAL TOXICOLOGY		
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility (b) (4)	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity assessment has been conducted in mice, rats and p53(+/-) heterozygous mice. A slight, but statistically significant, increase in two	(b) (4) (b) (4)

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
(b) (4)	common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg (90 mg/m^2 or 0.5 times the maximum daily human dosage of 185 mg/m^2) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No treatment related tumors were noted in a rat carcinogenicity study (dosing orally up to 30 mg/kg, 180 mg/m^2, or equivalent to the maximum daily human dosage) or in a second study where rats were treated up to 75 mg/kg/day for males and 100 mg/kg/day for females (approximately 2.4 and 3.2-fold (MDHD) for two years. However, the excessive decrease in body weight gain observed in the rat study might have reduced their sensitivity to any potential carcinogenic effect of the drug. No carcinogenic effect of tramadol was observed in p53(+/–)-heterozygous mice at oral doses up to 150 mg/kg/day (approximately 2.4-fold maximum daily human dose [MDHD] of 300 mg/day for a 60 kg adult based on body surface conversion) for 26 weeks.	(b) (4), all study results are recommended for this label as both products are being relied upon to support this drug product.
(b) (4)	Tramadol was not mutagenic in the following assays: a bacterial reverse mutation assay using *Salmonella* and *E. coli*, a mouse lymphoma assay (in the absence of metabolic activation), chromosomal aberration test in Chinese hamsters, bone marrow micronucleus test in mice and Chinese hamsters, and a dominant lethal mutation test in mice. Mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the weight of evidence from these tests indicates that	Proposed language is taken verbatim from NDA 21-692. The labeling from NDA 20-281 includes additional study results, which are added in blue text.

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
	tramadol does not pose a genotoxic risk to humans.	
No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg/day in male and female rats ((b) (4) MDHD).	No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg/day in male and female rats (1.6-fold the MDHD).	Sponsor's proposed labeling is verbatim from NDA 21-692. No additional changes recommended, as the information is consistent with that in the labeling for NDA 20-281.

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/s/

Asoke Mukherjee
1/16/2009 03:15:17 PM
PHARMACOLOGIST
Labels for Tramadol IR and Tramadol ER were reviewed for 505(b)(2) applications

R. Daniel Mellon
1/16/2009 04:10:02 PM
PHARMACOLOGIST
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	(b) (4)
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	7/05/06
PRODUCT:	CIP-Tramadol ER capsules
INTENDED CLINICAL POPULATION:	Management of moderate to moderately severe chronic pain
SPONSOR:	Cipher Pharmaceuticals Ltd.
DOCUMENTS REVIEWED:	Vol. 1 and 2 from modules 2 and 4
REVIEW DIVISION:	Division of Anesthesia, Analgesia, and Rheumatology Products
PHARM/TOX REVIEWER:	Asoke Mukherjee, Ph.D.
PHARM/TOX SUPERVISOR:	Daniel Mellon, Ph.D.
DIVISION DIRECTOR:	Bob Rappaport, M.D.
PROJECT MANAGER:	Kathleen Davies

Date of review submission to Division File System (DFS): April 12, 2007

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EXECUTIVE SUMMARY

Recommendations

A. **Recommendation on approvability:** From the nonclinical pharmacology/toxicology perspective, NDA (b) (4) for CIP Tramadol ER 100, 200 and 300 mg once a day capsules can be approved.

B. **Recommendation for nonclinical studies:** None

C. **Recommendations on labeling:** Recommendations for the label are shown below. The rest of the non-clinical section of the label proposed by the sponsor is acceptable.

Carcinogenicity:

A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg (90 mg/m^2 or (b) (4) 0.5 times the maximum daily human dosage of (b) (4) - 185 mg/m^2) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. (b) (4)

Mutagenicity:

(b) (4)

Fertility:

(b) (4)

Pregnancy:

Teratogenic Effects: Pregnancy Category C

(b) (4)

(b) (4)

Non-teratogenic Effects

(b) (4)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings:

The sponsor developed once a day oral dosage regimen for tramadol. The inactive ingredients used in the formulation can be found in other FDA approved drug products at comparable exposure levels. **No new pharmacology/toxicology studies were submitted in the NDA. Page 1, vol 1 of Module 2 stated that the non-clinical information included is literature based.** Among the published literature provided by the sponsor, following citations were published by R.W Johnson Pharmaceutical Research Institute/Ortho-McNeil Pharmaceuticals, sponsor of NDA 20-281:

1. Complementary and synergistic antinociceptive interaction between the enantiomers of tramadol by Raffa et al., JPET, 267, 331, 1993.
2. Metabolism of the analgesic drug, tramadol hydrochloride, in the rat and dog, Xenobiotica, 31, 423, 2001.

B. Pharmacologic activity:

Tramadol is a μ-opioid receptor agonist and inhibitor of monoamine uptake (serotonin and norepinephrine). It has an active metabolite (M1) that shares a similar pharmacological profile.

C. Nonclinical safety issues relevant to clinical use:

The major safety issues related to tramadol is seizure. However, no new nonclinical safety study has been submitted in the NDA.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

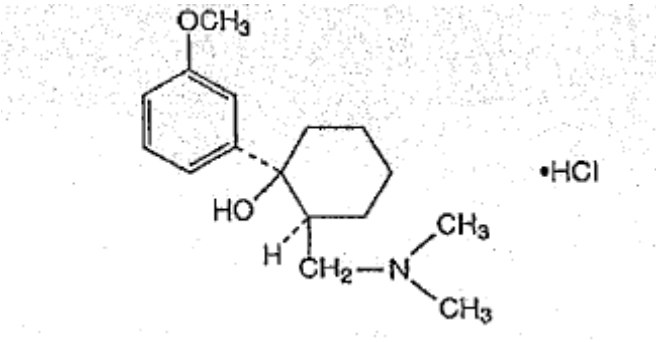
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: (b) (4)
Review number: One
Sequence number/date/type of submission: 000 / June 26, 2006 / Original NDA Submission
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Cipher Pharmaceuticals Ltd., Ontario Canada
Manufacturer for drug substance: (b) (4)

Reviewer name: Asoke Mukherjee, Ph.D.
Division name: Division of Anesthesia, Analgesia, and Rheumatology Products
HFD #: HFD-170
Review completion date: Dec 22, 2006

Drug:

Trade name: CIP-tramadol ER capsules
Generic name: Tramadol hydrochloride extended release capsule
Code name: Nil
Chemical name: (± Cis-2-[(Dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride
CAS registry number: 22204-88-2
Molecular formula/molecular weight: $C_{16}H_{25}NO_2HCl$, 299.84
Structure:



Relevant INDs/NDAs/DMFs:

The FDA has approved the following tramadol NDAs:

NDA#	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
20-281	Ultram	170	Oral	Approved	3/3/1995	Acute and chronic pain	Ortho McNeil Pharma.

21-123	Ultracet (Tramadol & APAP)	170	Oral	Approved	8/15/2001	Moderate to moderately severe pain	Ortho McNeil Pharma.
21-692	Ultram ER	170	100, 200, 300 mg Oral	Approved	9/8/2005	Moderate to moderately severe pain	Biovail Labs
21-693	Ultram ODT	170	50 mg Oral	Approved	5/5/2005	Moderate to moderately severe pain	Biovail Labs

Relevant IND: (b) (4)

Relevant DMF: (b) (4)

Drug class: Centrally acting analgesic

Intended clinical population: For the treatment of moderate to moderately severe chronic pain.

Clinical formulation:

Ingredient (and Test Standard)	Amount per Capsule (mg) 100 mg Strength	200 mg Strength	300 mg Strength
Tramadol HCl (EP)	100.0	200.0	300.0
Microcrystalline Cellulose (NF), (b) (4)	(b) (4)	(b) (4)	(b) (4)
Sucrose Stearate (b) (4)			
Hydroxypropyl Methylcellulose (b) (4) (USP)			
Talc (USP)			
Magnesium Stearate (NF)			
Polysorbate 80 (NF)			
Simethicone Emulsion (USP)			
Eudragit NE30D (EP)			
Lactose Monohydrate 200 mesh (NF)			
Povidone K30 (USP)			
Starch (NF)			
Sodium Starch Glycolate (NF)			
Gelatin Capsule (NF)	White Opaque Cap & Body ("G 252" on cap, "100" between lines on body, in blue ink)	White Opaque Cap & Body, ("G 253" on cap, "200" between lines on body, in violet ink)	White Opaque Cap & Body ("G 254" on cap, "300" between lines on body, in red ink)
Titanium dioxide (USP)	(b) (4)	(b) (4)	(b) (4)
Gelatin (NF)			
(b) (4)			
(b) (4)			
Shellac (NF)	Present	Present	Present
(b) (4)	y	y	y
	y	y	y
	y	y	y
	Present	Present	Present
	y	y	y
Titanium Dioxide (USP) (b) (4)	Present	Present	Present
D&C Red #7 Calcium Lake E-180	no	Present	Present
D&C Yellow #10 Aluminium Lake	no	no	Present
FD&C Blue #2 Aluminium Lake E-132	Present	Present	no
Size	1	0	00
Total Fill Weight	**324**	**517**	**770**

All of the above excipients have been used at equal to or higher levels for other FDA approved drug product formulations. There are no pharmacology toxicology concerns with the drug product formulation. The letter of authorization from individual DMF holder was obtained as indicated on volume 1 and module 1.

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA (b) (4) are owned by Cipher Pharmaceuticals LTD or are data for which Cipher Pharmaceuticals LTD has obtained a

written right of reference. Any information or data necessary for approval of NDA (b) (4) that Cipher Pharmaceuticals LTD does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Cipher Pharmaceuticals LTD does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA (b) (4).

Application type:	505(b)(2)
Reference Listed Drug Product:	ULTRAM® (Tramadol HCl tablets) Ortho-McNeil NDA 20-281

Studies reviewed within this submission:

There were no new Pharm/Tox studies were submitted.

Studies not reviewed within this submission: **N/A**

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary:

Tramadol is a centrally acting analgesic. It exits as racemic mixtures. The (+) enantiomer predominantly binds with the μ-opioid receptor and the (-) enantiomer preferentially inhibits monoamine uptake. Both enantiomers contribute to the analgesic activity of tramadol. The pharmacology of the drug was reviewed under Ultram NDA 20-281. Major active metabolite of tramadol (M1) is O-desmethyltramadol and it has greater affinity to the μ-opioid receptor. M1 metabolite is more potent than racemic tramadol. A sustained release formulation of tramadol was formulated for marketing under the NDA for once a day dosing as 100, 200 and 300 mg capsules.

2.6.2.2 Primary pharmacodynamics

No new primary pharmacodynamic study for tramadol was submitted in the NDA.

2.6.2.3 Secondary pharmacodynamics

No secondary pharmacology study for tramadol was submitted in the NDA.

2.6.2.4 Safety pharmacology

No new safety pharmacology data were submitted in the NDA. However, a summary of safety of tramadol is provided by the sponsor from published literature (see a list of references in vol 1, module 2 under Pharmacology and Toxicology). Respiratory

depression was reported in rats at 2 mg/kg/IV infusion of (+) M1. The effect was stereoselective. (b) (4)

2.6.2.5 Pharmacodynamic drug interactions

No pharmacodynamic drug interaction study for tramadol was submitted in the NDA.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

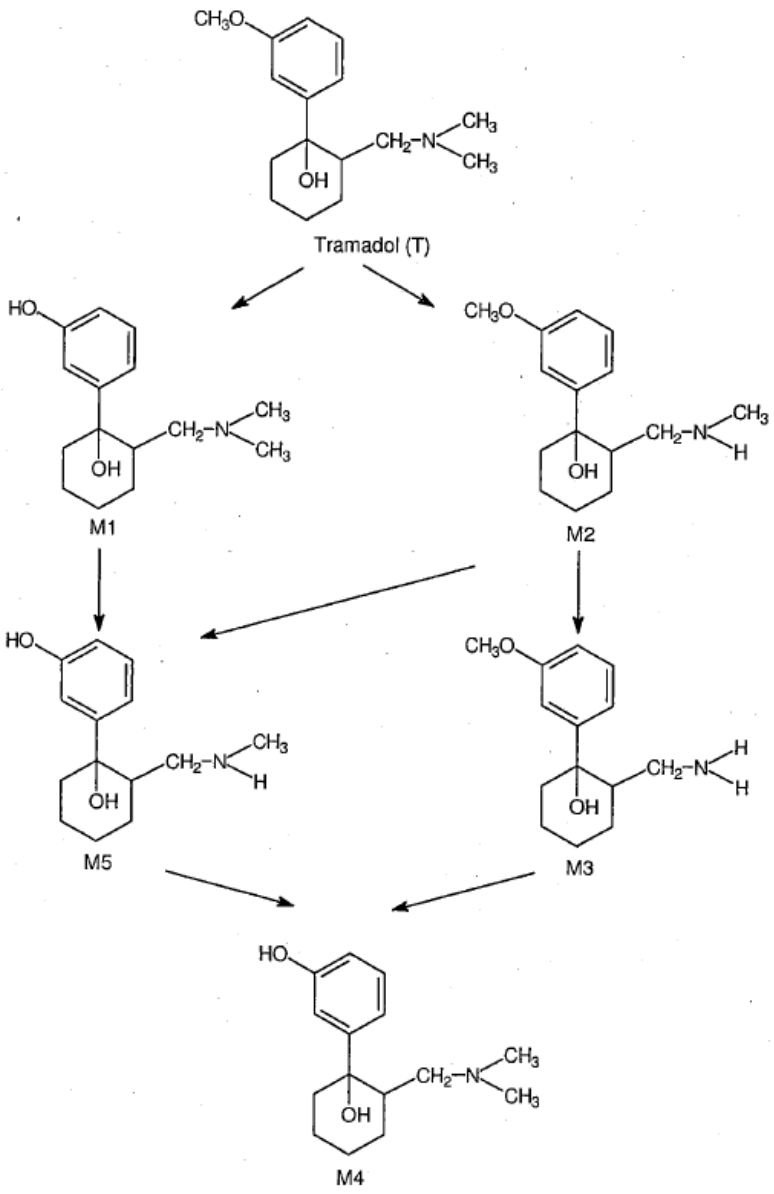
No new pharmacology data were submitted in the tabulated summary in the NDA.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The sponsor provided a brief summary of metabolism of tramadol in animals. The metabolic profile of tramadol in rats and dogs was qualitatively similar to humans. N and O-demethylation of tramadol were major Phase 1 metabolites. Conjugation of these metabolites with glucuronide and sulfate were Phase 2 metabolites of tramadol. Kidney was the major organ for elimination of the unchanged drug and metabolites. The metabolism of tramadol was stereoselective in rats. The metabolism of tramadol in female rats was slow and that resulted in higher plasma concentrations of tramadol in female rats than male rats. Major metabolites of tramadol are shown below from the sponsor's submission on page 6, volume 1 and module 2.

Figure 2 Metabolism of Tramadol



2.6.4.2 Methods of Analysis:

[see under individual study reviews]

2.6.4.3 Absorption

No new nonclinical data for absorption of tramadol were submitted in the NDA.

2.6.4.4 Distribution

No new nonclinical data for distribution of tramadol were submitted in the NDA.

2.6.4.5 Metabolism

No new nonclinical data for metabolism of tramadol were submitted. However, metabolic pathway from the published literature is shown above under summary section. Major pathway of metabolism of tramadol is O- and N-demethylation. A total of 11 Phase 1 and Phase 2 metabolites were identified which were identical in rats, dogs and humans.

2.6.4.6 Excretion

No new nonclinical data for excretion were submitted in the NDA. However, a summary of published data indicated that the unchanged drug and its metabolites were excreted in the urine.

2.6.4.7 Pharmacokinetic drug interactions

No new nonclinical data for drug interactions of tramadol were submitted in the NDA.

2.6.4.8 Other Pharmacokinetic Studies

N/A

2.6.4.9 Discussion and Conclusions

A summary of ADME from the published literature was provided by the sponsor. Tramadol is metabolized to an active M1 metabolite and several other Phase 1 and Phase 2 metabolites. Both the unchanged drug and its metabolites were excreted in the urine. Gender difference in the metabolism of tramadol was observed in rats. Female rats showed higher plasma levels of tramadol than male rats.

2.6.4.10 Tables and figures to include comparative TK summary

No new comparative TK data and its table were submitted in the NDA.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

No new data for pharmacokinetic was submitted in the tabulated summary in the NDA. However, module 2, vol 1 provided a summary table of PK data in Wistar rats following oral doses of racemic tramadol as a single and multiple doses. The table is shown below.

Table 2.6.3.7-1 Pharmacokinetics of Tramadol (+) and (-) and its Metabolites (M1) (+) and (-) in Male and Female Rats					
		Male		Female	
Tramadol		(+)tramadol	(-)tramadol	(+)tramadol	(-)tramadol
Single oral	C_{max}	191.99	72.84	712.49	224.31
Dose	T_{max}	0.67	0.58	0.50	0.50
30 mg/kg	AUC	518.76	153.02	2,677.49	887.67
	CL/F	531.62	1,960.44	94.34	283.96
	$T_{1/2}$ B	3.04	5.76	3.90	4.24
Multiple	C_{max}	343.24	157.86	905.90	595.69
oral dose	T_{max}	0.50	0.50	0.50	0.50

Table 2.6.3.7-1 Pharmacokinetics of Tramadol (+) and (-) and its Metabolites (M1) (+) and (-) in Male and Female Rats					
		Male		Female	
Tramadol		(+)tramadol	(-)tramadol	(+)tramadol	(-)tramadol
14 days	AUC	840.13	306.60	2,942.08	1,364.46
30 mg/kg/day	CL/F	304.21	864.47	88.44	192.87
	$T_{1/2}$ B	2.51	2.67	2.99	2.92
M1		M1 +	M1 -	M1 +	M1 -
Single oral	C_{max}	150.96	255.92	287.40	255.16
Dose	T_{max}	0.50	0.50	0.58	0.50
30 mg/kg	AUC	384.78	835.28	1,511.99	607.84
	$T_{1/2}$ B	4.23	5.24	4.77	6.24
Multiple	C_{max}	120.88	205.19	165.65	148.77
oral dose	T_{max}	0.50	0.50	1.08	0.58
14 days	AUC	354.71	690.42	1,088.93	670.83
30 mg/kg/day	$T_{1/2}$ B	4.34	5.26	5.33	5.59

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: No new toxicology studies were conducted for the extended release product. However, the sponsor summarized information from published literature on tramadol on pages 1-11, module 2, vol 1. Two of the referenced articles were published by R.W. Johnson Pharmaceuticals (module 4 vol 2), citations are shown under executive summary. Clinical signs in the acute toxicity studies of tramadol in rats and mice were restlessness, unsteady gait, reduced spontaneous activity, exophthalmus, mydriasis, salivation, vomiting, tremor, convulsions, cyanosis and dyspnea. Repeat dose toxicity

studies were conducted in rats and dogs. The sponsor stated that convulsions were major findings at 25 mg/kg and higher doses.

Genetic toxicology:

No new genotoxicity data for tramadol were submitted in the NDA. Although the sponsor stated that both in vitro and in vivo tests showed no genotoxic risks in humans based on the information available in the approved package insert for the referenced drug product (Ultram PI, May 2004, cited on page 6, module 2, vol 2) indicates the presence of a positive mutagenic response in the presence of metabolic activation in in vitro mouse lymphoma assay and in vivo micronucleus assay in rats. Therefore, the package insert for the NDA should also include information on the same positive findings.

Carcinogenicity:

The sponsor did not conduct any new carcinogenicity study for the NDA.

Reproductive toxicology:

No new reproductive safety data were submitted in the NDA.

Special toxicology:

No studies were completed

2.6.6.2 Single-dose toxicity

The sponsor tabulated several acute studies published in the literature (vol 1, module 2). However, no new study was conducted by the sponsor.

2.6.6.3 Repeat-dose toxicity

No new repeat dose toxicity study was submitted. However, the sponsor provided a table in vol 1, module 2 indicating the published literature information.

2.6.6.4 Genetic toxicology

No new genetic toxicity studies were conducted.

2.6.6.5 Carcinogenicity

No new carcinogenicity studies were conducted.

2.6.6.6 Reproductive and developmental toxicology

No new reproductive safety study was submitted in the NDA.

2.6.6.7 Local tolerance

N/A

2.6.6.8 Special toxicology studies

N/A

2.6.6.9 Discussion and Conclusions

Tramadol immediate release and sustained release products have been approved by the FDA. In the present NDA, the sponsor did not submit any new non-clinical data for a review and the NDA was submitted under 505(b)(2) with the reference listed drug product identified as Ultram (NDA 20-281). The sponsor listed a reference for the patent search in vol 1, module 1. It is stated that a user patent for tramadol (U-435) is valid up to Oct 12, 2019. However, the sponsor states that the present application does not infringe the existing patent. From the nonclinical pharmacology toxicology perspective, the NDA (b) (4) can be approved based upon the Agency's previous findings of safety made for Ultram in NDA 20-281.

2.6.6.10 Tables and Figures

Not submitted

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not submitted.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The NDA can be approved from pharm/tox point of view. There is no non-clinical issue related to the NDA review.

Unresolved toxicology issues (if any): None

Recommendations: From non-clinical pharmacology toxicology perspective, the NDA (b) (4) can be approved.

Suggested labeling:

The sponsor's proposed label written according to the Federal Register notice dated Jan 2006 for requirements on content and format of labeling for human prescription drug and biological products.

Carcinogenicity:

(b) (4)

Reviewer response:

A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg (90 mg/m^2 or (b) (4) 0.5 times the maximum daily human dosage of (b) (4) - 185 mg/m^2) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No such finding occurred in a rat carcinogenicity study (dosing orally up to 30 mg/kg - 180 mg/m^2 or (b) (4) equal to the maximum daily human dosage).

Mutagenicity:

(b) (4)

Reviewer's response:

(b) (4)

Fertility:

(b) (4)

Reviewer's response:

(b) (4)

Pregnancy:

(b) (4)

Reviewer's response:

Teratogenic Effects: Pregnancy Category C

(b) (4)

(b) (4)

Non-teratogenic Effects

(b) (4)

Labor and delivery:

(b) (4)

Reviewer's response:

SAME AS SUGGESTED BY THE SPONSOR

(b) (4)

Reviewer's response:

SAME AS SUGGESTED BY THE SPONSOR

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

N/A

C.C:

NDA (b) (4) Div File

CDER/OND/DAARP/PM/Paul Balcer
CDER/OND/DAARP/Pharmacologist/Asoke Mukherjee
CDER/OND/DAARP/Supervisory Pharmacologist/Daniel Mellon
CDER/OND/DAARP/Medical Officer/Keith Burkhart
CDER/OND/DAARP/Chemist/Al-Hakim Ali

NDA (b) (4) Oct62006.doc

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/s/

Asoke Mukherjee
4/12/2007 04:24:55 PM
PHARMACOLOGIST/TOXICOLOGIST

R. Daniel Mellon
4/12/2007 05:05:34 PM
PHARMACOLOGIST/TOXICOLOGIST
I concur with Dr. Mukherjee, NDA (b) (4) may be approved from the nonclinical pharmacology toxicology perspective.