CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-962

Name: Tramadol Hydrochloride Tablets, 50 mg

Sponsor: Watson Laboratories, Inc.

Approval Date: June 24, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Approvable Letter	X
Labeling	X
Labeling Reviews	X
Medical Review(s)	
Chemistry Reviews	X
Bioequivalence Reviews	X
Statistical Review	
Microbiology Review	
Administrative Documents	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

APPROVAL LETTER

ANDA 75-962

JUN 24 2002

Watson Laboratories, Inc.
Attention: Ernest E. Lengle, Ph.D.
311 Bonnie Circle
Corona, CA 92880

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 1, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Tramadol Hydrochloride Tablets, 50 mg.

Reference is also made to the Approvable Letter issued by this Office on January 15, 2002, and to your amendments dated December 4, 2000, and June 13, 2002.

The listed drug product (RLD) referenced in your application, Ultram Tablets, 50 mg, of R.W. Johnson Pharmaceutical Research Institute, is subject to a period of patent protection which expires on April 12, 2020 (U.S. Patent No. 6,339,105). Your application contains a statement under Section 505(j)(2)(A) of the Act and 21 CFR 314.94(a)(12)(iii)(A) stating that U.S. Patent No. 6,339,105 is a method of use patent, and that your labeling for this drug product does not include any indication or use covered by this patent.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Tramadol Hydrochloride Tablets, 50 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ultram Tablets, 50 mg, of the R.W. Johnson Pharmaceutical Research Institute). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies that may be identified.

Sincerely yours,

Gary Buehler 6/24/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-962
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
Endorsements:
HFD-649/ERamos/6/24/02
HFD-649/GJSmith/6/24/02
HFD-617/J.Min/6/24/02
HFD-613/C.Park/6/19/02
HFD-613/L.Golson/6/19/02

Robert Lewis 6/24/2002

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F/T by: rlw/6/24/02

APPROVAL/ PACT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

APPROVABLE LETTER

ANDA 75-962

JAN 15 2002

Watson Laboratories, Inc.
Attention: Ernest Lengle
311 Bonnie Circle
Corona, CA 92880

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 1, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act) for Tramadol Hydrochloride Tablets, 50 mg.

Reference is made to your amendments dated December 4, 2000; and April 23, June 1, and July 18, 2001.

We have completed the review of this ANDA as submitted, and have concluded that the application is **approvable.** However, before the application may receive final approval, issues involving the approved labeling for the reference listed drug product, Ultram® Tablets of R.W. Johnson Pharmaceutical Research Institute, and related exclusivity as described in 21 CFR 314.108(b)(5) will require resolution. The agency expects to complete its review of these issues as promptly as possible and you will be advised of the outcome. There is no additional material that you should submit to FDA at this time to obtain approval of your ANDA. The agency's recommendations will be provided to all ANDA applicants for this product at the appropriate time.

Any significant changes in the conditions outlined in your abbreviated new drug application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to agency review before final approval of the application will be made.

This is not an approval letter. This drug product may not be marketed without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 301(d) of the Act.

Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under Section 505 of the Act and will not be listed in "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), published by the agency.

A copy of the recently approved package insert for Ultram® Tablets is available on the FDA Website at http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html. Please contact Robert L. West or Peter Rickman at (301) 827-5846 if you have further questions about this issue.

Sincerely yours,

Gary Buehler 1/15/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-962
Division File
Field Copy
GCF-1 Liz Dickinson
GCF-1 Kim Dettelbach
HFD-610/R.West
HFD-92
HFD-330
HFD-205/F.O.I.
HFD-92

Endorsements:
HFD-645/E.Ramos/ For Mahnaz Farahani 12,21,01
HFD-647/G.Smith/Mayra Pineiro for 9/11/01 12/21/01
HFD-617/J.Min/8/24/01 12/21/01
HFD-613/C.Park/12/19/01 12/21/01
HFD-613/C.Hoppes/ 12/21/01 12/22/2001

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F/t by rad12/20/01

APPROVABLE

comc satisfactory.
12/26/01.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

LABELING

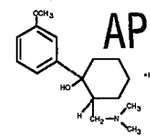
Tramadol Hydrochloride
Tablets

Issued: May 2002

Rx only

DESCRIPTION

Tramadol hydrochloride tablets are a centrally acting analgesic. The chemical name for tramadol hydrochloride is (±)-*cis*-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride. Its structural formula is:



Molecular formula: $C_{16}H_{25}NO_2 \cdot HCl$ Molecular weight: 299.84

Tramadol hydrochloride is a white, bitter, crystalline and odorless powder. It is readily soluble in water and ethanol and has a pKa of 9.41. The n-octanol/water log partition coefficient (logP) is 1.35 at pH 7. Each tablet, for oral administration contains 50 mg of tramadol hydrochloride and is white in color. In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate, pregelatinized starch and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the *O*-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol hydrochloride. Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.

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

Pharmacokinetics

The analgesic activity of tramadol hydrochloride is due to both parent drug and the M1 metabolite (see **CLINICAL PHARMACOLOGY, Pharmacodynamics**). Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. Tramadol is well absorbed orally with an absolute bioavailability of 75%. Tramadol has a volume of distribution of approximately 2.7L/kg and is only 20% bound to plasma proteins. Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. One metabolite, M1, is pharmacologically active in animal models. The formation of M1 is dependent upon CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see **PRECAUTIONS, Drug Interactions**). Tramadol and its metabolites are excreted primarily in the urine with observed plasma half-lives of 6.3 and 7.4 hours for tramadol and M1, respectively. Linear pharmacokinetics have been observed following multiple doses of 50 and 100 mg to steady-state.

Absorption

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a 100 mg oral dose is approximately 75%. The mean peak plasma concentration of racemic tramadol and M1 occurs at two and three hours, respectively, after administration in healthy adults. In general, both enantiomers of tramadol and M1 follow a parallel time course in the body following single and multiple doses although small differences (~10%) exist in the absolute amount of each enantiomer present.

Steady-state plasma concentrations of both tramadol and M1 are achieved within two days with q.i.d. dosing. There is no evidence of self-induction (see Figure 1 and Table 1 below).

Figure 1: Mean Tramadol and M1 Plasma Concentration Profiles after a Single 100 mg Oral Dose and after Twenty-Nine 100 mg Oral Doses of Tramadol HCl given q.i.d.

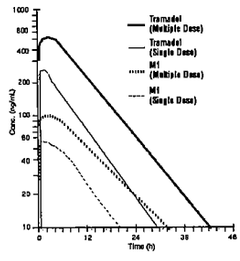


Table 1
Mean (%CV) Pharmacokinetic Parameters for Racemic Tramadol and M1 Metabolite

Population/ Dosage Regimen[a]	Parent Drug/ Metabolite	Peak Conc. (ng/mL)	Time to Peak(hrs)	Clearance/F[b] (mL/min/Kg)	$t_{1/2}$ (hrs)
Healthy Adults, 100 mg qid, MD p.o.	Tramadol	592 (30)	2.3 (61)	5.90 (25)	6.7 (15)
	M1	110 (29)	2.4 (46)	c	7.0 (14)
Healthy Adults, 100 mg SD p.o.	Tramadol	308 (25)	1.6 (63)	6.50 (31)	5.6 (20)
	M1	55.0 (36)	3.0 (51)	c	6.7 (16)
Geriatric, (>75 yrs) 50 mg SD p.o.	Tramadol	208 (31)	2.1 (19)	6.89 (25)	7.0 (23)
	M1	d	d	c	d
Hepatic Impaired, 50 mg SD p.o.	Tramadol	217 (11)	1.9 (16)	4.23 (56)	13.3 (11)
	M1	19.4 (12)	9.8 (20)	c	16.5 (15)
Renal Impaired, CL_{cr} 10-30 mL/min 100 mg SD i.v.	Tramadol	c	c	4.23 (54)	10.6 (31)
	M1	c	c	c	11.5 (40)
Renal Impaired, CL_{cr}<5 mL/min 100 mg SD i.v.	Tramadol	c	c	3.73 (17)	11.0 (29)
	M1	c	c	c	16.9 (18)

a SD = Single dose, MD = Multiple dose, p.o. = Oral administration, i.v. = Intravenous administration, qid = Four times daily
b F represents the oral bioavailability of tramadol
c Not applicable
d Not measured

Food Effects

Oral administration of tramadol hydrochloride with food does not significantly affect its rate or extent of absorption, therefore, tramadol hydrochloride can be administered without regard to food.

Distribution

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

Metabolism

Tramadol is extensively metabolized after oral administration. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. The major metabolic pathways appear to be *N*- and *O*-demethylation and glucuronidation or sulfation in the liver. One metabolite (*O*-desmethyltramadol, denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see **PRECAUTIONS, Drug Interactions**).

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive, metabolizers", while M1 concentrations were 40% lower. Concomitant therapy with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and quinidine could result in significant drug interactions. *In vitro* drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and

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Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 are 6.3 ± 1.4 and 7.4 ± 1.4 hours, respectively. The plasma elimination half-life of racemic tramadol increased from approximately six hours to seven hours upon multiple dosing.

Special Populations

Renal

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, adjustment of the dosing regimen is recommended (see **DOSAGE AND ADMINISTRATION**). The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose.

Hepatic

Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver, resulting in both a larger area under the concentration time curve for tramadol and longer tramadol and M1 elimination half-lives (13 hrs. for tramadol and 19 hrs. for M1). In cirrhotic patients, adjustment of the dosing regimen is recommended (see **DOSAGE AND ADMINISTRATION**).

Geriatric

Healthy elderly subjects aged 65 to 75 years have plasma tramadol concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. In subjects over 75 years, maximum serum concentrations are elevated (208 vs. 162 ng/mL) and the elimination half-life is prolonged (7 vs. 6 hours) compared to subjects 65 to 75 years of age. Adjustment of the daily dose is recommended for patients older than 75 years (see **DOSAGE AND ADMINISTRATION**).

Gender

The absolute bioavailability of tramadol was 73% in males and 79% in females. The plasma clearance was 6.4 mL/min/kg in males and 5.7 mL/min/kg in females following a 100 mg IV dose of tramadol. Following a single oral dose, and after adjusting for body weight, females had a 12% higher peak tramadol concentration and a 35% higher area under the concentration-time curve compared to males. The clinical significance of this difference is unknown.

Clinical Studies

Tramadol hydrochloride has been given in single oral doses of 50, 75, and 100 mg to patients with pain following surgical procedures and pain following oral surgery (extraction of impacted molars).

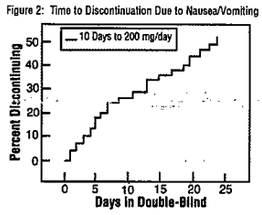
In single-dose models of pain following oral surgery, pain relief was demonstrated in some patients at doses of 50 mg and 75 mg. A dose of 100 mg tramadol hydrochloride tended to provide analgesia superior to codeine sulfate 60 mg, but it was not as effective as the combination of aspirin 650 mg with codeine phosphate 60 mg.

Tramadol hydrochloride has been studied in three long-term controlled trials involving a total of 820 patients, with 530 patients receiving tramadol hydrochloride. Patients with a variety of chronic painful conditions were studied in double-blind trials of one to three months duration. Average daily doses of approximately 250 mg of tramadol hydrochloride in divided doses were generally comparable to five doses of acetaminophen 300 mg with codeine phosphate 30 mg (TYLENOL® with Codeine #3) daily, five doses of aspirin 325 mg with codeine phosphate 30 mg daily, or two to three doses of acetaminophen 500 mg with oxycodone hydrochloride 5 mg (TYLOX®) daily. Tylenol® with Codeine #3 and Tylox® are the registered trademarks of Johnson RW.

Titration Trials

In a randomized, blinded clinical study with 129 to 132 patients per group, a 10-day titration to a daily tramadol hydrochloride dose of 200 mg (50 mg q.i.d.), attained in 50 mg increments every 3 days, was found to result in fewer discontinuations due to dizziness or vertigo than titration over only 4 days or no titration.

Figure 2: Time to Discontinuation Due to Nausea/Vomiting



INDICATIONS AND USAGE

Tramadol hydrochloride tablets are indicated for the management of moderate to moderately severe pain in adults.

CONTRAINDICATIONS

Tramadol hydrochloride should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or opioids. Tramadol hydrochloride is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. Tramadol hydrochloride may worsen central nervous system and respiratory depression in these patients.

WARNINGS

Seizure Risk

Seizures have been reported in patients receiving tramadol hydrochloride within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol hydrochloride above the recommended range. Concomitant use of tramadol hydrochloride increases the seizure risk in patients taking:

- **Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or**
- **Other opioids.**

Administration of tramadol hydrochloride may enhance the seizure risk in patients taking:

- **MAO inhibitors (see also WARNINGS, Use with MAO Inhibitors),**
- **Neuroleptics, or**
- **Other drugs that reduce the seizure threshold.**

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol hydrochloride overdose, naloxone administration may increase the risk of seizure.

Anaphylactoid Reactions

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol hydrochloride. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive tramadol hydrochloride (see **CONTRAINDICATIONS**).

Respiratory Depression

Administer tramadol hydrochloride cautiously in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of tramadol hydrochloride are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see **WARNINGS, Seizure Risk** and **OVERDOSAGE**).

Interaction with Central Nervous System (CNS) Depressants

Tramadol hydrochloride should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol hydrochloride increases the risk of CNS and respiratory depression in these patients.

Increased Intracranial Pressure or Head Trauma

Tramadol hydrochloride should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving tramadol hydrochloride tablets (see **Respiratory Depression**).

Use in Ambulatory Patients

Tramadol hydrochloride may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Use with MAO Inhibitors and serotonin re-uptake inhibitors

Use tramadol hydrochloride with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with concomitant administration. Concomitant use of tramadol hydrochloride with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.

Withdrawal

Withdrawal symptoms may occur if tramadol hydrochloride is discontinued abruptly (see **DRUG ABUSE AND DEPENDENCE**). These symptoms may include: anxiety, sweating, insomnia, tremor, nausea, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be relieved by lowering the medication.

Physical Dependence and Abuse

Tramadol hydrochloride may induce psychic and physical dependence of the morphine-type (μ-opioid) (see **DRUG ABUSE AND DEPENDENCE**). Tramadol

Use with MAO Inhibitors and serotonin re-uptake inhibitors
Use tramadol hydrochloride with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of tramadol hydrochloride with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.

Withdrawal
Withdrawal symptoms may occur if tramadol hydrochloride is discontinued abruptly (see **DRUG ABUSE AND DEPENDENCE**). 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.

Physical Dependence and Abuse
Tramadol hydrochloride may induce psychic and physical dependence of the morphine-type (μ-opioid) (see **DRUG ABUSE AND DEPENDENCE**). Tramadol hydrochloride should not be used in opioid-dependent patients. Tramadol hydrochloride 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.

Risk of Overdosage
Serious potential consequences of overdosage with tramadol hydrochloride are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment (see **OVERDOSAGE**).

PRECAUTIONS

Acute Abdominal Conditions
The administration of tramadol hydrochloride may complicate the clinical assessment of patients with acute abdominal conditions.

Use in Renal and Hepatic Disease
Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, dosing reduction is recommended (see **DOSAGE AND ADMINISTRATION**). Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. In cirrhotic patients, dosing reduction is recommended (see **DOSAGE AND ADMINISTRATION**).

With the prolonged half-life in these conditions, achievement of steady-state is delayed, so that it may take several days for elevated plasma concentrations to develop.

Information for Patients
- Tramadol hydrochloride tablets may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- Tramadol hydrochloride tablets should not be taken with alcohol containing beverages.
- Tramadol hydrochloride tablets should be used with caution when taking medications such as tranquilizers, hypnotics or other opiate containing analgesics.
- The patient should be instructed to inform the physician if they are pregnant, think they might become pregnant, or are trying to become pregnant (see **PRECAUTIONS, Labor and Delivery**).
- The patient should understand the single-dose and 24-hour dose limit and the time interval between doses, since exceeding these recommendations can result in respiratory depression, seizures and death.

Drug Interactions
In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

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

Use with Quinidine
Tramadol is metabolized to M1 by the CYP2D6. **Quinidine** is a selective inhibitor of that isoenzyme, so that concomitant administration of quinidine and tramadol hydrochloride results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

Use with Inhibitors of CYP2D6
In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.

Use with Cimetidine
Concomitant administration of tramadol hydrochloride with **cimetidine** does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the tramadol hydrochloride dosage regimen is recommended.

Use with MAO Inhibitors
Interactions with **MAO inhibitors**, due to interference with detoxification mechanisms have been reported for some centrally acting drugs (see **WARNINGS, Use with MAO Inhibitors**).

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

Carcinogenesis, Mutagenesis, Impairment of Fertility
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 0.36 times the maximum daily human dosage of 246 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/m2, or 0.73 times the maximum daily human dosage).

Tramadol was not mutagenic in the following assays: Ames *Salmonella* microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Weakly 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 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 (300 mg/m^2) in male rats and 75 mg/kg (450 mg/m^2) in female rats. These dosages are 1.2 and 1.8 times the maximum daily human dosage of 246 mg/m2, respectively.

Pregnancy
Teratogenic Effects: *Pregnancy Category C*
Tramadol has been shown to be embryotoxic and fetotoxic in mice (120 mg/kg or 360 mg/m2), rats (≥25 mg/kg or 150 mg/m2), and rabbits (≥75 mg/kg or 900 mg/m2) at maternally toxic dosages but was not teratogenic at these dose levels. These dosages on a mg/m^2 basis are 1.4, ≥0.6, and ≥3.6 times the maximum daily human dosage (246 mg/m2) for mouse, rat and rabbit, respectively.

No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg or 420 mg/m2), rats (up to 80 mg/kg or 480 mg/m2), or rabbits (up to 300 mg/kg or 3600 mg/m2) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg (3600 mg/m2), a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the maximum daily human dosage (246 mg/m2), respectively.

Non-teratogenic Effects
Tramadol was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/m2 or 1.2 times the maximum daily human tramadol dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m2 or 1.9 times the maximum daily human dose).

There are no adequate and well-controlled studies in pregnant women. Tramadol hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during post-marketing.

Labor and Delivery
Tramadol hydrochloride should not be used in pregnant women prior to or 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**). 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 given tramadol during labor.

The effect of tramadol hydrochloride, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers
Tramadol hydrochloride 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 16 hours postdose was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg of M1.

Pediatric Use
The safety and efficacy of tramadol hydrochloride in patients under 16 years of age have not been established. The use of tramadol hydrochloride in the pediatric population is not recommended.

Geriatric Use
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. In patients over 75 years of age, daily doses in excess of 300 mg are not recommended (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

A total of 455 elderly (65 years of age or older) subjects were exposed to tramadol hydrochloride in controlled clinical trials. Of those, 145 subjects were 75 years of age and older.

In studies including geriatric patients, treatment-limiting adverse events were higher in subjects over 75 years of age compared to those under 65 years of age. Specifically, 30% of those over 75 years of age had gastrointestinal treatment-limiting adverse events compared to 17% of those under 65 years of age. Constipation resulted in discontinuation of treatment in 10% of those over 75.

ADVERSE REACTIONS

Tramadol hydrochloride was administered to 550 patients during the double-blind or open-label extension periods in U.S. studies of chronic nonmalignant pain. Of these patients, 375 were 65 years old or older. Table 2 reports the cumulative incidence rate of adverse reactions by 7, 30 and 90 days for the most frequent reactions (5% or more by 7 days). The most frequently reported events were in the central nervous system and gastrointestinal system. Although the reactions listed in the table are felt to be probably related to tramadol hydrochloride administration, the reported rates also include some events that may have been due to underlying disease or concomitant medication. The overall incidence rates of adverse experiences in these trials were similar for tramadol hydrochloride and the active control groups, TYLENOL® with Codeine #3 (acetaminophen 300 mg with codeine phosphate 30 mg), and aspirin 325 mg with codeine phosphate 30 mg (Tylenol® with Codeine #3 is the registered trademark of Johnson RW). However, the rates of withdrawals due to adverse events appeared to be higher in the tramadol hydrochloride groups.

Table 2
Cumulative Incidence of Adverse Reactions for Tramadol Hydrochloride in Chronic Trials of Nonmalignant Pain (N = 427)

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Dizziness/Vertigo	22%	24%	26%

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Table 2
Cumulative Incidence of Adverse Reactions for Tramadol Hydrochloride in Chronic Trials of Nonmalignant Pain (N = 427)

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Dizziness/Vertigo	26%	31%	33%
Nausea	24%	34%	40%
Constipation	24%	38%	46%
Headache	18%	26%	32%
Somnolence	16%	23%	25%
Vomiting	9%	13%	17%
Pruritus	8%	10%	11%
"CNS Stimulation" [1]	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry Mouth	5%	9%	10%
Diarrhea	5%	6%	10%

[1] "CNS Stimulation" is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability and hallucinations.

Incidence 1% to less than 5%, possibly causally related:
The following lists adverse reactions that occurred with an incidence of 1% to less than 5% in clinical trials, and for which the possibility of a causal relationship with tramadol hydrochloride exists.

Body as a Whole: Malaise.
Cardiovascular: Vasodilation.
Central Nervous System: Anxiety, Confusion, Coordination disturbance, Euphoria, Miosis, Nervousness, Sleep disorder.
Gastrointestinal: Abdominal pain, Anorexia, Flatulence.
Musculoskeletal: Hypertonia.
Skin: Rash.
Special Senses: Visual disturbance.
Urogenital: Menopausal symptoms, Urinary frequency, Urinary retention.

Incidence less than 1%, possibly causally related:
The following lists adverse reactions that occurred with an incidence of less than 1% in clinical trials and/or reported in post-marketing experience.

Body as a Whole: Accidental injury, Allergic reaction, Anaphylaxis, Death, Suicidal tendency, Weight loss, Serotonin syndrome (mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma).
Cardiovascular: Orthostatic hypotension, Syncope, Tachycardia.
Central Nervous System: Abnormal gait, Amnesia, Cognitive dysfunction, Depression, Difficulty in concentration, Hallucinations, Paresthesia, Seizure (see **WARNINGS**), Tremor.
Respiratory: Dyspnea.
Skin: Stevens-Johnson syndrome/Toxic epidermal necrolysis, Urticaria, Vesicles.
Special Senses: Dysgeusia.
Urogenital: Dysuria, Menstrual disorder.

Other adverse experiences, causal relationship unknown:
A variety of other adverse events were reported infrequently in patients taking tramadol hydrochloride during clinical trials and/or reported in post-marketing experience. A causal relationship between tramadol hydrochloride and these events has not been determined. However, the most significant events are listed below as alerting information to the physician.

Cardiovascular: Abnormal ECG, Hypertension, Hypotension, Myocardial ischemia, Palpitations, Pulmonary edema, Pulmonary embolism.
Central Nervous System: Migraine, Speech disorders.
Gastrointestinal: Gastrointestinal bleeding, Hepatitis, Stomatitis, Liver failure.
Laboratory Abnormalities: Creatinine increase, Elevated liver enzymes, Hemoglobin decrease, Proteinuria.
Sensory: Cataracts, Deafness, Tinnitus.

DRUG ABUSE AND DEPENDENCE

Tramadol hydrochloride may induce psychic and physical dependence of the morphine-type (μ-opioid)(see **WARNINGS**). 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. The risk in patients with substance abuse has been observed to be higher. Tramadol hydrochloride is associated with craving and tolerance development. Withdrawal symptoms may occur if tramadol hydrochloride 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 reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

OVERDOSAGE

Serious potential consequences of overdosage are respiratory depression, lethargy, coma, seizure, cardiac arrest and death (see **WARNINGS**). Fatalities have been reported in post marketing in association with both intentional and unintentional overdose with tramadol hydrochloride. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol hydrochloride the risk of seizures is also increased with naloxone administration. In animals convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

DOSAGE AND ADMINISTRATION

Adults (17 years of age and over)
For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of tramadol hydrochloride can be improved by initiating therapy with a titration regimen. The total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After titration, tramadol hydrochloride tablets 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, **not to exceed 400 mg per day.**

For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, tramadol hydrochloride tablets 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, **not to exceed 400 mg per day.**

Individualization of Dose
Good pain management practice dictates that the dose be individualized according to patient need using the lowest beneficial dose. Studies with tramadol in adults have shown that starting at the lowest possible dose and titrating upward will result in fewer discontinuations and increased tolerability.

- In all patients with **creatinine clearance less than 30 mL/min,** it is recommended that the dosing interval of tramadol hydrochloride tablets be increased to 12 hours, with a maximum daily dose of 200 mg. Since only 7% of an administered dose is removed by hemodialysis, **dialysis patients** can receive their regular dose on the day of dialysis.
- The recommended dose for adult patients with **cirrhosis** is 50 mg every 12 hours.
- In general, dose selection for an elderly patient over 65 years old should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. For elderly patients **over 75 years** old, total dose should not exceed 300 mg/day.

HOW SUPPLIED

Tramadol hydrochloride tablets, 50 mg are available as white, round, film coated tablets, debossed with "466" on one side and "WATSON" on the other. Each tablet contains 50 mg of tramadol hydrochloride. They are supplied in bottles of 100, 500 and 1000 tablets.

Store at controlled room temperature 15°-30°C (59°-86°F). [See USP.]
Dispense in a tight container as defined in the USP.

Watson Laboratories, Inc.
Corona, CA 92880 USA

30354-1
Issued: May 2002

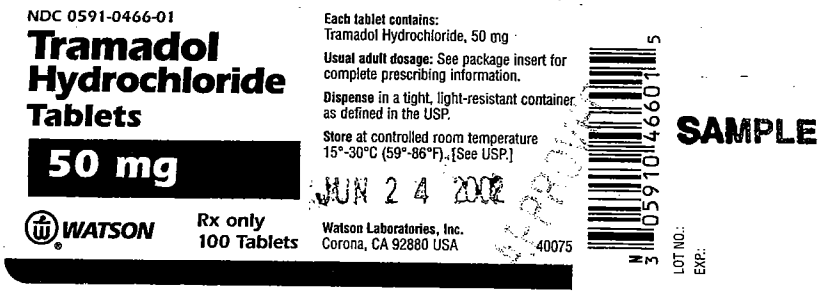
Tramadol Hydrochloride
Tablets
Issued: May 2002
Rx only

Original

Container Labeling

Tramadol Hydrochloride Tablets, 50 mg

100 Tablets



Original

Container Labeling
Tramadol Hydrochloride Tablets, 50 mg
500 Tablets

NDC 0591-0466-05

Tramadol Hydrochloride Tablets

50 mg

WATSON

Rx only
500 Tablets

Each tablet contains:
Tramadol Hydrochloride, 50 mg

Usual adult dosage: See package insert for complete prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F). [See USP.]

JUN 2 4 2002 APPROVED

Watson Laboratories, Inc.
Corona, CA 92880 USA

40076

3 05910 46605 3

SAMPLE

LOT NO.:
EXP.:

Container Labeling
Tramadol Hydrochloride Tablets, 50 mg
1000 Tablets

NDC 0591-0466-10

Tramadol Hydrochloride Tablets

50 mg

WATSON

Rx only
1000 Tablets

Each tablet contains:
Tramadol Hydrochloride, 50 mg

Usual adult dosage: See package insert for complete prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F). [See USP.]

JUN 2 4 2002

APPROVED

Watson Laboratories, Inc.
Corona, CA 92880 USA

40077

SAMPLE

LOT NO.:
EXP.:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-962 Date of Submission: September 1, 2000

Applicant's Name: Watson Laboratories, Inc.

Established Name: Tramadol Hydrochloride Tablets, 50 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. We acknowledge that you have not included the titration information approved on August 21, 1998 and December 23, 1999 for the insert labeling of the reference listed drug, Ultram®. We have reviewed the labeling submitted and have the following comments.

      Pending resolution of issues regarding the differences between your proposed dosing information of this drug product and that information in the last approved for the reference listed drug, Ultram®, we defer comment at this time.

   b. Revise the storage temperature statement to read "Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP]".

2. CONTAINER – 100s, 500s, & 1000s

   a. Revise the established name to read "tramadol hydrochloride tablets".

   b. Revise to read:

      ...contains: Tramadol hydrochloride.....50 mg

   c. Refer to the general comment (b) above.

3. INSERT

   a. GENERAL

      i. Refer to the general comments above.

      ii. It is preferable to use the term "mcg" rather than "µg" throughout the text.

   b. DESCRIPTION

      Please identify the ingredients contained in your coating material, ———White ——— so that we can verify the listing of inactive ingredients.

   c. CLINICAL PHARMACOLOGY

      i. See general comment (a) above.

ii. Clinical Studies – Last paragraph, last sentence:

We encourage that you include a disclaimer identifying two brand names, "TYLENOL® with Codeine #3" and "TYLOX®". [e.g., Tylox® is the registered trade mark of Johnson RW]

d. INDICATIONS AND USAGE

... hydrochloride tablets are indicated... [add "tablets"]

e. PRECAUTIONS (Increased ... Trauma) – Last sentence:

... receiving tramadol hydrochloride tablets.

f. ADVERSE REACTIONS - First paragraph, last sentence:

See comment (c) above.

g. DOSAGE AND ADMINISTRATION

See general comment (a) above.

h. HOW SUPPLIED

i. Please note that the innovator has changed the scoring configuration from "unscored" to "scored" for Ultram® tablets. Please change the scoring configuration of your drug product to be same as the innovator's and revise this section accordingly.

ii. Refer to the general comment (b) above.

We will not request final printed insert labeling until we are able to provide adequate guidance regarding the differences of dosing information between your proposed labeling and that of the reference listed drug.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling review branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES/QUESTIONS TO THE CHEMIST:

i. We asked the sponsor to change the scoring figuration from "unscored" to "scored" to be the same as the innovator. Please follow up on this revision in terms of chemistry requirement. Please refer to OGD MaPP on this subject.

2. Please see comment 3(b) regarding inactive ingredients.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the		x	

package insert accompany the product?			
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD? (see FTR)	x		
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x

USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	x		

FOR THE RECORD:

1. MODEL LABELING – Ultram® Tablets (NDA 20-281/S-014 & 016, approved on August 21, 1998 and December 23, 1999, respectively)

2. This drug product is not the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 90-E, B.1.1.

4. Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020281	**002**	**D-44**	**AUG 21,2001**
020281	**002**	**NCE**	**MAR 03,2000**
020281	**002**	**PED**	**SEP 03,2000**
020281	**002**	**PED**	**FEB 21,2002**

D-44 (most likely tied with the pediatric exclusivity expires on 2/21/2002) was granted for the new titration information approved in S-014 on August 21, 1998. Another new titration information, which supersedes the subject of D-44, was approved on December 23, 1999 in S-016. At this time, the decision has not been made whether another exclusivity would be granted for this new titration information approved on December 23, 1999. The firm has carved out all titration information in order to market their product prior to the expiration of the exclusivity.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   Both RLD and the ANDA: Store at controlled room temperature (up to 25°C, 77°F). See general comment (b).

6. DISPENSING STATEMENT

RLD – Dispense in a tight container.

ANDA - Dispense in a tight container as defined in the USP.

7. PACKAGING CONFIGURATIONS

RLD: 100s, 500s & unit-doses of 100
ANDA – 100s, 500s, & 1000s

8. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.591

9. SCORING

The RLD is scored for both 50 mg & 100 mg strengths. ✓
The ANDA proposes unscored for 50 mg tablet.

The scoring of RLD has been changed from "unscored" to "scored" in association with the new titration information (starting with 25 mg) approved in S-016.

10. It has been determined between Charlie, Chan & Peter that the scoring of generic drug products should be the same as the innovators (i.e., scored) regardless whether the generic labeling should be allowed for the carving out of the titration information or not in accordance with OGD MaPP.

11. CLOSURE

Container – HDPE
Closure – 100s, 500s & 1000s (Non-CRC) [see p.461-462, B1.2]

12. Watson Laboratories, Inc. is the manufacturer of this product. (p.229, B.1.1)

Date of Review: 11/28/00 **Date of Submission: September 1, 2000**

Primary Reviewer: Chan Park Chan Park **Date:** 12/1/00

Team Leader: **Date:**

Charlie Hoppes 12/1/00

cc:

ANDA: 75-962
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
V:\FIRMSNZ\WATSON\LTRS&REV\75962na1.LABELING
Review

2.1 Veritas, S

(This review supersedes the one prepared on 11/28/01)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-962 Date of Submission: September 1, 2000

Applicant's Name: Watson Laboratories, Inc.

Established Name: Tramadol Hydrochloride Tablets, 50 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Please note that a dosing exclusivity (D-63) was granted for the new titration information approved on December 23, 1999, for the insert labeling of the reference listed drug, Ultram®. Please update your Exclusivity Statements accordingly.

   b. We acknowledge that you have not included the titration information approved on August 21, 1998 and December 23, 1999 for the insert labeling of the reference listed drug, Ultram®. We have reviewed the labeling submitted and have the following comments.

      Pending resolution of issues regarding the differences between your proposed dosing information of this drug product and that information in the last approved for the reference listed drug, Ultram®, we defer comment at this time.

   c. Revise the storage temperature statement to read "Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP]".

2. CONTAINER – 100s, 500s, & 1000s

   a. Revise the established name to read "tramadol hydrochloride tablets".

   b. Revise to read:

      ...contains: Tramadol hydrochloride.....50 mg

   c. Refer to the general comment (b) above.

3. INSERT

   a. GENERAL

      i. Refer to the general comments above.

      ii. It is preferable to use the term "mcg" rather than "µg" throughout the text.

   b. DESCRIPTION

      Please identify the ingredients contained in your coating material, ——— White ——— so that we can verify the listing of inactive ingredients.

c. CLINICAL PHARMACOLOGY

i. See general comment (a) above.

ii. Clinical Studies – Last paragraph, last sentence:

We encourage that you include a disclaimer identifying two brand names, "TYLENOL® with Codeine #3" and "TYLOX®". [e.g., Tylox® is the registered trade mark of Johnson RW]

d. INDICATIONS AND USAGE

... hydrochloride tablets are indicated... [add "tablets"]

e. PRECAUTIONS (Increased ... Trauma) – Last sentence:

... receiving tramadol hydrochloride tablets.

f. ADVERSE REACTIONS - First paragraph, last sentence:

See comment (c) above.

g. DOSAGE AND ADMINISTRATION

See general comment (a) above.

h. HOW SUPPLIED

i. Please note that the innovator has changed the scoring configuration from "unscored" to "scored" for Ultram® tablets. Please change the scoring configuration of your drug product to be same as the innovator's and revise this section accordingly.

ii. Refer to the general comment (b) above.

We will not request final printed insert labeling until we are able to provide adequate guidance regarding the differences of dosing information between your proposed labeling and that of the reference listed drug.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling review branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES/QUESTIONS TO THE CHEMIST:

i. **We asked the sponsor to change the scoring figuration from "unscored" to "scored" to be the same as the innovator. Please follow up on this revision in terms of chemistry requirement. Please refer to OGD MaPP on this subject.**

2. **Please see comment 3(b) regarding inactive ingredients.** Included 4/23/01 ps,

---

FOR THE RECORD:

1. MODEL LABELING – Ultram® Tablets (NDA 20-281/S-014 & 016, approved on August 21, 1998 and December 23, 1999, respectively)

2. This drug product is not the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 90-E, B.1.1.

4. Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

020281	002	D-63	DEC 23,2002
020281	002	D-44	AUG 21,2001
020281	002	NCE	MAR 03,2000
020281	002	PED	SEP 03,2000
020281	002	PED	FEB 21,2002

D-44 (tied with the pediatric exclusivity expires on 2/21/2002) was granted for the new titration information approved in S-014 on August 21, 1998. Another new titration information, which supersedes the subject of D-44, was approved on December 23, 1999 in S-016. Another exclusivity D-63 was granted for this new titration information.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   Both RLD and the ANDA: Store at controlled room temperature (up to 25°C, 77°F). See general comment (b).

6. DISPENSING STATEMENT

   RLD – Dispense in a tight container.

   ANDA - Dispense in a tight container as defined in the USP.

7. PACKAGING CONFIGURATIONS

   RLD: 100s, 500s & unit-doses of 100
   ANDA – 100s, 500s, & 1000s

8. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.591

9. SCORING

The RLD is scored for both 50 mg & 100 mg strengths.
The ANDA proposes unscored for 50 mg tablet.

The scoring of RLD has been changed from "unscored" to "scored" in association with the new titration information (starting with 25 mg) approved in S-016.

10. It has been determined between Charlie, Chan & Peter that the scoring of generic drug products should be the same as the innovators (i.e., scored) regardless whether the generic labeling should be allowed for the carving out of the titration information or not in accordance with OGD MaPP.

11. CLOSURE

Container – HDPE
Closure – 100s, 500s & 1000s (Non-CRC) [see p.461-462, B1.2]

12. Watson Laboratories, Inc. is the manufacturer of this product. (p.229, B.1.1)

13. ADVERSE REACTIONS

The following is the e-mail sent to PM in the new drug division regarding an adverse reaction "SKIN: Pruritis". We are awaiting the answer and will ask the firm a revision on this if necessary after receiving the answer.

Hi Yoon,

We note that the last item under ADVERSE REACTIONS "Skin: Pruritis" appearing in the insert labeling approved on August 21, 1998 (S-014) is NOT found in the labeling approved on December 23, 1999 (S-016). There is no reference to this change in the approval letter of S-016. Could it be an inadvertent omission ? Please let me know. Thank you,

---

Date of Review: 2/21/01 **Date of Submission: September 1, 2000**

Primary Reviewer: Chan Park **Date:** 2/22/01

Team Leader: **Date:** 2/22/01

cc:

ANDA: 75-962
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
V:\FIRMSNZ\WATSON\LTRS&REV\75962na1A.LABELING
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-962 Date of Submission: April 23, 2001 & July 18, 01

Applicant's Name: Watson Laboratories, Inc.

Established Name: Tramadol Hydrochloride Tablets, 50 mg

Labeling Deficiencies:

INSERT

1. General

   a. Please revise your insert labeling to be in accordance with new labeling changes in the attached insert labeling for Ultram®, which was approved on August 15, 2001.

   b. We acknowledge that you do not seek approval of labeling that includes the new dosing schedule protected by the D-44 and D-63 exclusivities. We have reviewed the labeling submitted and have the following comments.

      Pending resolution of issues regarding the differences between your proposed dosing information of this drug product and that information in the last approved for the reference listed drug, Ultram®, we defer comment at this time.

2. Clinical Pharmacology - Figure 1

   It appears that the legends in this figure do not accurately represent the graph. Please revise the legends or graph so that they match each other.

3. How Supplied

   We encourage that you retain the NDC numbers.

We will not request final printed insert labeling until we are able to provide adequate guidance regarding the differences of dosing information between your proposed labeling and that of the reference listed drug.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: A copy of the last approved labeling for Ultram®.

FOR THE RECORD:

1. MODEL LABELING – Ultram® Tablets (NDA 20-281/S-029, approved on August 15, 2001). New labeling changes for S-029 are to strengthen WARNINGS and PRECAUTIONS sections, which is not associated with exclusivity.

2. This drug product is not the subject of a USP monograph.

3. Container labels are satisfactory in FPL as of 4/23/01 submission.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 90-E, B.1.1. See also Exibit 1 of the 4/23/01 submission regarding the inactive ingredients contained in the coating material.

5. Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020281	002	PED	FEB 21,2002
020281	002	PED	JUN 23,2003
020281	002	D-63	DEC 23,2002
020281	002	D-44	AUG 21,2001

D-44 (tied with the pediatric exclusivity expires on 2/21/2002) was granted for the new titration information approved in S-014 on August 21, 1998. Another new titration information, which supersedes the subject of D-44, was approved on December 23, 1999 in S-016. Another exclusivity D-63 was granted for this new titration information.

The sponsor's update Exclusivity statement is accurate.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD : Store at controlled room temperature (up to 25°C, 77°F).
ANDA: Store at controlled room temperature, 15 to 30°C (59 to 86°F). [see USP]

DISPENSING STATEMENT

RLD – Dispense in a tight container.

ANDA - Dispense in a tight container as defined in the USP.

7. PACKAGING CONFIGURATIONS

RLD: 100s, 500s & unit-doses of 100
ANDA – 100s, 500s, & 1000s

8. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.591. The sponsor has changed the tablet code numbers on the tablet from —— to "446". The related chemistry information has been submitted for review in the submission of 4/23/01.

9. SCORING

The RLD is scored for both 50 mg & 100 mg strengths.
The ANDA is scored.

The scoring of RLD has been changed from "unscored" to "scored" in association with the new titration information (starting with 25 mg) approved in S-016. We have to resolve this scoring issue in conjunction with the exclusivity issue.

10. It has been determined between Charlie, Chan & Peter that the scoring of generic drug products should be the same as the innovators (i.e., scored) regardless whether the generic labeling should be allowed for the carving out of the titration information or not in accordance with OGD MaPP.

11. CLOSURE

Container – HDPE
Closure – 100s, 500s & 1000s (Non-CRC) [see p.461-462, B1.2]

12. Watson Laboratories, Inc. is the manufacturer of this product. (p.229, B.1.1)

13. It has been determined between OGD and the new drug division that the generic labeling should contain the first titration information approved August, 1998. However, we determined that generic does not have to wait for the expiration of the exclusivity granted for the new titration information approved December, 1999, which means that the generic labeling would not have to contain the second titration information for an approval. Therefore, OGD will allow the generic sponsors use the discontinued RLD labeling (without the second titration information). GC is working with the new drug division to develop a guidance regarding this issue to provide a legal basis for going back to the discontinued RLD labeling. New labeling changes for S-029 are to strengthen WARNINGS and PRECAUSTIONS SECTIONS, which is not associated with exclusivity.

Date of Review: 8/28/01 **Date of Submission: 4/23/01**

Primary Reviewer: Chan Park **Date:** 8/29/01

Team Leader: **Date:** 8/29/01

cc:

ANDA: 75-962
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
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Review

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-962 Date of Submission: June 13, 2002

Applicant's Name: Watson Laboratories, Inc.

Established Name: Tramadol Hydrochloride Tablets, 50 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS: 100s, 500s, & 1000s

Satisfactory in FPL as of 6/13/02 submission (vol. 3.1, 100s - #40075; 500s - #40076; 1000s - #40077)

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of 6/13/02 submission (Issued May 2002, Code# 30354-1, vol. 3.1)

REVISIONS NEEDED POST-APPROVAL - INSERT:

1. GENERAL

   Increase the prominence, the figures in particular.

2. HOW SUPPLIED

   The issue date should be "June 02" rather than "May 2002".

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Ultram® Tablets

NDA Number: 20-281

NDA Drug Name: Ultram® Tablets

NDA Firm: R.W, Johnson

Date of Approval of NDA Insert and supplement #: August 15, 2001/S-029

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? **Yes**

Based on the OGD labeling proposal sent to the sponsor on June 11, 2001 via e-mail attachment.

If yes, give date of labeling guidance: June 11, 2002

FOR THE RECORD:

1. MODEL LABELING – Ultram® Tablets (NDA 20-281/S-029, approved on August 15, 2001).

   However, this labeling was modified due to the exclusivity and patent issue associated with 16-day titration information. The OGD proposal for the sponsors was based on the numerous consults with the HFD-550 and G.C. OGD carved out the information specific to the 16-day titration and also made some editorial changes in the D&A section.

2. This drug product is not the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 90-E, B.1.1. See also Exibit 1 of the 4/23/01 submission regarding the inactive ingredients contained in the coating material.

4. Patent Data

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020281	002	6339105	OCT 12,2019	U-435
020281	002	6339105*PED	APR 12,2020	U-435

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020281	002	PED	FEB 21,2002
020281	002	PED	JUN 23,2003
020281	002	D-63	DEC 23,2002

6,339,105 - Analgesic regimen

D-63 - TO ALLOW A TITRATION DOSING REGIMEN USING A 25MG DOSE

U-435 A TITRATION DOSING REGIMEN FOR THE TREATMENT OF PAIN USING AN INITIAL DOSE OF ABOUT 25MG

5. The sponsor's updated Patent and Exclusivity statement submitted June 13, 2002 (signed June 11, 2002) is accurate.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   RLD : Store at controlled room temperature (up to 25°C, 77°F).
   ANDA: Store at controlled room temperature, 15 to 30°C (59 to 86°F). [see USP]

   DISPENSING STATEMENT

   RLD – Dispense in a tight container.

   ANDA - Dispense in a tight container as defined in the USP.

7. PACKAGING CONFIGURATIONS

RLD: 100s, 500s & unit-doses of 100
ANDA – 100s, 500s, & 1000s

8. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.591. The sponsor has changed the tablet code numbers on the tablet from —— to "446". The related chemistry information has been submitted for review in the submission of 4/23/01.

9. SCORING

The RLD is scored for both 50 mg & 100 mg strengths.
The ANDA is unscored per Agency's request

The scoring of RLD has been changed from "unscored" to "scored" in association with the new titration information (starting with 25 mg) approved in S-016. This scoring is associated with the 25 mg, 16-day titration and hence, it was determined that this scoring configuration is also protected by exclusivity and patent.

10. CLOSURE

Container – HDPE
Closure – 100s, 500s & 1000s (Non-CRC) [see p.461-462, B1.2]

11. Watson Laboratories, Inc. is the manufacturer of this product. (p.229, B.1.1)

12. See file holder for the detailed information associated with the decision on the OGD proposed labeling.

Date of Review: 6/19/02 **Date of Submission: 6/13/02**

Primary Reviewer: Chan Park C Park **Date:** 6/19/02

Acting Team Leader: Lillie Golson **Date:** 6/19/02

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cc:

ANDA: 75-962
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

CHEMISTRY REVIEWS

It is believed the Chemistry Reviews are misnumbered. Only three reviews were located in the archived volumes, though they are numbered 1, 3, and 5.

Wtm0001.004

1. CHEMISTRY REVIEW NO. 1 2. ANDA # 75962

3. NAME AND ADDRESS OF APPLICANT
Watson Laboratories, Inc.
311 Bonnie Circle
Corona, CA 92880

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Ultram manufactured by R.W. Johnson. The patent expiration date is listed as 09/03/00. Exclusivity for dosing in effect.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Tramadol Hydrochloride Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
September 1, 2000 - Original submission
December 4, 2000 - Bio. Amendment

10. PHARMACOLOGICAL CATEGORY
Centrally acting analgesic

11. Rx or OTC
Rx

12. RELATED DMFs
See DMF Checklist or item #37

13. DOSAGE FORM
Tablet

14. POTENCY
50 mg

15. CHEMICAL NAME AND STRUCTURE

(±)cis-2-[(dimethylamino)methyl]-1-(3-meth oxyphenyl) cyclohexanol hydrochloride. Molecular weight is 299.8. Soluble in water.

16. RECORDS AND REPORTS
None.

17. COMMENTS
Several minor deficiencies found.

The api and the finished drug product have no compendial monographs. Methods validation by and FDA Laboratory will be requested.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend not approvable letter to issue.

19. REVIEWER: Edwin Ramos

DATE COMPLETED: January 10, 2000

2/23/01

APPEARS THIS WAY
ON ORIGINAL

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

cc: ANDA 75-962
ANDA DUP
Division File

Endorsements:
HFD-649/Eramos/1/16/01 6/23/01

HFD-649/Gsmith/2/20/01 2/26/01

HFD-619/Jmin/2/22/01 2/26/01

CHEMISTRY REVIEW - Not APPROVABLE - Minor

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APPEARS THIS WAY
ON ORIGINAL

AD,1 6/1/01
Barbara Davit

1. CHEMISTRY REVIEW NO. 3 2. ANDA # 75-962

3. NAME AND ADDRESS OF APPLICANT
Watson Laboratories, Inc.
Attention: Ernest Lengle
311 Bonnie Circle
Corona, CA 92880

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Ultram manufactured by Ortho-McNeil Pharmaceutical. The patent expiration date is listed as 09/03/00. Exclusivities are now in effect.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Tramadol Hydrochloride Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
September 1, 00- Original submission
September 29, 00 New Correspondence (Bio)
December 4, 00 - Telecom (Bio)
February 1, 01 - Internal OGD Memo
February 27, 01- Deficiency letter
March 21, 01 - Bio Review adequate
April 23,01- Amendment
May 9, 01- New correspondence
June 1, 01- Telecom amendment
July 18, 01- Amendment
September 4, 01- Facsimile
September 17, 01-Labeling amendment

10. PHARMACOLOGICAL CATEGORY
Centrally acting analgesic

11. Rx or OTC
Rx

12. RELATED DMFs
See DMF Checklist or item #37

13. DOSAGE FORM
Tablet

14. POTENCY
50 mg

15. CHEMICAL NAME AND STRUCTURE

(±)cis-2-[(dimethylamino)methyl]-1-(3-meth oxyphenyl) cyclohexanol hydrochloride. Molecular weight is 299.8. Soluble in water.

16. RECORDS AND REPORTS
None.

17. COMMENTS
The drug substance raw material and the finished drug product have no compendial monographs. Methods validation by and FDA Laboratory was requested. Telecom issues are resolved (scored demonstration was manufactured and the accelerated stability data will be provided in the next annual report). The —— specification was revised from ——— to ———. Also, page 240a that pertains to a portion of the finished drug product tests and specification is now included.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approvable letter to issue.

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
December 17, 2001

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ON ORIGINAL

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CHEMISTRY REVIEW #"3"

cc: ANDA 75-962
Division File
Field Copy

Endorsements:
HFD-649/ERamos/7/3/01 For Mahnaz Farahani 12,21,01
HFD-649/GSmith/Mayra Pineiro for 9/11/01 12/21/01
HFD-619/JMin/8/24/01 12/21/01

CHEMISTRY REVIEW - APPROVABLE -????

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F/t by rad12/20/01

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 5 2. ANDA # 75962

3. NAME AND ADDRESS OF APPLICANT
Watson Laboratories, Inc.
311 Bonnie Circle
Corona, CA 92880

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Ultram manufactured by Ortho-McNeil Pharmaceutical. The patent expiration date is listed as 09/03/00. Exclusivities are now in effect.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Tramadol Hydrochloride Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
September 1, 00- Original submission
September 29, 00 New Correspondence (Bio)
December 4, 00 - Telecom (Bio)
February 1, 01 - Internal OGD Memo
February 27, 01- Deficiency letter
March 21, 01 - Bio Review adequate
April 23,01- Amendment
May 9, 01- New correspondence
June 1, 01- Telecom amendment
September 19, 2002 New correspondence Bio
December 17, 2001Chemistry review #3 TA
January 15, 2002-TA letter
February 22, 2002 New correspondence
February 24, 2002 P IV Certification
June 13, 2002- Amendment

10. PHARMACOLOGICAL CATEGORY
Centrally acting analgesic

11. Rx or OTC
Rx

12. RELATED DMFs
See DMF Checklist or item #37

13. DOSAGE FORM
Tablet

14. POTENCY
50 mg

15. CHEMICAL NAME AND STRUCTURE

(±)cis-2-[(dimethylamino)methyl]-1-(3-meth oxyphenyl) cyclohexanol hydrochloride. Molecular weight is 299.8. Soluble in water.

16. RECORDS AND REPORTS
None.

17. COMMENTS
The firm committed to resolve any issues identified in the method validation program after approval in the original submission (GJSmith).

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approvable letter to issue.

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
June 24, 2002

APPEARS THIS WAY
ON ORIGINAL

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW # "5"

cc: ANDA 75-962
Division File
Field Copy

Endorsements:
HFD-649/Eramos/6/24/02 6/24/02
HFD-649/Gsmith/6/24/02 6/24/02
HFD-619/Jmin6/24/02 6/24/02

CHEMISTRY REVIEW - APPROVABLE

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APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

BIOEQUIVALENCE REVIEWS

9

TRAMADOL HYDROCHLORIDE
50 mg TABLET
ANDA 75-962
Reviewer: Pradeep M. Sathe
file name:C/wpfiles/75962SD.900

WATSON LABORATORIES, INC.
Miami, FL
Submission Dates:
09/01/00
12/04/00

Review of Bioequivalence Studies and Dissolution Data (Electronic Submission)

Introduction

Indication: Centrally acting synthetic analgesic
Type of Submission: Electronic
Contents of Submission: One fasting study, One 'food challenge' study, Comparative Dissolution.
RLD: Ortho-McNeil's Ultram^{R}
Recommended Dose: 50 mg

Background

Tramadol Hydrochloride is a centrally acting synthetic analgesic. Opioid activity is due to low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol. Tramadol is administered as a racemate. Both (-) and (+) forms of tramadol and M1 are detected in blood. Tramadol is extensively metabolized by liver. Thirty (30)% of the dose is excreted in urine as unchanged drug while 60% of the dose is excreted as metabolites. The formation of M1 is dependent upon Cytochrome P-450 (CYP2D6). The observed plasma half-lives of tramadol and its metabolite are 6.3 and 7.4 hours, respectively.

Financial Disclosure: The firm has stated that it has not used services of any person with a conflicting financial interest or who has been debarred by the agency to conduct the study.

Protocol No.: P99-614, A RELATIVE BIOAVAILABILITY STUDY OF 50 MG TRAMADOL TABLETS UNDER FASTING CONDITIONS

Study Information

STUDY FACILITY INFORMATION
Clinical Facility: _____
Medical Director: _____ M.D.
Scientific Director: _____ Pharm.D.

Clinical Study Dates:	12/11/99 to 12/19/99
Analytical Facility	————————————
Principal Investigator:	————, M.S.
Analytical Study dates:	**01/04/00 to 01/25/00**

TREATMENT INFORMATION

Treatment ID:	1	2
Test or Reference:	T	R
Product Name:	Tramadol Hydrochloride	Ultram
Manufacturer:	Watson Laboratories, Inc.	Ortho-McNeil Inc.
Manufacture Date:	9/13/99	N/A
Expiration Date:	N/A	1/01
ANDA Batch Size:	———— tablets	N/A
Full Batch Size:	———— tablets	N/A
Batch/Lot Number:	R02099	CAA1982
Potency:	96.6%	96.1%
Content Uniformity:	94.9%	95.9%
Strength:	50 mg	50 mg
Dosage Form:	tablet	tablet
Dose Administered:	50 mg	50 mg
Study Condition:	fasting	fasting
Length of Fasting:	14 hours	14 hours

RANDOMIZATION		**DESIGN**	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N Two-way
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	7 DAYS

Randomization Scheme*:

Sequence	**Subjects**
AB	**1, 3, 4, 9, 10, 12, 15, 18, 19, 20, 21, 22, 23, 26, 27, 31, 34, 35**
BA	**5, 6, 7, 8, 11, 13, 14, 16, 17, 24, 25, 28, 29, 30, 32, 36, 37, 38**

*** Subjects 2 and 33 dropped out.**

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	38
Route of Administration:	oral	**No. of Subjects Completing:**	36
Dosing Interval:	hr	**No. of Subjects Plasma Analyzed:**	36
Number of Doses:	one	**No. of Dropouts:**	2
Loading Dose:	50 mg	**Sex(es) Included:**	male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	0

Dietary Restrictions:	No grapefruit products, caffeine, or Xanthine-containing food or drink
Activity Restrictions:	Only non-strenuous activity permitted. Subjects were not permitted to lie down or sleep during first 4 hours after dosing.
Drug Restrictions:	No prescription medication within 14 days of dosing

Blood Sampling: 0, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 30.0, 36.0 hours.

Study Results

1) Clinical Adverse Events: Twenty (20) adverse events were reported by nine (9) subjects during two phases. The adverse events ranged from dizziness, headache, hot flushes, nausea, fever, malaise (head cold) and pharyngitis. The events occurred with similar frequency for both treatments. None of the events were serious. They were of mild intensity and were resolved shortly.

Protocol Deviations:
Dropouts: Two subjects dropped out for the following reasons

SUBJECT NO.:	2	33
REASON:	dropped prior to Period II for positive drug screen at check-in	dropped prior to Period II for positive drug screen at check-in
PERIOD:	1	1
REPLACEMENT:	N	N

2) Analytical (Not to be Released Under FOI)

Pre-Study Assay Validation:

Analyte:	O-Desmethyltramadol	Tramadol
Assay method:	———	———
Matrix:	———	———

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of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW for 9/1/00 and 12/4/00 SUBMISSIONS
(page 4)

3) Pharmacokinetics and Statistics: Mean Plasma Concentrations, Pharmacokinetic Parameters, 90% Confidence Intervals and AUCt/AUCi ratios: Tables 1 through 6
Mean Plasma levels: Attachments I (a) and I (b)
Table 1
Mean(SD) Plasma Concentrations (ng/ml) of O-DESMETHYLTRAMADOL
Treatment 1 = Tramadol Hydrochloride, 50 mg tablet, Dose Administered = 50 mg, fasting
Treatment 2 = Ultram^{R}, 50 mg tablet, Dose Administered = 50 mg, fasting

Plasma Concentration (ng/ml) Data File WTM0001.eab

Time(HR)	Test Mean (1)	Test %CV (1)	Ref Mean (2)	Ref %CV (2)	T/R Ratio (1)/(2)
0.0	0.	0.	0.	0.	**
0.25	0.65	267.36	0.57	285.94	1.139
0.50	6.38	117.76	6.9	115.05	0.924
0.75	12.95	81.02	13.76	86.13	0.942
1.0	17.02	65.02	17.43	72.97	0.977
1.5	21.68	52.71	21.21	55.18	1.022
2.0	23.59	45.09	23.49	48.17	1.004
2.5	25.26	40.25	24.7	42.3	1.022
3.0	24.88	39.85	24.61	40.91	1.011
3.5	24.35	41.1	23.2	38.52	1.05
4.0	22.89	40.43	22.55	38.38	1.015
5.0	21.18	43.92	20.92	38.8	1.012
6.0	18.84	45.32	18.84	38.04	1.
8.0	15.21	46.3	14.94	40.68	1.018
12	9.62	52.03	9.88	45.83	0.973
16	6.31	50.12	6.3	46.97	1.001
24	2.64	53.86	2.65	48.38	0.999
30	1.29	58.09	1.26	59.06	1.025
36	0.4	132.44	0.42	108.72	0.945

Table 2

O-DESMETHYLTRAMADOL Pharmacokinetic Parameters
Treatment 1 = TRAMADOL HYDROCHLORIDE, 50 mg tablet (Watson), fasting
Treatment 2 = ULTRAM^{R} 50 mg Tablet, fasting

Mean Plasma PK Parameters

Parameter	Test Mean (1)	Test %CV (1)	Ref Mean (2)	Ref %CV (2)	T/R Ratio (1)/(2)
AUCT	285.542	39.726	284.233	37.094	1.005
AUCI	294.119	38.557	292.931	36.023	1.004
CMAX	27.473	43.507	26.924	43.376	1.02
TMAX	2.486	37.39	2.667	38.557	0.932
KEL	0.115	20.634	0.113	18.196	1.012
THALF	6.289	20.569	6.302	17.847	0.998
Geometric Means:					
AUCT	263.062		262.331		1.003
AUCI	272.645		271.777		1.003
CMAX	24.582		24.065		1.022

Units: AUC: hr*ng/ml, Cmax: ng/ml, Tmax and Thalf: hr

Table 3

Summary Statistics for O-DESMETHYLTRAMADOL
Treatment 1 = TRAMADOL HYDROCHLORIDE, 50 mg tablet (Watson), fasting
Treatment 2 = ULTRAM^{R} 50 mg TABLET, fasting

1 vs 2 Least Squares Means

Parameter	1	2	Ratio	Lower 90% CI	Upper 90% CI
lauci	272.647	271.765	100	97.5	103
lauct	263.065	262.314	100	97.5	103
lcmax	24.582	24.065	102	98.4	106
auci	294.1192	292.9237	100	97.3	103
thalf	6.28794	6.301707	99.8	97	103
tmax	2.486111	2.666667	93.2	84.8	102
auct	285.5485	284.223	100	97.3	104
cmax	27.47278	26.92444	102	97.9	106
kel (lambda)	0.114805	0.113456	101	98	104

Units: AUC: hr*ng/ml, Cmax: ng/ml, Tmax and Thalf: hr

Table 4

Mean(SD) Plasma Concentrations (ng/ml) of TRAMADOL
Treatment 1 = TRAMADOL HYDROCHLORIDE, 50 mg tablet (Watson), fasting
Treatment 2 = ULTRAM^{R} 50 mg TABLET, fasting

Plasma Concentration (ng/ml) Data File WTM0001.eaa

Time(HR)	Test Mean (1)	Test %CV (1)	Ref Mean (2)	Ref %CV (2)	T/R Ratio (1)/(2)
0.0	0.	0.	0.	0.	**
0.25	1.78	246.02	1.33	224.41	1.343
0.50	24.09	120.26	28.33	99.32	0.85
0.75	60.37	72.9	64.94	62.67	0.93
1.0	83.37	50.92	86.79	53.12	0.961
1.5	106.48	34.44	107.22	38.95	0.993
2.0	113.74	26.92	112.54	31.77	1.011
2.5	114.48	22.08	112.71	23.22	1.016
3.0	108.62	21.37	107.35	20.78	1.012
3.5	99.82	23.82	98.48	21.22	1.014
4.0	92.21	25.13	92.43	21.8	0.998
5.0	77.46	27.48	78.42	26.51	0.988
6.0	64.46	29.47	64.42	28.43	1.001
8.0	47.51	33.82	48.47	34.67	0.98
12	26.42	45.27	26.91	46.65	0.982
16	16.27	54.88	16.48	60.92	0.987
24	6.47	76.87	6.56	78.33	0.986
30	3.25	95.44	3.23	109.21	1.009
36	1.64	122.9	1.5	138.4	1.092

Table 5

TRAMADOL Pharmacokinetic Parameters
Treatment 1 = Tramadol Hydrochloride, 50 mg tablet (Watson), fasting
Treatment 2 = Ultram^{R}, 50 mg Tablet, fasting

Mean Plasma PK Parameters

Parameter	Test Mean (1)	Test %CV (1)	Ref Mean (2)	Ref %CV (2)	T/R Ratio (1)/(2)
AUCT	980.972	32.442	987.722	33.935	0.993
AUCI	1001.944	33.384	1009.083	34.824	0.993
CMAX	128.242	21.764	125.742	22.222	1.02
TMAX	2.083	33.082	2.07	34.226	1.006
KEL	0.129	25.677	0.132	20.334	0.977
THALF	5.774	28.625	5.483	21.678	1.053
Geometric Means:					
AUCT	931.88		937.168		0.994
AUCI	949.711		955.648		0.994
CMAX	125.238		122.591		1.022

Units: AUC: hr*ng/ml, Cmax: ng/ml, Tmax and Thalf: hr

Table 6

Summary Statistics for TRAMADOL
Treatment 1 = Tramadol Hydrochloride, 50 mg tablet (Watson), fasting
Treatment 2 = Ultram^{R}, 50 mg Tablet, fasting
Units: AUC: hr*ng/ml, Cmax: ng/ml, Tmax and Thalf: hr
1 vs 2 Least Squares Means

Parameter	1	2	Ratio	Lower 90% CI	Upper 90% CI
lauci	949.791	955.706	99.4	96.7	102
lauct	931.896	937.198	99.4	96.8	102
lcmax	125.238	122.591	102	97.7	107
auci	1002.041	1009.155	99.3	96.3	102
thalf	5.774546	5.483047	105	100	110
tmax	2.083333	2.070278	101	88.3	113
auct	980.965	987.7332	99.3	96.4	102
cmax	128.2417	125.7417	102	97.3	107
kel (lambda)	0.128795	0.131894	97.7	94.7	101

Protocol No.: P99-615, A LIMITED FOOD EFFECTS STUDY OF 50 MG TRAMADOL TABLETS

Study Information

STUDY FACILITY INFORMATION

Clinical Facility: [redacted]
Medical Director: [redacted], M.D.
Scientific Director: [redacted], Pharm.D.
Clinical Study Dates: 12/12/99 to 12/29/99
Analytical Facility [redacted]
Principal Investigator: [redacted], M.S.
Analytical Study Dates: 01/10/00 to 02/01/00

TREATMENT INFORMATION			
Treatment ID:	1	2	3
Test or Reference:	T	T	R
Product Name:	Tramadol-HCl	Tramadol-HCl	Ultram
Manufacturer:	Watson Laboratories	Watson Laboratories	Ortho-McNeil Inc.
Manufacture Date:	9/13/99	9/13/99	N/A
Expiration Date:	N/A	N/A	1/01
ANDA Batch Size:			
Full Batch Size:			
Batch/Lot Number:	R02099	R02099	CAA1982
Potency:			
Content Uniformity:			
Strength:	50 mg	50 mg	50 mg
Dosage Form:	tablet	tablet	TABLET
Dose Administered:	50 mg	50 mg	50 mg
Study Condition:	fasting	fed	fed
Length of Fasting:	14 HOURS	10 HOURS	10 HOURS
Standardized Breakfast:	N	Y	Y
Breakfast Specifics:	N/A	ONE BUTTERED ENGLISH MUFFIN, ONE FRIED EGG, ONE SLICE AMERICAN CHEESE, ONE SLICE CANADIAN BACON, ONE SERVING HASH BROWN POTATOES, SIX FLUID OUNCES OF ORANGE JUICE, EIGHT FLUID OUNCES OF WHOLE MILK	ONE BUTTERED ENGLISH MUFFIN, ONE FRIED EGG, ONE SLICE AMERICAN CHEESE, ONE SLICE CANADIAN BACON, ONE SERVING HASH BROWN POTATOES, SIX FLUID OUNCES OF ORANGE JUICE, EIGHT FLUID OUNCES OF WHOLE MILK

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	6	**Replicated Treatment Design:**	N Three way
No. of Periods:	3	**Balanced:**	Y
No. of Treatments:	3	**Washout Period:**	7 DAYS

Randomization Scheme:

Sequence	Subjects
ABC	9, 13, 17, 20
ACB	3, 5, 22, 23
BAC	12, 15, 19, 24
BCA	2, 11, 16, 18
CAB	4, 6, 10, 21
CBA	1, 7, 8, 14

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	24
Route of Administration:	Oral	**No. of Subjects Completing:**	24
Dosing Interval:	hr	**No. of Subjects Plasma Analyzed:**	24
Number of Doses:	One	**No. of Dropouts:**	0
Loading Dose:	50 mg	**Sex(es) Included:**	male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	0

Dietary Restrictions:	No grapefruit products, caffeine, or xanthine-containing food or drink
Activity Restrictions:	Only non-strenuous activity permitted. Subjects were not allowed to lie down or sleep during the first 4 hours after dosing
Drug Restrictions:	No prescription medication within 14 days of dosing

Blood Sampling: 0, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 30.0, 36.0 hours.

Study Results

1) Clinical Adverse Events:

Seven adverse events were reported by seven of twenty-four subjects. The adverse events were headache, malaise, coughing and pharyngitis. The events occurred with almost similar frequency in the fed and fasted treatments. Out of seven only one was probably related to study

medication. None of the adverse events were considered serious or required terminating any subject from the study participation.

Protocol Deviations:
Dropouts: No Dropouts Reported

2) Analytical (Not to be Released Under FOI): Similar to the previous study

3) Pharmacokinetics and Statistics: Mean Plasma Concentrations and Pharmacokinetic Parameters, ratios of Cmaxt/Cmaxi and AUCt/AUCi: Tables 7 through 12. Mean plasma levels: Attachment II(a) and II (b).

Table 7

Mean(SD) Plasma Concentrations (ng/ml) of O-DESMETHYLTRAMADOL
Treatment 1 = Tramadol Hydrochloride, 50 mg tablet, Dose Administered = 50 mg, fasting
Treatment 2 = Tramadol Hydrochloride, 50 mg tablet, Dose Administered = 50 mg, fed
Treatment 3 = Ultram^{R}, 50 mg Tablet, Dose Administered = 50 mg, fed

Plasma Concentration (ng/ml) Data File WTM0001.ead

Time(HR)	Test Mean (2)	Test %CV (2)	Ref Mean (3)	Ref %CV (3)	T/R Ratio (2)/(3)
0.0	0.	0.	0.	0.	**
0.25	0.21	239.76	0.34	252.88	0.627
0.50	2.35	142.31	3.08	115.07	0.762
0.75	7.39	110.34	7.24	93.94	1.022
1.0	11.58	86.69	12.7	84.89	0.912
1.5	20.14	62.74	18.45	58.1	1.092
2.0	23.87	46.29	21.91	39.77	1.09
2.5	26.25	37.7	25.12	33.88	1.045
3.0	26.91	35.48	26.26	30.97	1.025
3.5	26.54	33.38	25.69	33.57	1.033
4.0	25.17	34.51	25.29	33.06	0.995
5.0	23.69	34.16	23.26	31.98	1.018
6.0	20.45	33.47	20.5	32.54	0.998
8.0	16.33	35.22	15.93	34.01	1.025
12	10.1	34.78	10.07	38.62	1.003
16	6.18	39.06	6.1	36.58	1.013
24	2.45	39.71	2.45	45.1	0.999
30	1.02	51.93	0.96	68.87	1.06
36	0.24	149.25	0.23	147.5	1.032

Table 8

O-DESMETHYLTRAMADOL Pharmacokinetic Parameters
Treatment 1 = Tramadol Hydrochloride, 50 mg tablet, Dose Administered = 50 mg, fasting
Treatment 2 = Tramadol Hydrochloride, 50 mg tablet, Dose Administered = 50 mg, fed
Treatment 3 = Ultram^{R}, 50 mg Tablet, Dose Administered = 50 mg, fed

Mean Plasma PK Parameters: **Units: AUC: hr*ng/ml, Cmax: ng/ml, Tmax and Thalf: hr**

Parameter	Test Mean (2)	Test %CV (2)	Ref Mean (3)	Ref %CV (3)	T/R Ratio (2)/(3)
AUCT	290.075	34.277	285.858	30.924	1.015
AUCI	298.579	33.22	294.767	30.123	1.013
CMAX	28.842	36.38	27.753	34.391	1.039
TMAX	2.708	26.061	2.75	27.339	0.985
KEL	0.123	16.799	0.123	16.583	1.002
THALF	5.767	16.681	5.767	15.541	1.
Geometric Means:					
AUCT	270.552		269.072		1.006
AUCI	280.043		278.684		1.005
CMAX	26.582		25.821		1.029

Table 9

Summary Statistics for O-DESMETHYLTRAMADOL
Treatment 1 = Tramadol Hydrochloride, 50 mg tablet, Dose Administered = 50 mg, fasting
Treatment 2 = Tramadol Hydrochloride, 50 mg tablet, Dose Administered = 50 mg, fed
Treatment 3 = Ultram^{R}, 50 mg Tablet, Dose Administered = 50 mg, fed
Units: AUC: hr*ng/ml, Cmax: ng/ml, Tmax and Thalf: hr
2 vs 3 Least Squares Means

Parameter	2	3	Ratio	Lower 90% CI	Upper 90% CI
lauci	280.048	278.695	100	96.7	104
lauct	270.558	269.075	101	96.8	104
lcmax	26.582	25.821	103	99	107
auci	298.5846	294.7777	101	97.6	105
thalf	5.767342	5.767158	100	95.6	104
tmax	2.708333	2.75	98.5	84.4	113
auct	290.0768	285.8594	101	97.8	105
cmax	28.84208	27.75333	104	99.3	109
kel (lambda)	0.123415	0.123183	100	95.4	105

Table 10

Mean(SD) Plasma Concentrations (ng/ml) of TRAMADOL
Treatment 1 = Tramadol Hydrochloride, 50 mg tablet, Dose Administered = 50 mg, fasting
Treatment 2 = Tramadol Hydrochloride, 50 mg tablet, Dose Administered = 50 mg, fed
Treatment 3 = Ultram^{R}, 50 mg Tablet, Dose Administered = 50 mg, fed

Plasma Concentration (ng/ml) Data File WTM0001.eac

Time(HR)	Test Mean (2)	Test %CV (2)	Ref Mean (3)	Ref %CV (3)	T/R Ratio (2)/(3)
0.0	0.	0.	0.	0.	**
0.25	0.96	141.32	1.08	203.17	0.884
0.50	12.52	115.81	16.36	107.27	0.765
0.75	41.74	91.65	39.96	83.33	1.044
1.0	66.54	68.51	71.28	69.58	0.934
1.5	107.03	45.31	103.14	42.31	1.038
2.0	121.41	30.46	116.65	26.01	1.041
2.5	125.29	19.2	123.43	19.96	1.015
3.0	120.69	17.86	119.05	18.3	1.014
3.5	112.34	21.03	110.2	22.15	1.019
4.0	101.87	18.75	102.11	20.97	0.998
5.0	85.35	23.11	84.97	25.88	1.005
6.0	67.9	23.99	69.25	26.74	0.981
8.0	49.59	27.55	50.1	30.17	0.99
12	26.22	37.29	27.03	41.87	0.97
16	15.47	48.43	15.48	45.21	0.999
24	5.46	72.	5.6	62.73	0.975
30	2.39	106.83	2.47	90.29	0.969
36	0.86	191.44	1.04	127.4	0.829

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ON ORIGINAL

Table 11

TRAMADOL Pharmacokinetic Parameters
Treatment 1 = Tramadol Hydrochloride, 50 mg tablet, Dose Administered = 50 mg, fasting
Treatment 2 = Tramadol Hydrochloride, 50 mg tablet, Dose Administered = 50 mg, fed
Treatment 3 = Ultram^{R}, 50 mg Tablet, Dose Administered = 50 mg, fed

Mean Plasma PK Parameters **Units: AUC: hr*ng/ml, Cmax: ng/ml, Tmax and Thalf: hr**

Parameter	Test Mean (2)	Test %CV (2)	Ref Mean (3)	Ref %CV (3)	T/R Ratio (2)/(3)
AUCT	994.2	25.782	1002.608	26.767	0.992
AUCI	1009.813	26.539	1016.779	27.062	0.993
CMAX	141.946	19.213	137.442	16.994	1.033
TMAX	2.198	32.342	2.147	35.971	1.024
KEL	0.138	14.219	0.14	14.208	0.986
THALF	5.149	15.928	5.078	16.794	1.014
Geometric Means:					
AUCT	967.344		968.132		0.999
AUCI	981.642		981.673		1.
CMAX	139.489		135.393		1.03

Table 12

Summary Statistics for TRAMADOL
Treatment 1 = Tramadol Hydrochloride, 50 mg tablet, Dose Administered = 50 mg, fasting
Treatment 2 = Tramadol Hydrochloride, 50 mg tablet, Dose Administered = 50 mg, fed
Treatment 3 = Ultram^{R}, 50 mg Tablet, Dose Administered = 50 mg, fed
Units: AUC: hr*ng/ml, Cmax: ng/ml, Tmax and Thalf: hr

2 vs 3 Least Squares Means

Parameter	2	3	Ratio	Lower 90% CI	Upper 90% CI
lauci	981.649	981.668	100	95.7	104
lauct	967.347	968.137	99.9	95.6	104
lcmax	139.489	135.393	103	97.4	109
auci	1009.82	1016.77	99.3	94.8	104
thalf	5.148629	5.079763	101	97.1	106
tmax	2.197917	2.146667	102	86.5	118
auct	994.2039	1002.61	99.2	94.6	104
cmax	141.9458	137.4417	103	97.6	109
kel (lambda)	0.137527	0.139523	98.6	94.9	102

Waiver Request: No bio-study waivers are requested.

Formulation (Not to be released under FOI)

Ingredient	**Strength 50 mg**
Tramadol Hydrochloride	***50.0***
Croscarmellose Sodium NF	
Lactose Monohydrate ——— (NF)	
Magnesium Stearate NF	
Microcrystalline Cellulose NF ———	
——— White ———	
Pregelatinized Starch NF ———	
TOTAL WEIGHT (including film coat)	**257.5 mg**

Formulation Comments: Please refer to 'Deficiencies'.

Dissolution (Not to be released under FOI)

In the original EVA file WTM 0001.daa, dated 09/01/00, the firm did not provide the Dissolution Method information. In a telephone call on December 4, 2000, the project manager requested the firm to provide the information. In a fax amendment dated 12/4/2000, the firm provided the necessary information.

The firm has used the following dissolution method for the comparative dissolution.

Apparatus: USP apparatus I (basket)
RPM: 100
Medium: 0.1N HCL, 900ml
Proposed 'Q': Not less than — % in 45 minutes.

Though the firm's proposed dissolution method is similar to the agency recommended method for this product, the proposed dissolution specifications are different. In the electronic submission, the firm did not provide the dissolution method information or the table including mean, range and %CV. The following table has been generated by the reviewer based on the individual tablet dissolution data submitted in WTM 0001.daa file.

Watson Labs. ANDA 75-962
Tramadol Hydrochloride Dissolution

	Watson		10min	20min	30min	45min	60min
A	R02099	1					
A	R02099	2					
A	R02099	3					
A	R02099	4					
A	R02099	5					
A	R02099	6					
A	R02099	7					
A	R02099	8					
A	R02099	9					
A	R02099	10					
A	R02099	11					
A	R02099	12					
Mean			78.2	101.4	103.1	102.4	102.7
min							
max							
%cv			6.95	2.83	1.96	2.96	2.13
	Ortho						
B	CAA1982	1					
B	CAA1982	2					
B	CAA1982	3					
B	CAA1982	4					
B	CAA1982	5					
B	CAA1982	6					
B	CAA1982	7					
B	CAA1982	8					
B	CAA1982	9					
B	CAA1982	10					
B	CAA1982	11					
B	CAA1982	12					
Mean			62.1	96.9	100.8	100.7	100.9
min							
max							
%cv			9.40	2.61	2.32	2.68	2.39

COMMENTS:

a] Fasting Study:

1. The test and reference mean profiles are similar. The percent CV's are comparable.

2. The mean test and reference parameters are comparable. The 90% confidence intervals for the parameters are within 80-125%. The 50mg products are bioequivalent.

b] 'Food Challenge' Study:

1. The geometric LS mean ratio (T/R) for the pharmacokinetic parameters are within the limits 80-125%. The food challenge study is acceptable.

c] Dissolution:

1. Currently, there is no USP monograph for Tramadol tablet. The firm had originally (submission date: 09/01/00) submitted dissolution testing data in the EVA file WTM 0001.daa, which did not have dissolution information. On 12/04/00, the firm was requested to provide dissolution testing information. The firm faxed the information on the same day in the evening.

2. The comparative dissolution testing results are acceptable. However, based on the dissolution data, the firm is requested to conduct dissolution testing using the following specification: Not less than — % of the labeled amount dissolved in 30 minutes.

d) Formulation Characteristic: The labeling of the innovator and Watson's test product differes with respect to the following formulation characteristics:

How Supplied:

Ultram[R] 50mg tablet: White, <u>scored</u>, film coated, capsule shaped tablet, debossed "Ultram" on one side and "06 59" on the other side.
Watson's 50mg tablet: White, round, film coated tablet, debossed with ' —' on one side and "WATSON" on the other side.

DEFICIENCIES:

1. The reference formulation Ultram[R] 50mg tablet is a white, **<u>scored</u>**, film coated, capsule shaped tablet, debossed "Ultram" on one side and "06 59" on the other side. Watson's 50mg tablet is white, round, **<u>unscored</u>**, film coated tablet, debossed with "—" on one side and "WATSON" on the other side. The generic product is therefore not identical to the innovator product. After a discussion within the Division and with the Division of Labeling and Program support, it was determined that Watson Labs will have to score it's product to make it similar to the innovator product with respect to its release characteristics. The firm is therefore requested to score the 50mg tramadol tablet similar to the innovator Ultram[R] 50mg tablet.

2. Subsequent to scoring, the firm is requested to provide comparative dissolution on the 12 whole units of the new scored tablets versus 12 units of the Ultram[R] 50mg tablet using the following method and specification:

Method: USP 24 apparatus I (basket)
RPM: 100 rpm
Medium: 900 ml of 0.1N HCl at 37^{0}C using.
'Q': Not less than — % of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

RECOMMENDATIONS:

1. Firm's Dissolution and Bioequivalence testing results using the un-scored product appear to be adequate. The test product however is **not** scored like the reference product. Until the firm manufactures an acceptable scored formulation and conducts a comparative dissolution using it, from the bioequivalence perspective the application will be deemed as incomplete.

2. Deficiencies 1 and 2 should be forwarded to the firm.

12/11/00

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence
Review Branch II

12/14/2000

RD INITIALED BY SNERURKAR
FT INITIALED BY SNERURKAR

Concur:

Date: 12/22/00

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA 75-962 (original, duplicate), HFD-650 (Director), HFD-655 (Nerurkar, Sathe), Division File, Drug File.

2.1
NDA 75-962

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-962 APPLICANT: Watson Labs.

DRUG PRODUCT: Tramadol Hydrochloride 50mg tablet

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The reference formulation Ultram^{R} 50mg tablet is a white, **scored**, film coated, capsule shaped tablet, debossed "Ultram" on one side and "06 59" on the other side. Watson's 50mg tablet is white, round, **unscored**, film coated tablet, debossed with "——" on one side and "WATSON" on the other side. The generic product is therefore not identical to the innovator product. It is necessary to score your product to be similar to the innovator product with respect to release characteristics. You are requested to score your 50mg tramadol tablet similar to the innovator Ultram^{R} 50mg tablet.

2. Subsequent to scoring, you are requested to provide comparative dissolution on 12 whole units of the newly scored tablets versus 12 units of the Ultram^{R} 50mg tablet using the following method and specification:

Method: USP 24 apparatus I (basket)
RPM: 100 rpm
Medium: 900 ml of 0.1N HCl at 37^{0}C using.
'Q': Not less than —% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Sincerely yours,

Barbara Myers Davit
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-962
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

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Printed in final on 12/05/00

Endorsements: (Final with Dates)
HFD-655/ Reviewer (P.Sathe) 12/13/00
HFD-655/ Bio team Leader (SG Nerurkar) 12/14/00
for HFD-650/ D. Conner 12/22/00

BIOEQUIVALENCE - DEFICIENCIES submission dates: 09/01/00

1. **FASTING STUDY** (STF) Strength: 50mg
Clinical: [ ] ✓ **Outcome: AC**
Analytical: [

2. **FOOD STUDY** (STP) Strength: 50mg
Clinical: [ ] ✓ **Outcome: AC**
Analytical [

Outcome Decisions: **IC - Incomplete**

WinBio Comments: **Eva submission**

TRAMADOL HYDROCHLORIDE
50 mg TABLET
ANDA 75-962
Reviewer: Pradeep M. Sathe
file name:C/wpfiles/75962A.101

WATSON LABORATORIES, INC.
Miami, FL
Submission Dates:
09/01/00
12/04/00

Amendment to the Earlier Review Dated 12/22/2000

In the above electronic submission, the firm had submitted two bio-studies and comparative dissolution information. DBE completed the review of the application on 12/22/00 and the following deficiencies were cited:

DEFICIENCIES:

1. "The reference formulation Ultram^R 50mg tablet is a white, **scored**, film coated, capsule shaped tablet, debossed "Ultram" on one side and "06 59" on the other side. Watson's 50mg tablet is white, round, **unscored**, film coated tablet, debossed with " — " on one side and "WATSON" on the other side. The generic product is therefore not identical to the innovator product. After a discussion within the Division and with the Division of Labeling and Program support, it was determined that Watson Labs will have to score it's product to make it similar to the innovator product with respect to its release characteristics. The firm is therefore requested to score the 50mg tramadol tablet similar to the innovator Ultram^R 50mg tablet.

2. Subsequent to scoring, the firm is requested to provide comparative dissolution on the 12 whole units of the new scored tablets versus 12 units of the Ultram^R 50mg tablet using the following method and specification:

> Method: USP 24 apparatus I (basket)
> RPM: 100 rpm
> Medium: 900 ml of 0.1N HCl at 37^{0}C using.
> 'Q': Not less than —% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes".

Note:

As per the MAPP 5723.2 and an Email message (Attached), the firm does not have to submit dissolution testing on scored tablet for the approval of the ANDA. The OGD will request the firm for a post-approval commitment that it will submit dissolution testing data on its scored tablet.

Comment:

Based on the above policy, the DBE review of this application is being amended to delete the deficiencies and recommendation cited in the 12/22/00 review for manufacturing and testing of a new lot of the test product.

Recommendation:

Based on the bioequivalence studies and dissolution data presented in the Division of Bioequivalence review dated 22 December 2000, the firm has met requirements of in vivo bioequivalence and in vitro dissolution testing requirements on its tramadol HCl 50 mg tablet. However, due to different scoring configurations of the test and reference products evaluated in these studies, the Office of Generic Drugs should request a post-approval commitment from the sponsor to manufacture the test product with same scoring configuration as that of the reference products and meet the following Agency dissolution specifications:

> The dissolution testing should be conducted in 900 mL of 0.1N HCl using USP XXIV apparatus I (basket) at 100 rpm. The dissolution testing should meet the following specifications.
>
> > Not less than – % of the labeled amount of tramadol is dissolved from the dosage form in 30 minutes.

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch II.

RD INITIALED BY SNERURKAR
FT INITIALED BY SNERURKAR

Concur:

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Date: 4/24/2001

cc: ANDA 75-962 (original, duplicate), HFD-650 (Director), HFD-655 (Nerurkar, Sathe), Division File, Drug File.

Printed by Pat Beers-Block

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 04-Jan-2001 08:44am
From: Pat Beers-Block
BEERSBLOCKP
Dept: HFD-640 MPN2 E260
Tel No: 301-827-5849 FAX 301-443-3839

Subject: Tramadol ANDAs

Dale and Barbara,

I've been collecting the Tramadol ANDAs (with bio def); none have been transmitted to the applicants so far. I understand Vilayat spoke with you yesterday re: permitting the applicant to submit scoring information post approval.

I'll return the 3 reviews I have (ANDA 75-960, ANDA 75-982, and ANDA 75-962) to the PMs for appropriate changes. thanks, patbb

GJP ZAK PRADEEP

Tramadol ANDAs

Returning for changes

thanks

Steve

CC: ANDA 75-962
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

V:\firmsnz\watson\ltrs&rev\75962A.101
Printed in final on 1/12/01

Endorsements: (Final with Dates)
HFD-655/ Reviewer (P.Sathe) 1/12/01
HFD-655/ Bio team Leader (SG Nerurkar) 3/21/01
HFD-650/ D. Conner for Dwp 4/24/2001

BIOEQUIVALENCE - Acceptable submission dates: 09/01/00

1. **OTHER** (OTH) Strength: 50mg
Clinical:
Analytical: [ ] **Outcome: AC**
ENTER AS U.S. document

Outcome Decisions: **AC - Acceptable with post-approval commitment for scoring**

WinBio Comments: **Eva submission**

APPEARS THIS WAY
ON ORIGINAL

J. Min

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-962 APPLICANT: Watson Labs.

DRUG PRODUCT: Tramadol Hydrochloride 50mg tablet

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.1N HCl, at 37°C using USP Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

Not less than — %(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-962 SPONSOR: Watson Labs

DRUG AND DOSAGE FORM: **Tramadol Hydrochloride Tablet**

STRENGTH(S): **50 mg**

TYPES OF STUDIES: Fasting and Food challenge on the 50mg

CLINICAL STUDY SITE(S):

ANALYTICAL SITE(S):

SUMMARY: Studies acceptable. Conditional product-approval due to tablet-scoring issue.

DISSOLUTION: Acceptable

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic No New facility ____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: Pradeep M. Sathe, Ph.D. BRANCH: II

INITIAL: _____ DATE: 1/12/01

TEAM LEADER: Shrinivas G. Nerurkar, Ph.D. BRANCH: II

INITIAL: _____ DATE: 01/12/2001 04/04/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.

INITIAL: _____ DATE: 4/24/2001

TRAMADOL HYDROCHLORIDE
50 mg TABLET
ANDA 75-962
Reviewer: Pradeep M. Sathe
file name:C/wpfiles/75962A-401

WATSON LABORATORIES, INC.
Miami, FL
Submission Date:
April 23, 2001

Review of an Amendment

In the electronic submission dated **09/01/00 and 12/04/00**, the firm had submitted two bio-studies and comparative dissolution information. DBE completed the review of the application on 12/22/00 and the following deficiencies were cited. (The deficiencies were not sent to the firm by the Division, but were communicated to them by the Labeling Division):

DEFICIENCIES:

1. "The reference formulation Ultram^{R} 50mg tablet is a white, **scored**, film coated, capsule shaped tablet, de-bossed "Ultram" on one side and "06 59" on the other side. Watson's 50mg tablet is white, round, **unscored**, film coated tablet, de-bossed with — on one side and "WATSON" on the other side. The generic product is therefore not identical to the innovator product. After a discussion within the Division and with the Division of Labeling and Program support, it was determined that Watson Labs will have to score it's product to make it similar to the innovator product with respect to its release characteristics. The firm is therefore requested to score the 50mg tramadol tablet similar to the innovator Ultram^{R} 50mg tablet.

2. Subsequent to scoring, the firm is requested to provide comparative dissolution on the 12 whole units of the new scored tablets versus 12 units of the Ultram^{R} 50mg tablet using the following method and specification:

> Apparatus: USP 24 apparatus I (basket)
> RPM: 100 rpm
> Medium: 900 ml of 0.1N HCl at 37^{0}C using.
> 'Q': Not less than —% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes".

Current Amendment:

The amendment consists of firm's responses to the above deficiencies. The firm has provided comparative dissolution data using the 1) newly scored formulation lot, 2) previously un-scored bio-study lot and a new innovator product (scored) lot. The dissolution has been generated as per the above agency recommended method. The following Table lists the dissolution data.

Table. *In-Vitro* Dissolution Testing

Drug (Generic Name): Tramadol Hydrochloride
Dose Strength: 50mg Tablet
ANDA No.: 75-962
Firm: Watson Laboratories
Submission Date: April 23, 2001

I. Conditions for Dissolution Testing: Agency recommended method

USP XXIII, apparatus I (basket) RPM: 100
No. Units Tested: 12
Medium: 0.1N HCl, Volume: 900 mL
Specifications: NLT —% of the labeled amount is dissolved in 30 minutes.
Reference Drug: Ultram[R] by Ortho-McNeil

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product: Tramadol HCl 50mg Tablet (Watson, Unscored), Lot # R02099			Reference Product: Tramadol HCl, 50mg Tablet (Watson, Scored), Lot # R05201		
	Mean %	Range	%CV	Mean %	Range	%CV
10	86.1		3.5	79.8		8.7
20	100.5		3.0	102.9		1.0
30	101.2		3.3	103.0		1.0
45	101.1		2.8	103.1		0.9

III. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product: Tramadol HCl 50mg Tablet (Watson, Scored), Lot # R05201			Reference Product: Tramadol HCl, 50mg Tablet (Ultram[R], Scored), Lot # 90PO824E		
	Mean %	Range	%CV	Mean %	Range	%CV
10	79.8		8.7	72.4		8.8
20	102.9		1.0	101.4		2.8
30	103.0		1.0	101.6		2.8
45	103.1		0.9	102.3		2.2

Comment:

Dissolution on the 50mg scored test product is comparable to the innovator product Ortho McNeil's Ultram[R] 50mg tablet. The test and reference formulations met the dissolution specifications easily. The dissolution information is acceptable.

Recommendations:

1. The firm has previously conducted acceptable in-vivo bioequivalence studies (fasting and fed) comparing its 50 mg Tramadol HCl tablets with 50 mg tablets of the reference product, Ultram^{R} manufactured by Ortho-McNeil.

2. The dissolution testing conducted by Watson labs. on Tramadol HCl 50 mg tablet, lots # R02099 (unscored, bio-lot), R05201 (new, scored) and 90P0824E (Ultram^{R} manufactured by Ortho McNeil) is as per the Agency recommended method and is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing, controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1 N HCl at 37^{0}C using USP 24 apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than — % of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

4. The firm has met the bio-equivalence requirements for its test product.

01/08/02
Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch II.

RD/FT INITIALED BY SNERURKAR

Concur: 1/28/02 Date: 1/10/2002
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA 75-962 (original, duplicate), HFD-650 (Director), HFD-655 (Nerurkar, Sathe), Division File, Drug File.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-962 APPLICANT: Watson Labs.

DRUG PRODUCT: Tramadol Hydrochloride 50mg tablet

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs.

The dissolution testing is conducted in 900 mL of 0.1N HCl, at 37°C using USP Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

Not less than — %(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M. Davit

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-962
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

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Printed in final on 12/31/01

01/08/2002

Endorsements: (Final with Dates)
HFD-655/ Reviewer (P.Sathe) 12/31/01
HFD-655/ Bio team Leader (SG Nerurkar)
for HFD-650/ D. Conner 1/28/02

BIOEQUIVALENCE - Acceptable submission dates: 04/23/01

1. **OTHER** (OTH) Strength: 50mg

Outcome Decisions: **AC - Acceptable**

WinBio Comments:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-962 SPONSOR: Watson Laboratories Inc.

DRUG AND DOSAGE FORM: **Tramadol Hydrochloride Tablet**

STRENGTH(S): **50mg**

TYPES OF APPLICATION: Amendment for dissolution testing on scored tablet

CLINICAL STUDY SITE(S): N/A

ANALYTICAL SITE(S): N/A

SUMMARY: Dissolution testing acceptable

DISSOLUTION: Acceptable

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic No New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: Pradeep M. Sathe, Ph.D. BRANCH: II

INITIAL: _____ DATE: 01/08/02

TEAM LEADER: Shrinivas G. Nerurkar, Ph.D. BRANCH: II

INITIAL: _____ DATE: 1/10/2002

for DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.

INITIAL: Barbara M Davit DATE: 1/28/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

ADMINISTRATIVE DOCUMENTS

75962

Subject: Tramadol Dosage Titration

The meeting was called to assess the impact of the two exclusivities granted to Ultram on the approval of generic equivalents.

Date: February 1, 2001 Time: 2:30PM

Attendees: Bob West, Jeen Min, Chan Park, Charles Hoppes, Cecelia Paris, Glen Smith, Don Hare, Larry Goldkind, Christina Fang, Dennis Bashaw, and Yoon Kong

- ORM representatives questioned whether a generic drug can have a different dosage titration in its labeling then the one currently approved for Ultram?
  - No. An ANDA can't contain clinical trails which would be needed for support an alternative titration. If a generic firm wanted a dosage titration prior to the expiration of Ultram's exclusivity, they would have to submit a supplement under 505(b)(2).
- The following are some examples where FDA approved a generic drug when the reference listed drug (RLD) was protected by exclusivity.
  - BMS had exclusivity on one of their indications for their captopril tablets. OGD carved out the protected indication from the generic labeling and approved the ANDA(s) with different labeling from the RLD. The FDA was sued by BMS and FDA prevailed.
  - A generic propofol injection was approved with a different inactive ingredient from the RLD, i.e. sodium metabisulfite in lieu of EDTA. The innovator had marketing exclusivity on the EDTA formulation. The innovator claimed that the generic formulation was not as safe as their EDTA formulation. FDA was sued and FDA prevailed.
  - An innovator received marketing exclusivity for showing that the IV route in addition to the IM route could used by the parenteral drug product. OGD approved a generic with only the IM route of administration. The innovator claimed that the generic drug product was unsafe because it did not have the IV route of administration in its labeling.
- With regard to Ultram: The innovator (RW Johnson) has exclusivity for the first dosage titration until August 21, 2001. With pediatric exclusivity, this initial exclusivity is extended until February 21, 2002. The second dosage titration's exclusivity expires December 23, 2002.

- Discussion:
  - Could generic versions of Ultram be marketed safely if they did not contain one or both of the dosage titrations in their labeling? Carving out one or both titrations would permit the generic to be marketed prior to the expiration of the respective exclusivity.
  - It was agreed that the ORM review division would evaluate whether or not the labeling for generic tramadols could exclude one or both of the labeling revisions providing for the dosage titrations.
  - OGD recommended that the first titration be included in the labeling of forthcoming generic tramadol applications to provide a greater assurance that the intended population would use the drug in a safe manner. OGD suggested that the second titration be "carved-out" of the labeling of the generics as it could be regarded as a further refinement/clarification of the first titration, and by itself, did not contribute significantly to the safe use of the product. Thus, OGD suggested a compromise to include the initial titration in the labeling of all generic versions of Ultram, but delete the labeling changes provided for by the second titration. If the review division were to agree, generic tramadol could be introduced into the marketplace upon the expiration of the initial exclusivity (2/21/02) rather than upon the expiration of the second exclusivity (12/23/02).
  - Issues such as the economics of having a generic tramadol in the marketplace, as well as the possibility that Ultram may be granted additional periods of exclusivity based upon additional labeling changes were also discussed.
  - The review division agreed to respond formally to OGD's consult request ASAP, in approximately 1 month.

CC:

ANDA 75-980
ANDA ~~75-974~~
ANDA 75-964
ANDA 76-003
ANDA 75-968
ANDA ———
ANDA 75-983
ANDA 75-986
ANDA 75-982
ANDA 75-977
ANDA 75-981
ANDA 75-962 ✓
Division File
Field Copy

Endorsements:

HFD-610/Bob West Robert 2/13/01

HFD-617/Jeen Min Jeen Min 2/13/01

V:\DIVISION\CHEM2\Tramadol Dosage Titration Meeting.doc

Medical Officer's Consult: From Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

To Office of Generic Drug Products: HFD 615
Attention: Harvey Greenberg

This consult is in response to a request dated November 20, 2000. In that consult the Office of Generic Drugs (OGD) requested clinical guidance as to whether generic tramadol products could be marketed without currently patented information related to titration of dose without rendering the product less safe or effective. There is draft guidance to industry entitled " Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications" dated October 2000. This guidance informs the current consult. The draft guidance states that:

> **III. PROPOSED APPROACH**
>
> The Agency has determined that in certain circumstances an ANDA should be permitted to reference discontinued labeling for a listed drug. This generally should occur when:
>
> 1. The holder of the NDA for the innovator drug has obtained approval for a change in the drug labeling.
>
> 2. That change has received either a patent listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*) or market exclusivity under the Act.
>
> 3. The NDA sponsor has removed or revised the labeling describing the corresponding unprotected aspects of the drug.
>
> 4. The change to the drug product is not one for which a suitability petition may be filed (21 CFR 314.93).
>
> 5. The sponsor wishing to reference the discontinued labeling has submitted a petition requesting that the Agency determine whether the previous labeling was withdrawn for reasons of safety or effectiveness, or the Agency has undertaken its own inquiry regarding the withdrawal of the previous labeling.
>
> 6. The Agency has determined that the previous innovator labeling was not withdrawn for reasons of safety or effectiveness.
>
> 7. The Agency has determined that omission of the protected information will not render the drug product less safe or effective than the currently marketed innovator product.

Points number 6 and 7 are relevant to the current consult and will be addressed specifically in this consult.

Regulatory background

Ultram™ (tramadol) was originally approved 3/3/95 based on data submitted in NDA 20,281. The approved label recommended dosing of 50 to 100 mg every 4 to 6 hours not to exceed 400 mg/day. The reader is referred to the adverse event table that appears in the current label (Table #2). In this table the substantial adverse event profile is outlined with dizziness, vertigo, nausea, vomiting, constipation, headache or somnolence occurring in up to 25% of patients exposed chronically to the drug at therapeutic doses.
This adverse event profile limits the value of the product. The sponsor submitted an NDA supplement (SLR-014) on 8/21/97 in an attempt to improve the tolerability of the drug in patients not requiring ***acute*** analgesia. SLR-014 included the results of a study showing that the adverse event profile could be improved if patients were started at 50 mg/day and titrated up by 50mg/day every three days until an ***effective dose*** was achieved. The percent of subjects in that study that withdrew due to adverse events was 31% in those starting therapy at the minimally therapeutic labeled dose of 50 mg four times a day (200mg/day), 24% in the group starting at 50mg/ day and titrating up to 200 mg/day over 4 days and 15% in those starting at 50mg/day and increasing by 50 mg/day every 3 days. As dizziness and vertigo and nausea specifically are the most common adverse events reported with Ultram, these adverse events were most prominently decreased in the slow titration group compared to the other two groups. These findings formed the basis for approval of a labeling change that added the following paragraph to the DOSAGE AND ADMINISTRATION section of the label:

"In a clinical trial, fewer discontinuations due to adverse events, especially dizziness and vertigo, were observed when titrating the dose in increments of 50mg/day every three days until an effective dose (not exceeding 400mg/day) was achieved."

Implicit in a slow titration starting at an ineffective dose is that effective therapy for pain will not occur until therapeutic doses have been reached. For acute pain requiring only a single dose, this is not an issue. For acute pain that lasts beyond a single 4-6 hour dosing interval and for chronic pain; relief cannot be anticipated until day 10 when the daily dose of 200mg/day is achieved. This is a significant clinical drawback to the titration option. Nonetheless, the supplement was approved. The new label informed prescribers of the therapeutic dose ***and*** the possibility of decreasing the withdrawal rate due to adverse events ***if*** a slow titration was clinically appropriate.

The sponsor submitted another supplement SE2- 16 on 2/23/99 containing an additional trial that studied an even slower titration schedule beginning with 25 mg/day. The reader is referred to the medical officer's review dated 7/1/99 for details of the study. In that study, an open label run-in period of 14 days was employed that exposed all subjects to Ultram 50 mg on day one (a sub-therapeutic level). The dose was titrated to 50-mg qid by day four and continued for an additional 10 days. Out of 932 subjects in the open label cohort 212 (23%) discontinued due to adverse events. 167/212 of those subjects that did not tolerate Ultram in the original open label titration program continued in a randomized trial that studied the withdrawal rates due to adverse events in this ***enriched population of tramadol intolerant subjects*** when a different set of titration protocols was employed.

This study found that the group that started at 25 mg/day and increased to 200 mg/day over 16 days experienced fewer withdrawals due to adverse events than the group that started at 50 mg/day and increased to 200 mg/day over 10 days (34% versus 54%). The results of this study suggest that:

> ***In patients who cannot tolerate tramadol, even following slow titration of dose over 4 days to achieve therapeutic dosing; an even slower titration over 16 days to get to the approved lowest therapeutic dose for more than single dose usage may result in better toleration as defined by withdrawal due to adverse events.***

The analgesic efficacy during these various titration schedules cannot be well assessed due to the trial design. It can be assumed that patients naïve to tramadol may well not experience analgesia until they reach a dose of 50mg qid. This conclusion is based on a review of the results in the original NDA. This review revealed that ***none*** of the pivotal studies studied doses below 50 mg based on the earlier dose ranging studies. Only 1out of 8 single dose studies of acute pain showed efficacy for the 50-mg dose. The three-month chronic pain study in the original NDA only employed the 50-mg qid dose.

Thus, the sponsor's request to add the 16-day titration schedule ***prioritizes*** establishing tolerance in already documented intolerant patients over efficacy for the product. The division approved this label change at the request of the sponsor. However, it is not obvious that this represents a safety advantage for the population of subjects that have not received tramadol previously. One may argue that for tramadol naïve subjects who do not tolerate tramadol at 50 mg qid from the outset or following a 10-day titration schedule; an alternative analgesic is indicated rather than exposing these subjects to further exposure to tramadol that requires sub-therapeutic doses for 16 days and still results in a 34% withdrawal rate due to adverse events.

The medical reviewer for supplement 16, Dr. Averbuch stated on page 34 of his review that:

> "The 10-day titration schedule is not recommended anymore under the proposed DOSAGE AND ADMINISTRATION section and therefore, there is no apparent reason to provide details of this regimen under the CLINICAL STUDIES section. Moreover, adding this not-recommended information may create a significant confusion among readers."

The "not recommended" information is based on the sponsor's request for labeling changes rather than a judgement by the division that the drug is less safe *overall* without the 16-day titration schedule. It was the sponsor's judgement that information indicating that reintroduction of the drug to intolerant patients is an alternative option to discontinuing tramadol and changing to a different therapy; and that an initial extremely slow titration may have overall value.

It should be noted that while reference is made frequently in the supplement 16 and in the review to nausea and vomiting, it is the overall withdrawal rate that is most relevant. This reviewer has therefore addressed the overall withdrawal rate as the parameter by which to consider the safety issue presented in this consult.

Conclusions:

1. Deletion of the labeling approved with supplement 14 will not diminish the efficacy of tramadol as an analgesic. The information regarding the potential benefit of dose titration for some patients ***(who do not require effective analgesia for up to 10 days)*** may be valuable. It allows the prescribing physician to weigh the risks and benefits of slow titration versus immediate analgesia. Removal may therefore render the drug less safe for some patients.

2. Deletion of the labeling approved with supplement 16 will not diminish the efficacy of tramadol as an analgesic. It may in fact enhance the efficacy by shortening the time to pain relief.

3. Deletion of labeling approved with supplement 016 cannot be assumed to diminish the safety of this drug for tramadol naïve patients. The study results supporting this labeling supplement only pertain to subjects with proven intolerance to the drug. The study submitted in supplement 016 did not test tht hypothesis that a 16 day titration schedule will result is better tolerance than a 10 day titration schedule in tramadol naïve patients. Those subjects, who do not tolerate the drug and discontinue it will likely be switched to another analgesic. This may spare a significant percentage of patients adverse events related to reintroduction of a slower titration schedule (34% in the clinical study). No conclusions regarding the safety of other analgesics can be made.

Recommendations for regulatory action:

1. The approved labeling change in SLR-014 should be required in all tramadol labels
2. The approved labeling change in SLR-016 can be deleted without a decrease in safety or efficacy of the drug.

Lawrence Goldkind MD 3/4/01
Lawrence Goldkind M.D.
Medical Team Leader: Anti-inflammatory team

Record of Telephone Conversation

APPEARS THIS WAY
ON ORIGINAL

FDA requested the firm (Watson) to do the following:

1. Please provide accelerated stability data for the scored tablets.

2. Please revise the [redacted] specifications to [redacted].

3. Please provide a missing page between pp 240 and 241 from your last amendment.

Date:
May 16, 2001

ANDA Number:
75-962

Product Name:
Tramadol HCl
Tablets

Firm Name:
Watson

Firm Representative:
Ernest Lengle

Phone Number:
909-270-1400 X4334

FDA Representative:
Jeen Min
Edwin Ramos

Signatures:

Jeen Min 5/23/01

CC: ANDA 75-962

V:\FIRMSNZ\WATSON\TELECONS\75962.TC.doc

Record of Telephone Conversations
For Tramadol

Due to Tramadol's exclusivity protection the following information has been communicated to all Tramadol Hydrochloride Tablet, 50 mg applicants:

1) We recommend that firms do not manufacture any validation batches, scored or unscored tabs, until the exclusivity issues have been resolved. There is uncertainty over the proper scoring configuration.

2) The Office of Generic Drugs is awaiting final clearance of the "Discontinued Labeling Guidance", but currently is uncertain of the timeline for publication.

3) We will be issuing **Approvable** Letters, not to be confused with Approval Letters. Approvable Letters only indicate that the chemistry, bioequivalency, and cGMP sections of the applications have been found acceptable at this time. Labeling remains unresolved. When you receive the Approvable Letter, please do not send in any more labeling. OGD will communicate its recommendations on the appropriate labeling and scoring once it has been determined.

Date:
January 9, 2002

ANDA Number:
75-960 Purepac
75-962 Watson
75-963 Able
75-964 Caraco

75-968 Eon
75-974 Asta
75-977 Teva
75-980 Alphapharm
75-981 Torpharm
75-982 Sidmak
75-983 Mallinckordt
75-986 Mylan
76-003 Corepharma
76-100 Mutual

FDA Representative:
Jeen Min

Signatures:
Jeen Min 1/9/02

V:\FIRMSNZ\PUREPAC\MEMOS\75960ExcMemo.doc

Patent and Exclusivity Search Results from query on 020281 002.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
~~020281 002~~	~~PED~~	~~FEB 21,2002~~	
020281 002	PED	JUN 23,2003	
020281 002	D-63	DEC 23,2002	
020281 002	D-44	AUG 21,2001	
	PED	FEB 21,2002	

To allow a titration dosing regimen using a 25 mg dose.

... titrating dose in increments of 50mg/day every 3 days until an effective dose (not exceeding 400mg/day) was reached.

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

Through consultation with the ORH review division, the D-44 exclusivity should be retained in the generic labeling due to safety reasons.

The division did not agree that the D-63 titration needs to be included in the generic labeling. Plan is to "carve it out" once the "Discontinued Labeling Guidance" issues in final. The deletion of the D-63 titration from the generic labeling would not render the generics "less safe" than Ultram tablets.

tablets should be unscored!

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-962 Applicant Watson

g Tramadol Hydrochloride Tablets Strength 50 mg

...PROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☑

REVIEWER:	DRAFT RECEIPT	FINAL ACTION
1. Project Manager Jeen Min Review Support Branch 9	Date 12/14/01 Initials JM	Date Initials

Application Summary:

Original Rec'd date 9/1/00
Date Acceptable for Filing 9/5/00 J
Patent Certification (type) II
Date Patent/Exclus.expires 2/21/01 & 6/23/03
Citizens Petition/Legal Case Yes ☑ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☑
(If YES, check PETS)
Pediatric Exclusivity Tracking System (PETS)
Date checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 11/8/00
Date of Office Bio Review 4/24/01
Date of Labeling Approv. Sum
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☑ No ☐
30 Day Clock Start End
Commitment Rcd. from Firm Yes ☐ No ☐

Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def./N/A Minor issued ☐ Date
Comments:

2. Div. Dir./Deputy Dir. Chemistry Div. I or II Comments:	Date 12/21/01 Initials	Date 12/26/01 Initials ome satisfactory.
3. Frank Holcombe Assoc. Dir. For Chemistry Comments: (First generic drug review) NA Refer to ANDA for ESI/Lecleide - Rec'd 12/21/2001	Date Initials	Date Initials
4. Pat Beers Block Supv., Review Support Branch	Date 12/26/01 Initials PmBB	Date 12/27/01 Initials PmBB

EER Status: Acceptable for all facilities as of 11/8/2000 (NOTE: The Two Watson facilities are covered by the same CFN; none DMF).

Bioequivalence sites:

Clinical site:
Inspection needed: ☐ yes ☒ no
Status: ☒ acceptable ☐ unacceptable ☐ pending
Date of status:
Reason: Based on OSI inspection history

Analytical site:
Inspection needed: ☐ yes ☒ no
Status: ☒ acceptable ☐ unacceptable ☐ pending
Date of status:
Reason: Based on OSI inspection history

Bioequivalence office level sign off: Fed and fasting study acceptable (evaluated on 50 mg Strength, monolayered tablet). Dissolution for only film coated tablet acceptable.

Labeling Status: pending

Microbiology status: NA

Patent Certification: Para I certification. Exclusivity carried out for D-44

Controlled Correspondence/Cit.Pet:

Comments: RLD =

→ OBE relied upon MAPP 5723.2 to defer dissolution testing requirement on coated tablet. Bio sign off dtd. 4/24/01 with post-approval commitment for dissolution data on coated tablet

REVIEWER:

		DRAFT RECEIPT	FINAL ACTION
5.	Gregory Davis Supv., Reg. Support Branch	Date 12/27/2001 Initials GJD	Date 12/27/01 Initials GJD

Contains GDEA certification: Yes ☒ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐ PI
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ No ☐ N/A
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day N/A
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
Date Checked Previously granted
Nothing Submitted ☐
Written request issued ☐ NDA
Study Submitted ☐ 20-281

RLD = Ultram tablets 50mg
RW Johnson Pharmaceutical Research Institute

Comments: There are no unexpired patents on this drug product. Watson has addressed the D-44 exclusivity and the D-63 exclusivity.

6.	Peter Rickman Acting Director, DLPS	Date 12/27/01 Initials GJD	Date 12/27/01 Initials GJD

Comments: Acceptable EES dated 11/5/01 (verified 12/26/01). No OAI alerts noted. Bioequivalence review - bio studies on 50mg tablet (fasting & non-fasting) found acceptable. Non-scored dissolution data acceptable. Bio would like to see comparative dissolution data on scored tablets post approval. Data already submitted and commented upon by chemist. E Hatt & S Hazzard to have office-level bio endorsed. CMC acceptable 12/21/01. Methods validation pending.

7.	Robert L. West Acting Deputy Director, OGD	Date 12/27/01 Initials GJD	Date 12/27/2001 Initials Robert West

Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: 1) Documentation has been received from the review division stating that the exclusivity should be included in the generic labeling, but that the D-63 exclusivity may be "carved out" - memo in file. We are currently awaiting publication of the "Discontinued labeling Guidance" in final format. Once that occurs, and scoring issues are resolved, we will request FPL (package insert).

8.	Gary Buehler Acting Director, OGD Comments:	Date 1/15/02 Initials GB	Date 1/15/02 Initials GB
	~~Janet Woodcock, M.D. Director Center for Drug Evaluation And Research~~	Date Initials	Date Initials

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

9.	Project Manager Jeen Min Review Support Branch	Date 1/15/02 Initials JM	Date 1/15/02 Initials JM

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3:40 PM Time notified of approval by phone 4:00 PM Time approval letter faxed

FDA Notification:
N/A Date e-mail message sent to "OGD approvals" account
1/15/02 Date Approval letter copied to "//cder/drugapp" directory

v:\reports\approval\approvrou

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: June 10, 2002

From: Gary Buehler 6/10/02
Director
Office of Generic Drugs

Subject: Approval of Tramadol Abbreviated New Drug Applications

To: Abbreviated New Drug Applications (Listed Below)
Citizen Petition 01P-0495

Background

The new drug application (NDA) for Ultram (tramadol) Tablets is held by R. W. Johnson Pharmaceutical Research Institute ("Johnson"). The product was approved for marketing March 3, 1995, and is indicated for the management of moderate to moderately severe pain. The dosing regimen in the originally approved labeling recommended a dose of 50 to 100 mg every four to six hours, not to exceed 400 mg per day. Because of the side effects of dizziness, vertigo, nausea and vomiting there was a relatively high rate of discontinuance. On August 21, 1998, R. W. Johnson received approval for new labeling that included a titrated dosage and administration schedule (SLR-014). A clinical study with the titrated dosage schedule found there were fewer discontinuations due to adverse events, especially dizziness and vertigo, when the dose was titrated in increments of 50 mg/day and increasing over ten days to 200 mg/day. Discontinuations for nausea and vomiting were also decreased but did not reach statistical significance in this trial. This titrated dosing schedule beginning with 50 mg/day was granted a 3-year period of exclusivity (to expire August 21, 2001) and was listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) as D-44. Its expiration was extended to February 21, 2002, when Ultram was awarded pediatric exclusivity.

Another study was done to determine whether an even slower titration schedule would result in significant reduction of nausea and vomiting leading to termination of therapy. An open-label, run-in was used in the trial. Out of 932 patients, 212 did not tolerate the product and discontinued use. A portion of those 212 patients (167) continued in an open label trial with titration of the product. In this enriched population of patients known to not tolerate the product, there was a reduction in discontinuations of tramadol with a titration schedule beginning with 25 mg. On December 23, 1999, R. W. Johnson received approval for a labeling change providing for an additional titration for administration of the product (SE2-016). This titration starts with an initial dose of 25

mg/day with gradual dosing increases to 200 mg/day through a 16-day titration schedule. This new titration was granted three years of exclusivity which was to expire on December 23, 2002. R. W. Johnson then received a patent (6,339,105), which is listed in the Orange Book for a titration dosing regimen for the treatment of pain using an initial dose of about 25 mg. This patent will expire October 12, 2019. Pediatric exclusivity extends the expiration date to April 12, 2020.

Over time, a total of 15 abbreviated new drug applications have been submitted using Ultram as the reference listed drug (RLD). Various proposals, through a number of mechanisms, have been made to delete, "carve out" or otherwise modify the 25 mg dosage titration text that is protected by patent and/or exclusivity.

Previous Proposals

In a citizen petition, Apotex requested that FDA return to previously discontinued labeling after making a determination that, "Ultram's sponsor did not discontinue the 50 mg to 100 mg every four to six hours not to exceed 400 mg per day dosing schedule from the drug product's labeling due to safety or effectiveness reasons." To grant this request would require FDA to determine that omission of the titration dosing schedule using 25 mg increments would not render the proposed generic product less safe or effective than the innovator product. The petition contends that the change in labeling was not made in response to any concerns regarding safety or efficacy of the titration regimen. The petition states, "if immediate pain relief is needed, the medical examiner suggested that the old regimen would be more appropriate than the new titration regimen." The petitioner stated that the change in the dosing schedule was to reduce the incidence of discontinuations of use of the product, not for safety concerns.

FDA is authorized to approve an ANDA that omits an indication or other aspect of labeling of the listed drug that is protected by patent or exclusivity. 21 CFR 314.94(a)(8)(iv). The Best Pharmaceuticals for Children Act (BPCA) was signed into law in January of 2002. Section 11 of the BPCA allows incorporation of language in the labeling of generic products that informs health care practitioners that the reference listed drug has been approved for pediatric use. Teva utilized this concept to make two proposals for labeling to allow FDA to approve generic tramadol products omitting the protected 25 mg titration dosing schedule. The firm suggested that the Dosage and Administration section recommend use only in patients for whom rapid onset of pain relief is required, retaining the same language in the approved Ultram labeling, and, un-like the approved Ultram labeling, not recommend the 25 mg titration dosing schedule that has exclusivity. The alternative approach was to use that approach with added statements in the Dosage and Administration and Titration Trials section to alert prescribers to the fact that the reference product includes a 25 mg titration dosing for certain other patient subsets.

In proposing the approaches for the labeling, Teva noted that the medical review of the supplement for the 25 mg titration dosing stated that there was no evidence that the 25 mg dose would provide acute pain relief and it was not expected to do so. Teva also

noted that the 25 mg dose was not approved based on evidence from acute pain sufferers. Accordingly, Teva proposed to delete all information relating to the titrated use of tramadol and to obtain approval only for a non-titrated dosing regimen for patients requiring "rapid onset of analgesic relief." Teva argued that no patent or exclusivity applied to the non-titrated use of tramadol and that a generic product with only this dosing regimen for "acute" pain should be approved immediately. Johnson responded that Ultram was never separately approved for acute pain and the non-titration instructions are only interpretable if read in conjunction with the titration instructions.

On January 22, 2002, Johnson submitted a response to the Apotex petition. The firm contended that 21 CFR 314.161 (the process utilizing a determination that a particular product was not withdrawn for reasons of safety or efficacy) is not applicable to the tramadol labeling issues. Further, Johnson does not agree that there is a difference in changing labeling for reducing the discontinuation rate and for labeling changes due to safety and effectiveness. The response states that "withdrawals based on adverse reactions are considered to be for reasons of safety." The firm contends administration of the product with labeled directions that further reduce the incidence of adverse reactions is an improvement in the product, and a generic product that omitted the titration regimen would not be as safe and effective as the reference listed drug.

Apotex responded to Johnson's comments on February 12, 2002, taking issue with those comments. Again, approval of the generic products was sought.

The Generic Pharmaceutical Association (GPhA) also expressed an opinion (dated February 14, 2002) regarding the various issues that had been raised with respect to tramadol. After a reiteration of the history of the issue, the association asserted that there are no legal or regulatory impediments to the approval of the generic applications without the 25 mg titration regimen. GPhA cited regulations concerning permitted labeling differences. Also, it was of the opinion that the passage of the Best Pharmaceuticals for Children Act (BPCA) supported the ability of FDA to approve the generic tramadol products. It was also noted that the BPCA clarified that three-year innovator exclusivity for pediatric labeling changes. Such changes were not intended to prevent approval or access of the drugs to the entire population

Johnson also submitted a letter dated February 14, 2002, addressed to Mr. Daniel Troy, FDA Chief Counsel. The firm provided a history of the labeling issue and stated its opposition to the use of discontinued labeling by generic firms. The reason for the submission was to react to an assertion by Teva in a press release that the generic product would be AB-rated to the innovator's Ultram even though Teva was planning to use discontinued labeling. The letter stated that such a rating in that circumstance would violate FDA's standards. The letter discussed information from the Orange Book about equivalence of products under the same conditions of use.

On February 15, 2002, TorPharm submitted the previously mentioned letter from GPhA with a cover letter requesting approval of the firm's tramadol application.

Johnson submitted additional requested information for listing the US Patent 6,339,105 submitted to the agency on February 22, 2002. The firm declared that the patent covers the composition, formulation and/or method of use of Ultram (tramadol hydrochloride tablets) and that the product is currently approved.

On February 28, 2002, Dr. Lee Simon, Director, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550 wrote a memorandum regarding approach described in the referenced Apotex petition. He noted that the 25 mg dose titration allows some patients who had previously discontinued use of tramadol due to side effects to potentially and eventually experience the full efficacy of the drug product. He stated that it can be concluded that the regimen change was made with concerns first for safety and then for efficacy by increasing the number of patients who might be able to tolerate the ultimate efficacious dose.

The issue of whether the generic firms could carve out the 25 mg titration without compromising safety was then discussed at an internal meeting April 3, 2002. The meeting included the Office of the Chief Counsel, ODE V, HFD-550, the Office of Medical Policy, the Director of the Office of New Drugs, and the Office of Generic Drugs. Though no conclusion was reached, it was identified that with the 25 mg titration protected information carved out, and only information related to 50 mg use remaining, there was a question regarding a recommended starting dose. Although no starting dose is specified, titration in 50 mg increments every 3 days over 10 days assumes a 50 mg starting dose. It was noted that in Ultram's labeling after the 50 mg, 10 day titration schedule was approved, but before the 25 mg, 16 day titration regimen was approved, no explicit starting dose was given. The possibility of 505(b)(2) submissions utilizing a different dosing titration developed from publicly available literature sources was also discussed as a possible mechanism for new tramadol products to enter the marketplace.

Apotex submitted additional information to the petition docket on April 11, 2002. The attachment was a letter from a Michael Byas-Smith, M.D. with an opinion on the safety of the generic labeling after omission of the protected titration regimen given at the request of Apotex. Dr. Byas-Smith was of the opinion there were no safety issues.

The GPhA supplemented its February 14, 2002 letter with additional information on April 19, 2002. The letter primarily addresses what GPhA terms "tactics" used by brand name firms. GPhA states brand name companies are increasingly seeking and obtaining patent protection and other exclusivity based on dosing titration schedules in order to delay generic entry into the market place. The association places blame on FDA for preserving brand-name monopoly. The letter takes issue with the assertion that generic products without the titration would be unsafe. GPhA supports use of labeling with the 25 mg titration carved out and does not see it as a safety issue. The issue of safety of the higher dose should have been addressed with review of the original NDA, in the association's view.

Teva submitted a Citizen Petition dated April 30, 2002, requesting immediate final approval of Teva's ANDA for Tramadol Hydrochloride Tablets, 50 mg, ANDA 75-977.

In that petition, Teva proposed labeling that would preserve the exclusivity of the innovator product while allowing approval of the generic product. This proposed labeling, which in essence depended upon a distinction between "chronic" and "acute" pain was reviewed by the clinicians.

Drs. Simon and Goldkind provided input in a memo dated May 14, 2002, to respond to the Teva Citizen Petition. They pointed out that the ten-day titration schedule is uniquely important as it was based on data derived from patients naïve to tramadol. They noted that the petition is based on the presumption that "patients for whom rapid onset of analgesic effect is required" equates to an indication for acute pain. The clinicians distinguished between acute pain patients and patients for whom rapid onset of analgesic relief is required.

On May 30, 2002, Caraco submitted a citizen petition seeking immediate approval of its ANDA. Because FDA can approve generic tramadol labeling as described below, FDA does not need to reach the issues presented in Caraco's submission.

Teva submitted additional comments to the docket on June 5, 2002.

Resolution of Tramadol ANDA Labeling Issues

Further internal discussions occurred on May 22, 2002. The Office of Generic Drugs again conferred with the clinical review division and the Office of the Chief Counsel to consider the labeling in light of the clinical and legal arguments raised in the various letters and petitions. The clinicians reiterated the points made in their May 14, 2002, memorandum regarding the distinction between acute pain relief and rapid onset pain relief in the discussion. During that discussion, the parties addressed alternative approaches to labeling tramadol without reliance on the current protected Utram labeling. Ultimately, the physicians concluded, in conjunction with OGD and OCC, that the agency does not need to resolve the question of Ultram's approval for acute vs. chronic pain in order to respond to the petitions, because it was possible to develop a label that describes both titrated and non-titrated use of the tramadol without impeding on Johnson's exclusivity.

Based on the above discussions and after careful consideration of all issues and submissions, the consultative reviews, and the NDA approval records, the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products and OGD have concluded that generic tramadol applications can be approved without including the 25 mg titration schedule. This labeling will be acceptable under 21 CFR 314.127(a)(7). Proposed labeling and the basis for the decision are described and summarized in a June 10, 2002, review memorandum from Lee Simon, M.D., Director, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products. Additional issues related to specific labeling statements for tramadol product also are addressed in the memo from the Division.

V. Tablet Scoring

FDA may approve ANDAs for generic tramadol tablets that are not scored. Drug products approved under Section 505(j) of the Act are required to be the same as the listed drug in certain enumerated ways. Section 505(j)(2)(A). Neither the statute nor the regulations implementing these provisions, 21 CFR 314.94, address ANDA approval requirements when the listed drug is scored to permit a drug to be administered in doses smaller than the labeled strength of the drug product. However, because drug products are scored to permit dosing of the drug in accordance with the Dosage and Administration section of the approved labeling, it is appropriate to use the approved labeling of the innovator product as the reference point for considering whether the generic product must also be scored.

The current Ultram labeling describes a titration regimen using a 25 mg dose. Ultram 50 mg tablets are scored so that tablets may be divided into two 25 mg doses that may be used for this 25 mg titration dosing regimen. When generic tramadol products do not include the 25 mg titration schedule in the labeling (as is proposed), it is reasonable to conclude that the tablets need not be scored to achieve that dose. The 50 mg minimum dose in the labeling for the generic products may be achieved by administering the entire 50 mg tablet. Because the unscored 50 mg tablet will permit the patient to use the product in accordance with the approved labeling, the lack of scoring is not a bar to approval of the ANDA.[1]

OGD also concludes that, because of Johnson's exclusivity, scored generic tramadol tablets may not be approved.

The 25 mg dosing regimen is protected by three-year exclusivity. Johnson asserts that therefore FDA may not approve a scored generic tramadol product without violating Ultram's exclusivity. May 17, 2002 Johnson letter at 8-9. FDA agrees with Johnson that the score was added to the Ultram tablet to allow users of the product to split the tablet to reach a 25 mg starting dose. Because that starting dose is part of the 16-day titration regimen and has no other basis in the approved labeling, and because that regimen remains protected by exclusivity and patent, the Agency currently will not approve an ANDA for a scored generic tramadol product.

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[1] ***FDA's Orange Book acknowledges that certain permissible differences among therapeutically equivalent products may require attention on the part of the health professional. It states that in such cases, "[t]he Agency will use notes in this publication to point out special situations such as potential differences between two drug products that have been evaluated as bioequivalent and therefore therapeutically equivalent, when they should be brought to the attention of health professionals. . . . For example, in rare instances, there may be variations among therapeutically equivalent products in their use or in conditions of administration. Such differences may be due to patent or exclusivity rights associated with such use. When such variations may, in the Agency's opinion, affect prescribing or substitution decisions by health professionals, a note will be added to section 1.8." Orange Book at xv.***

The general approach to scoring issues is described in MAPP 5223.2 "Scoring Configuration of Generic Drug Products." OGD's treatment of generic tramadol is consistent with the MAPP.

VI. AB Rating

Johnson argues that Teva's tramadol product, using the labeling Teva proposes, cannot be AB-rated as therapeutically equivalent to Ultram because the safety profile of Teva's product would be "far different" from the safety profile of Ultram. May 17, 2002 Johnson letter at 7. Johnson supports its position with a number of statements from FDA's Orange Book (21st ed.):

> "Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." Orange Book at viii.
>
> "Products evaluated as therapeutically equivalent can be expected, in the judgment of FDA, to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling." Orange Book at xii.

Johnson also refers to the statement in the Orange Book that drugs considered to be therapeutically equivalent may differ only in "minor aspects of labeling (e.g., the presence of specific pharmacokinetic information)." Orange Book at viii. Johnson argues that the "reference to pharmacokinetic information is telling because such information would rarely if ever be used by a physician in prescribing a product. By contrast, an entirely different dosing regimen for a product would be pivotal to how it is used and could hardly be characterized as a difference in a minor aspect of its labeling." May 17, 2002 Johnson letter at 8.

FDA disagrees with Johnson that a generic tramadol product cannot be AB-rated to Ultram. As noted above, FDA routinely approves ANDAs that omit a condition of use, such as an indication, found in the innovator's labeling. Although the labeling that FDA would approve in this instance does not omit an indication, it does omit a portion of the labeling that is protected by exclusivity and patent. In assessing whether two drugs may be rated as therapeutically equivalent to each other, FDA assesses whether they "can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." In this case, dosing the generic product in conformance with the proposed labeling set forth in section IV above permits a generic tramadol to be as safe and effective as Ultram when used in conformance with its labeling. This assessment involves the same considerations as the determination under 21 C.F.R. 314.127(a)(7) that an omission of protected labeling information from a generic will not render the proposed product less safe or effective for the remaining, non-protected conditions of use.

The issue of AB ratings when one product is scored and the other is not also bears mentioning. The Orange Book discussion of therapeutic equivalence notes that drug products are considered by FDA to be therapeutically equivalent if they meet the criteria described in the Orange Book "even though they may differ in certain other characteristics such as ... scoring configuration... . When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity." Because the generic product will not be scored and the 25 mg starting dose for the titration schedule suggested in Ultram's labeling cannot be obtained using an unscored tablet, FDA anticipates that this difference may be brought to the attention of health care professionals through an Orange Book notation. Therefore, the absence of scoring on generic tramadol would not mean it may not be AB rated to Ultram.

FDA has consistently maintained that the omission of information protected by exclusivity will not be a basis for altering a therapeutic equivalence rating. 59 Fed. Reg. 50338, 50357 (October 3, 1994). In the present case, FDA has determined there is no reason to believe that a tramadol product approved under an ANDA would not be therapeutically equivalent to Ultram, when administered to patients under the conditions specified in the labeling.

cc:	Tramadol ANDAs
75-980	Alphapharm
75-977	Teva
75-981	TorPharm
75-962	Watson
75-963	Able
75-964	Caraco
76-003	CorePharma
75-983	Mallinckrodt
75-960	Purepac
76-100	Mutual
75-986	Mylan
75-982	Sidmak
75-968	Eon Labs
75-974	Asta Medica

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: June 10, 2002

From: Lee Simon, M.D. Lee Simon 6/10/02
Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

Subject: Approval of Tramadol Abbreviated New Drug Applications

To: Abbreviated New Drug Applications (Listed Below)

Background

For a complete background on tramadol, please see the memorandum from Gary Buehler, Director, Office of Generic Drugs.

The Office of Generic Drugs (OGD) consulted this division regarding whether the generic firms could carve out the 25 mg titration without compromising safety or effectiveness for the remaining non-protected conditions of use. To finalize the decision, the issue was first discussed at an internal meeting April 3, 2002. The meeting included the Office of the Chief Counsel, ODE V, HFD-550, the Office of Medical Policy, the Director of the Office of New Drugs, and the Office of Generic Drugs. Though no conclusion was reached, it was identified that with the protected information carved out, there was no recommended starting dose. It was felt that even without a clearly stated starting dose, that this dose was implied by the information in the clinical trials section which would inform the clinician and the patient how to proceed. The possibility of 505(b)(2) submissions utilizing a different dosing titration developed from publicly available literature sources was also discussed as a possible mechanism for new tramadol products to enter the marketplace.

The division also reviewed labeling submitted in a Citizen Petition dated April 30, 2002, by Teva requesting immediate final approval of that firm's ANDA for Tramadol Hydrochloride Tablets, 50 mg, ANDA 75-977. In that petition Teva proposed labeling that would preserve the exclusivity of the innovator product while allowing approval of the generic product.

Dr. Goldkind and I provided input to respond to the petition from Teva Pharmaceuticals. The response includes our judgment that the ten-day titration schedule is uniquely important as it was based on data derived from a study in patients naïve to tramadol. However, we are of the view that the 16 day, 25 mg titration schedule is of more limited

utility as this supporting trial was conducted in an enriched population of patients previously shown to be intolerant of tramadol and we cannot assume that its results can be generalized to the population as a whole. (See the consultative review dated May 13, 2002). Furthermore, we believe that there is no evidence that a 25 mg dose of tramadol is an effective analgesic dose.

Teva's petition proposes to delete all information regarding titrated use of tramadol. The petition is based on the presumption that the first paragraph in the dosing instructions (regarding titration) is intended for patients with chronic pain, and "patients for whom rapid onset of analgesic effect is required" in the second paragraph of the dosing instruction equates to an indication for acute pain. Johnson argues that Ultram was never separately approved for acute pain and the second paragraph of the dosing instructions are not interpretable in the absence of the first paragraph.

Further internal discussions on generic approvals and appropriate labeling occurred May 22, 2002. The Office of Generic Drugs again requested this division's input as well as that of the Office of the Chief Counsel to consider the labeling in light of the clinical and legal arguments raised in the various letters and petitions (See memo by Gary Buehler dated June 7, 2002). The distinction between acute pain relief and rapid onset pain relief was emphasized in the discussion. The Office of Generic Drugs pointed out that the labeling proposed by Teva was not what OGD would recommend in terms of carving out the titration starting with 25 mg. Issues of concern to this division regarding the clinical studies and dosage and administration sections were addressed by an alternative labeling approach proposed by OGD to accommodate the innovator's protected labeling and address safety and effectiveness concerns. It was concluded that the question of whether Ultram is indicated separately for acute and chronic pain does not need to be resolved at this juncture for FDA to approve a generic tramadol during Johnson's patent and exclusivity for the 25 mg, 16 day titration regimen. ANDAs for tramadol may be approved without deleting the first paragraph of the dosing and administration section in its entirety. Portions of the labeling that relate to the 10 day, 50 mg titration schedule are not protected by patent or exclusivity and they can and should remain in the labeling.

Under the approach proposed by OGD and acceptable to this division, the DOSAGE AND ADMINISTRATION section of the package insert for generic tramadol will read:

> For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of tramadol can be improved by initiating therapy with a titration regimen. The total daily dose may be increased by 50 as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After titration, tramadol 50 – 100 mg can be administered as needed for pain relief every 4 to 6 hours **not to exceed 400 mg/day.**
>
> For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, tramadol 50 mg to 100 mg can be

administered as needed for pain relief every four to six hours, **not to exceed 400 mg per day.**

The adverse events information will remain the same as that in Ultram's labeling and will acquaint physicians with the high incidence of dizziness, vertigo, nausea and vomiting associated with use of this drug. The titration trials section of the labeling will read as follows:

> In a randomized, blinded clinical study with 129 to 132 patients per group, a 10-day titration to a daily ULTRAM dose of 200 mg (50 mg q.i.d.) attained in 50 mg increments every 3 days, was found to result in fewer discontinuations due to dizziness or vertigo than titration over only 4 days or no titration.

Resolution of Tramadol ANDA Labeling Issues

The Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products believes that generic tramadol applications can be approved without including the 25 mg titration schedule, because such omission will not render such products less safe or effective than the listed drug for all remaining, non-protected conditions of use. In addition, the proposed label does not include information protected by Johnson's existing patent and exclusivity. The study submitted in supplement 016 (and granted exclusivity) did not test the hypothesis that a 16 day titration schedule will result in better tolerance than a 10-day titration schedule in tramadol naïve patients. The 16-day titration study was done using an enriched population of patients who had already previously discontinued use of tramadol due to side effects including nausea and vomiting. It showed a statistically significant reduction in nausea and vomiting in patients who had previously discontinued tramadol therapy due to tramadol intolerance when compared to 4 and 10 day titration schedules. Whether a general population of persons not previously exposed to tramadol would benefit from a 16 day titration with a 25 mg starting dose was not answered by the trial reported in supplement 016. Therefore, deletion of labeling approved with supplement 016 (25 mg titration) cannot be assumed to diminish the safety of this drug for tramadol naïve patients. There is no evidence nor is it obvious that when compared to titration over 10 days with a 50 mg starting dose, the slower 16-day, 25 mg titration schedule increases tolerability of tramadol for patients who have not been shown previously to be tramadol intolerant. Thus, it is also not obvious that slower titration in a general population of tramadol users (patients initially naïve to tramadol use) would result in a higher proportion of patients who will tolerate tramadol well enough to reach an effective dose. The use of tramadol by naïve patients is the most important target of any titration schedule. It could be argued that for tramadol naïve subjects who do not tolerate tramadol at 50 mg four times a day from the outset or following a 10-day titration schedule, use of an alternative analgesic may be preferable to exposing these subjects further to tramadol on a dosing schedule that requires sub-therapeutic doses for up to 16 days and still results in a 34% withdrawal rate due to adverse events. In addition, the 16 day titration schedule will delay the availability of a therapeutic dose when compared to

the 10 day titration or no titration regimens. There is no evidence that tramadol has analgesic efficacy at 25mg.

By contrast, the information regarding the first titration beginning with 50 mg is of value for the general population of patients and should be retained in the labeling. It provides the prescribing physician with important information to enable him to weigh the risks and benefits of slow titration versus those of rapid analgesia in the general population for whom tramadol will be prescribed. Removal of that information could render the drug less safe for some patients.

The failure to specify that 50 mg is the starting dose for the 10 day titration schedule does not render generic tramadol unsafe. With respect to the question of the starting dose for the ANDA labeling, the Dosage and Administration section for a generic tramadol would say: *For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of ULTRAM can be improved by initiating therapy with a titration regimen. The total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.).* The identification of this as a "titration regimen", coupled with the description of the 10 day, 50 mg titration trial described in the titration trials section (and the reference to the total daily dose being increased by 50 mg every 3 days) is adequate for the health care provider to understand how to dose a patient. Ultram's labeling (before the 25 mg, 16-day titration schedule was added), also did not include a specific starting dose in the context of the 10-day, 50 mg titration regimen.

Scope of Exclusivity

In a recent submission, Johnson argues that a statement related to the use of tramadol for rapid onset of analgesic effect is protected by the exclusivity granted for the 25 mg, 16 day titration study. Johnson claims that the following underlined portion of the labeling can not be used by the ANDA applicants:

> For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, ULTRAM 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, **not to exceed 400 mg per day.**

Johnson is incorrect that this labeling statement is protected. Although it was not included in the Ultram labeling until the 1999 supplement was approved, the statement is based upon information that was available to FDA in the Ultram NDA before the 25 mg, 16 day titration study was submitted. The underlined portion of the labeling relies upon information related to risk of discontinuation due to adverse events associated with the higher doses (50 mg and greater on a non-titrated schedule), which was available to the division in data from the 50 mg, 10 day titration trial, and the original approval trials. The 25 mg, 16 day titration trial information was not essential for approval of this portion of the labeling.

cc:	Tramadol ANDAs
75-980	Alphapharm
75-977	Teva
75-981	TorPharm
75-962	Watson
75-963	Able
75-964	Caraco
76-003	CorePharma
75-983	Mallinckrodt
75-960	Purepac
76-100	Mutual
75-986	Mylan
75-982	Sidmak
75-968	Eon Labs
75-974	Asta Medica

M E M O R A N D U M

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

Date: June 13, 2002

To: The Record

From: Director, Office of Generic Drugs 6/13/02

Subject: Approval Process for Generic Tramadol Hydrochloride Tablets

On June 11, 2002, the agency's comments regarding the content and format of acceptable package insert labeling for generic tramadol hydrochloride tablets was provided electronically to all applicants. Within the next few days, many of the applicants will submit a MINOR AMENDMENT – FINAL APPROVAL REQUESTED providing final-printed package inserts and possibly other information. These minor amendments will be forwarded initially to the labeling review branch (LRD) for review and preparation, if appropriate, of the labeling approval summary. The LRB will review the minor amendments in the order in which they were received by OGD.

In the past, a final chemistry review would be completed and, if acceptable, approval letters and packages would be drafted and assembled by the chemistry branch project manager (PM). The PM would circulate the packages through the labeling and chemistry branches before forwarding them to the chemistry division level for clearance. Upon concurrence at the chemistry division level, the packages would be forwarded to the OGD front office for final audit and/or review and signature. Because many of the tramadol packages were in approvable status prior to the transmission of the labeling comments, we will make an exception to the final approval process for those tramadol applications that meet all of the following criteria:

1. The application was in approvable status at the time of receipt of the MINOR AMENDMENT – FINAL APPROVAL REQUESTED. (Note: "Approvable" indicates that all regulatory, cGMP, and scientific issues associated with the application (with the exception of the content of the final printed package insert) have been satisfactorily resolved and found satisfactory for approval. In such cases, "approvable" letters are issued by OGD to inform the firm that final approval is blocked until agreement can be reached within the agency to address those aspects of innovator labeling that are protected by exclusivity).

2. The applicant has stated in its MINOR AMENDMENT that no chemistry, manufacturing, or control changes were made to the application since the receipt of the approvable letter.

3. Since tramadol hydrochloride tablets is a non-compendial drug product, the methods validation process has not been initiated, or has been initiated and no deficiencies have been identified and transmitted to OGD, or the validation has been completed and found acceptable by the field. Deficiencies known to OGD must be satisfactorily resolved prior to approval.

4. All final printed labeling has been reviewed and found to be acceptable by the labeling reviewer and endorsed by the Labeling Review Branch team leader.

5. CGMP status as revealed in CDER's EES System is "Acceptable". This assessment is verified prior to final approval.

6. The applicant clearly intends to manufacture and market unscored tablets. If the application provides for scored tablets, and the applicant has not revised the specifications to provide for an unscored tablet, approval may still be granted provided the applicant has provided the preapproval commitments specified in CDER's MAPP 5223.2 under "Reporting Requirements". Data to satisfy the commitments are to be included in a supplemental application for which the applicant may request expedited review. The applicant may not market unscored tablets until this supplemental application is approved. Furthermore, applicants may not distribute scored tablets because that would be a violation of the NDA holder's exclusivity for the reference drug product, Ultram Tablets.

Applications and completed labeling reviews will be forwarded directly to the Acting Director, Division of Labeling and Program Support or to the Acting Deputy Director, Office of Generic Drugs. They will assure compliance with the criteria stated above. All applications for which the scoring configuration is unclear or the proper data have not been submitted to change the scoring configuration to an unscored tablet will be referred to the chemistry review branch team leader. Otherwise, if the criteria are met, one of these individuals will complete an approval summary and prepare the approval letter in final signature-ready format. The approval letter will be forwarded to the Director, Office of Generic Drugs for signature. Once signed, the approval letter and supporting documentation will be forwarded for the chemistry team project manager who will inform the applicant of the approval by means of a telephone call and facsimile copy.

Amendments submitted by applicants whose tramadol applications are not currently in approvable status will be placed in the chemistry reviewer's queue.

This modification to the routine OGD final approval process is similar to processes previously implemented by OGD for Buspirone Hydrochloride Tablets and Metformin Hydrochloride Tablets.

OFFICE OF GENERIC DRUGS APPROVAL ROUTING SUMMARY

TRAMADOL HYDROCHLORIDE TABLETS, 50 MG

ANDA NUMBER: 75-962

APPLICANT: Watson Laboratories, Inc.

Date of Issuance of Approvable Letter: January 15, 2002

Date of Submission of Final-printed Package Insert Labeling: JUNE 13, 2002

Final-printed Labeling (FPL) Reviewed and Found Acceptable On: JUNE 19, 2002

CGMP Status (Attach Copy of EES Summary): Acceptable (copy attached)

Methods Validation Status: Pending - Standard commitment has been received.

Has Applicant Initiated Changes to the CMC Section of the Application Since Issuance of the Approvable Letter? Yes, Changes have been reviewed and found acceptable. See Chemistry review #5.

Recommendation:

Please refer to the OGD Routing Summary completed upon issuance of the approvable letter for a comprehensive summary of the CMC, bioequivalence, and regulatory issues supporting approval of this application. The applicant has submitted final-printed labeling in accord with the text provided by OGD on June 11, 2002. This labeling has been reviewed and found acceptable for approval. Tablet scoring issues have been resolved and the applicant will market unscored tablets. In addition, the application meets the criteria specified in the memorandum dated June 13, 2002, pertaining to the final approval process for generic tramadol hydrochloride tablets.

This application is recommended for approval.

Robert L. West 6/24/2002

Wm. Peter Rickman (Date)
Acting Director
Division of Labeling and Program Support

or

Robert L. West (Date)
Acting Deputy Director
Office of Generic Drugs

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-962

CORRESPONDENCE

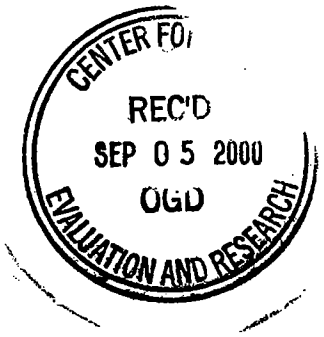
WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

adc for filing 10/2/00
S. Middleton
505(j)(2)(A)

ARCHIVAL COPY

September 1, 2000

Gary Buehler, R.Ph.
Acting Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773



RE: **Abbreviated New Drug Application**
Tramadol Hydrochloride Tablets, 50mg

Dear Mr. Buehler:

Watson Laboratories, Inc. submits herein an original Abbreviated New Drug Application for Tramadol Hydrochloride Tablets, 50 mg.

The drug product described above is the same as Ultram® (tramadol HCl tablets) 50 mg, manufactured by Ortho-McNeil Pharmaceutical Inc (NDA holder - RW Johnson). We have submitted comparative information to indicate that our product is the same as the reference listed drug product. This information is presented in tabular form, comparing active ingredient, condition of use, route of administration, dosage form, strength, bioequivalence, and labeling for the products as supplied by Watson Laboratories, Inc. and by Ortho Mc-Neil Pharmaceutical Inc.

Please note that Royce Laboratories became a wholly owned subsidiary of Watson Pharmaceuticals in April 1997 and is now operating as Watson Laboratories, Inc., Miami, Florida. Due to this transition, the documents in this application may contain the Royce name, the Watson name, or both names.

Watson Laboratories, Inc. commits to resolve any issues identified in the method validation program after approval.

We have enclosed one (1) archival and one (1) review copy. As required, two (2) additional separately bound copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active pharmaceutical ingredient and finished dosage form) are included as one of the volumes of the archival copy of this ANDA.

ARCHIVAL COPY

The number of volumes in the archival, review, and field copies of the ANDA are as follows:

Blue Archival Copy	- 10 volumes
Orange Review Copy	- 8 volumes
Red Review Copy	- 2 volumes
Burgundy Field Copy	- 2 volumes

In addition, for the Bioequivalence Section, we have also enclosed four (4) computer diskettes (two per study) with the analytical data and bioavailability parameters in the format prescribed by the FDA. These diskettes are located at the front of Section VI of the Orange Review Copy of this application.

In accordance with the Guidance for Industry entitled "Preparing Data for Electronic Submission in ANDA's", Section VII. B., dated September 1999, we will be providing electronic BA/BE, CMC and Labeling submission within 30 days after this paper submission is accepted by the Agency.

One (1) field copy of the application will be forwarded to the Florida District Office. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application.

We trust the information submitted is sufficient for this Abbreviated New Drug Application to be evaluated. Please contact me by phone at (909) 270-1400 or by fax at (909) 278-0967 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Ernest Lengle, Ph.D.
Senior Director
Regulatory Affairs

EL/alb

ANDA 75-962

Watson Laboratories, Inc.
Attention: Ernest Lengle, Ph.D.
311 Bonnie Circle
Corona, CA 92880-2882

OCT 13 2000

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Tramadol Hydrochloride Tablets, 50 mg

DATE OF APPLICATION: September 1, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 5, 2000

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-962
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/NMahmud, Chief, RSB Davis for date 10/13/00
HFD-615/Smiddleton, CSO S. Middleton date 10/4/00
Word File
V:\FIRMSNZ\WATSON\LTRS&REV\75962.ACK
F/T mjl/10/5/00
ANDA Acknowledgment Letter!

ARCHIVAL COPY

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

December 4, 2000

Gary Buehler, R.Ph.
Acting Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Telephone Amendment

NDA ORIG AMENDMENT
AB

RE: Tramadol Hydrochloride Tablets, 50mg
ANDA 75-962

Dear Mr. Buehler:

Watson Laboratories, Inc. received a telephone call from Ms. Krista Scardina of the Bioequivalence Division on 12/4/00 requesting for the dissolution information pertaining to our Tramadol Hydrochloride Tablet application. Specifically, Ms Scardina was looking for the proposed Q value, mean, CV, method and dissolution medium for our Tramadol HCl 50 mg tablets. The information Ms. Scardina has requested was included in our original ANDA application, Section XXI.1 (pp. 1001-1004) submitted on September 1, 2000. To facilitate Ms. Scardina's request, we are submitting this telephone amendment with a copy of Section XXI.1 in the following attachment (see **Exhibit 1**).

We have enclosed one (1) archival and one (1) review copy of this Telephone Amendment.

We trust the information submitted is sufficient for this Telephone Amendment to be evaluated. Please contact me by phone at (909) 270-1400 or by fax at (909) 278-0967 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Ernest Lengle, Ph.D.

Ernest Lengle, Ph.D.
Executive Director
Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 06 2000
OGD

311 Bonnie Circle, P.O. Box 1900, Corona, California 92878-1900 • Tel: 909/270-1400 • Fax: 909/270-1096

ARCHIVAL COPY

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

April 23, 2001

ORIG AMENDMENT

Gary Buehler, R.ph.
Acting Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Minor Amendment

CENTER FOR DRUG EVALUATION AND RESEARCH
APR 24 2001
OGD

RE: ANDA 75-962
Tramadol Hydrochloride Tablets, 50 mg

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this amendment to provide a complete response to the comments included in the FDA facsimile dated February 27, 2001 (copy attached) pertaining to Tramadol Hydrochloride Tablets, 50 mg, ANDA 75-962. OGD requested in comment 7 of the faxed letter that Watson should submit information of our scored tablets as a "Prior Approval Supplement – Expedited Review". However, Watson has manufactured an exhibit batch with the scored configuration and has included the relevant CMC information in this Amendment. No changes were made to the previously submitted batch record except for the description of the tablets and the tooling and the clarification of the coating instructions. The changes to the coating batch records are detailed in our response to comment 6. For convenience of review, your comments are provided in bold face type followed by our responses.

Chemistry Deficiencies

1. [redacted]

2. [redacted]

311 Bonnie Circle, P.O. Box 1900, Corona, California 92878-1900 • Tel: 909/270-1400 • Fax: 909/270-1096

Redacted 3 page(s)

of trade secret and/or

confidential commercial

information from

4/23/2001 WATSON LETTER

Watson acknowledges the Agency's comment. Samples and methods were requested and sent to the FDA Field Laboratory on February 15, 2001 to the following address:

U.S. Food and Drug Administration
60 Eighth Street, N.E.
Atlanta, Georgia 30309
Attention: Stanley Roberts

Labeling Deficiencies

1. GENERAL COMMENTS

a. Please note that a dosing exclusivity (D-63) was granted for the new titration information approved on December 23, 1999, for the insert labeling of the reference listed drug, Ultram®. Please update your Exclusivity Statements accordingly.

b. We acknowledge that you have not included the titration information approved on August 21, 1998 and December 23, 1999 for the insert labeling of the reference listed drug, Ultram® . We have reviewed the labeling submitted and have the following comments.

Pending resolution of issues regarding the differences between your proposed dosing information of this drug product and that information in the last approved for the reference listed drug, Ultram®, we defer comment at this time.

c. Revise the storage temperature statement to read "Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP]"

We have revised our exclusivity statement to reflect the new titration information for the reference listed drug (see **Exhibit 14**). We have revised the storage temperature statement as recommended by the Agency. Watson Laboratories, Inc. acknowledges that the Agency has deferred comment at this time on differences between our proposed dosing information and that of the Reference Listed Drug, Ultram®.

2. CONTATINER – 100s, 500s,, & 1000s

a. Revise the established name to read "tramadol hydrochloride tablets".

b. Revise to read:
...contains: Tramadol hydrochloride....50 mg

c. Refer to the general comment (b) above.

We have revised the container label according to the Agency's recommendations.

We have provided a total of twelve (12) copies of final printed container labels, eleven (11) labels with the Archival copy of the application and one (1) label with the review copy of the application (see **Exhibit 15**).

In order to facilitate the review of the submission, and in accordance with 21 CFR 314.94 (a) (8) (iv), we have provided a side-by-side comparison of our proposed container label and our final print container label. All differences have been annotated and explained (see **Exhibit 16**).

3. INSERT

a. GENERAL

i. Refer to the general comment above.

ii. It is preferable to use the term "mcg" rather than "µg" throughout the text.

b. DESCRIPTION

Please identify the ingredients contained in your coating material, ——— White ——— so that we can verify the listing of inactive ingredients.

c. CLINICAL PHARMACOLOGY

i. See general comment (a) above.

ii. Clinical Studies – Last paragraph, last sentence:

We encourage that you include a disclaimer identifying two brand names, "TYLENOL® with Codeine #3 and TYLOX®". [e.g., Tylox is the registered trade mark of Johnson RW.

d. INDICATIONS AND USAGE

...hydrochloride tablets are indicated... [add "tablets"]

e. PRECATUIONS (increased...Trauma) – Last sentence:

...receiving tramadol hydrochloride tablets.

f. ADVERSE REACTIONS – First paragraph, last sentence:

See comment (c) above.

g. DOSAGE AND ADMINISTRATION
See general comment (a) above.

h. HOW SUPPLIED

i. Please note that the Innovator has changed the scoring configuration from "unscored" to "scored" for Ultram tablets. Please change the scoring configuration of your drug product to be same as the innovator's and revise this section accordingly.

ii. Refer to the general comment (b) above.

We will not request final printed insert labeling until we are able to provide adequate guidance regarding the differences of dosing information between your proposed labeling and that of the reference listed drug.

We have made all the changes as recommended by the Agency. Watson Laboratories, Inc. acknowledges that the Agency has deferred comment at this time on differences between our proposed dosing information and that of the Reference Listed Drug, Ultram®.

We acknowledge that the Agency is not requesting Final Printed Labeling at this time however, Watson has decided to provide Final Printed Labeling for your review. We have provided a total of twelve (12) copies of final printed container labels, eleven (11) labels with the Archival copy of the application and one (1) label with the review copy of the application (see **Exhibit 17**).

In order to facilitate the review of the submission, and in accordance with 21 CFR 314.94 (a) (8) (iv), we have provided a side-by-side comparison of our proposed container label and our final print container label. All differences have been annotated and explained (see **Exhibit 18**).

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes:

Watson Laboratories, Inc. acknowledges that further revisions to our labeling may be necessary subsequent to approved changes in the reference listed drug. We commit to routinely monitor the FDA website for any approved labeling changes.

We have enclosed one (1) archival and one (1) review copy of this amendment. In accordance with 21 CFR § 314.94 (d)(5), one (1) field copy of this amendment will be forwarded to the Florida District Office. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copies of this amendment.

We trust the information submitted is sufficient for this Minor Amendment to be evaluated. Please contact me by phone at (909) 270-1400 or by fax at (909) 278-0967 if you have any questions or if I can assist you with the review of this application.

Sincerely,

E. M. Choy

Ernest Lengle, Ph.D.,
Executive Director
Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

ARCHIVAL COPY

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

NEW CORRESP
NC

May 9, 2001

Gary Buehler, R.Ph.
Acting Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

New Correspondence

RE: ANDA 75-962
Tramadol Hydrochloride Tablets, 50 mg

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this correspondence in response to Mr. Jeen Min's comment on May 8, 2001 regarding our unscored formulation that was submitted in the original application on September 1, 2000 and our amended scored formulation submitted in our Minor Amendment, April 23, 2001.

Per Mr. Min's request, Watson Laboratories hereby certifies that there are no differences between the unscored formulation and the amended scored formulation. The only difference is in the tooling for compression of the tablets. For your convenience we are resubmitting the formulation pages of the original ——— batch record (unscored) and of the ——— batch record (scored) submitted in the amendment to demonstrate that the formulations are identical (see **Exhibits 1** and **2**).

We have enclosed one (1) archival and one (1) review copy of this correspondence. In accordance with 21 CFR § 314.94 (d)(5), one (1) field copy of this correspondence will be forwarded to the Florida District Office. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copies of this correspondence.

We trust the information submitted is sufficient for this application to be evaluated. Please contact me by phone at (909) 270-1400 or by fax at (909) 278-0967 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Ernest Lengle, Ph.D.
Executive Director
Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 10 2001
OGD

311 Bonnie Circle, P.O. Box 1900, Corona, California 92878-1900 • Tel: 909/270-1400 • Fax: 909/270-1096

ARCHIVAL COPY

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

NDA ORIG AMENDMENT
N/AM

June 01, 2001

Gary Buehler, R.Ph.
Acting Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Telephone Amendment

CENTER FOR DRUG EVALUATION AND RESEARCH
JUN 04 2001
OGD

RE: ANDA 75-962
Tramadol Hydrochloride Tablets, 50 mg

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this amendment to provide a complete response to the telephone comments from Mr. Jeen Min, Project Manager and Ed Ramos, Review Chemist of the OGD on May 16, 2001, pertaining to our amendment of April 23, 2001 for Tramadol Hydrochloride Tablets, 50 mg, ANDA 75-962. For convenience of review, the OGD's comments are provided in bold face type followed by our responses.

Chemistry Deficiencies

1. [redacted]

2. [redacted]

NW 6/5/01

311 Bonnie Circle, P.O. Box 1900, Corona, California 92878-1900 • Tel: 909/270-1400 • Fax: 909/270-1096

3. **There appears to be a page missing in the application. Page 240 starts to present specifications. However, page 241 does not present the rest of the specifications. Was there a page 240A that contains the missing specifications?**

   We acknowledge that we inadvertently did not include page 240A which includes the rest of the specifications (5., 6., 7., page 19 of 20). This page is being included for your review. (See **Exhibit 3**).

We have enclosed one (1) archival and one (1) review copy of this amendment. In accordance with 21 CFR § 314.94 (d)(5), one (1) field copy of this amendment will be forwarded to the Florida District Office. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copies of this amendment.

We trust the information submitted is sufficient for this Telephone Amendment to be evaluated. Please contact me by phone at (909) 270-1400 or by fax at (909) 278-0967 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Ernest Lengle, Ph.D.
Executive Director
Regulatory Affairs
EL/nl

ARCHIVAL COPY

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

July 18, 2001

N/AF

ORIG ASSIGNMENT

Gary Buehler, R. Ph.
Acting Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Tramadol Hydrochloride Tablets, 50 mg
ANDA 75-962 **Expedited Review Requested**

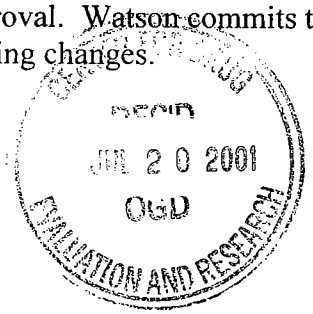
Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this amendment to correct an error in the April 23, 2001 submitted insert. A statement referring to a patent exclusivity was erroneously included in the submitted insert. Watson discovered this error during a Quality Review of the insert prior to its release to the Packaging Department. This statement has been eliminated. In addition, spelling errors have been corrected. No other changes to the text have been made.

We have provided a total of twelve (12) copies of final printed inserts. Eleven (11) copies are with the Archival Copy of the application and one (1) insert is with the Review Copy of the application (see Exhibit 1).

In order to facilitate the review of the submission, and in accordance with 21 CFR 314.94(a)(8)(iv), we have provided a side-by-side comparison of our previously submitted insert and our final printed insert. All differences have been annotated and explained (see Exhibit 2)

Watson Laboratories, Inc. acknowledges that further revisions to our labeling may be necessary subsequent to ANDA approval. Watson commits to routinely monitor the FDA website for any approved labeling changes.



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We believe the application is complete and request approval. Please contact me by phone at (909) 270-1400 or by fax at (909) 278-0967 if you have any questions of if I can assist you with the review of this application.

Sincerely,

Ernest Lengle, Ph.D.
Executive Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ARCHIVAL COPY

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

September 19, 2001

Dale P. Conner, Pharm. D.
Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Correspondence

RE: **ANDA 75-962**
Tramadol Hydrochloride Tablets, 50 mg

Dear Dr. Conner:

Watson Laboratories, Inc. is submitting this correspondence to provide confirmation to the comments included in the FDA facsimile dated September 04, 2001 (copy attached) pertaining to the referenced ANDA. For convenience of review, our responses are given in the order in which the comments appear in your letter and your comments are provided in bold face type.

Facsimile dated September 04, 2001

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The following dissolution testing should be conducted in 900 mL of 0.1 N HCl, at 37°C using USP Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

Not less than —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

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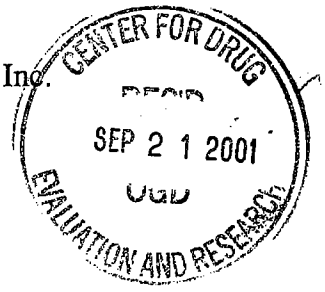
We confirmed that we are conducting dissolution testing identical to the parameters and specifications listed above. The analytical methods were submitted in the minor amendment on April 23, 2001 for stability (pages 242 to 243 Doc # RD0466S1B) and quality control programs (pages 223 to 224 Doc # RD0466B). During our review, we noticed that the "limit" listed on the Stability Data forms for Lot R02099 is incorrect (P. 270 and 272). The stability forms have been revised from "[redacted]" to "[redacted]". Also, we have included updated 18 month stability data (See **Exhibit 1**).

Please note the "description" of the **blank** stability forms has been revised to include the new product code "466" and tablet description to reflect the score configuration of the tablet as indicated in our May 9, 2001 and June 01, 2001 amendments (See **Exhibit 2**). All testing is being performed in accordance with our submitted analytical methods.

We have enclosed one (1) archival, one (1) review and one (1) field copy of this correspondence. We trust this information is sufficient for this application to be evaluated. If I can assist with the review of this application, please contact me by phone at (909) 493-5446 or by fax at (909) 493-5806 if you have any questions.

Sincerely,

Ernest Lengle, Ph.D.
Executive Director
Regulatory Affairs
Watson Laboratories, Inc.
EL/nl



NAF
MMS 3-5-02

February 22, 2002

Gary Buehler, R. Ph.
Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

NEW CORRESP

NC

RE: Tramadol IR Tablets, 50 mg (ANDA 75-962)

Dear Mr. Buehler:

We wish to amend our pending application for Tramadol Tablets to add a new Patent Certification and Exclusivity Statement for Patent No. 6339105, which has just been added to the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

If you have any questions regarding this information, please contact me by phone at (301) 762-5212 or Ernie Lengle at (909) 493-5446 or by fax at (909) 493-5806.

Sincerely,

Joe Suntum, Esq.
Authorized Agent
Watson Pharmaceuticals, Inc.

1 Copy

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

NAE MMS 3-5-02

NC

NEW CORRESP

February 22, 2002

Gary Buehler, R. Ph.
Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: Tramadol IR Tablets, 50 mg (ANDA 75-962)
Paragraph IV Certification

Dear Mr. Buehler:

We wish to amend our pending application for Tramadol Tablets to add a new Patent Certification and Exclusivity Statement for Patent No. 6,339,105, which has just been added to the Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book) A Paragraph IV Certification has been sent to you via courier through our agent Mr. Joe Suntum today. In the abundance of caution, we are sending this certification via facsimile. Please disregard this certification if the earlier submitted certification is effective. This certification is not intended to jeopardize in any way the earlier submitted certification.

If you have any questions regarding this information, please contact me by phone at (909) 493-5446 or by fax at (909) 493-5806.

Sincerely, Ph.D.

Ernest Lengle, Ph.D.
Executive Director
Regulatory Affairs

CENTER FOR DRUG
FEB 25 2002
EVALUATION AND RESEARCH

NAI
gm 3/12/02

311 Bonnie Circle, P.O. Box 1900, Corona, California 92878-1900 • Tel: 909/270-1400 • Fax: 909/270-1096

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: Watson Laboratories, Inc. TEL: 909-493-5446

ATTN: Ernest Lengle FAX: 909-493-5806

FROM: Jeen Min PROJECT MANAGER: 301-594-0338

Number of pages: 1
(excluding the cover sheet)

Comments:

Bioequivalence comments for ANDA 75-962 (Tramadol).

Or 3/22/02

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-962 APPLICANT: Watson Labs.

DRUG PRODUCT: Tramadol Hydrochloride 50mg tablet

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs.

The dissolution testing is conducted in 900 mL of 0.1N HCl, at 37^{0}C using USP Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

Not less than ___ %(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Barbara M Davit

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Park, Chan H

From: Park, Chan H
Sent: Tuesday, June 11, 2002 11:12 AM
To: 'elengle@watsonpharm.com'
Subject: 75-962 (Tramadol)

Importance: High

The Office of Generic Drugs (OGD) in consultation with the Office of New Drugs has agreed on the content of a package insert that represents safe and effective package insert labeling for generic Tramadol Hydrochloride Tablets. The labeling, which appears below is based on the current approved labeling (August 2001) for the reference listed drug, Ultram Tablets of the R.W. Johnson Pharmaceutical Research Institute. It is being transmitted simultaneously to all applicants for an Abbreviated New Drug Application (ANDA) for the drug product which has been found acceptable for filing by OGD.

Please revise your insert labeling to be in accord with the labeling presented below. Please note that you should delete the 16-day titration graphic from Figure 2 under Titration Trials, and retain only the 10-day graphic. Then prepare and submit 12 copies of the final printed insert. You should also submit final printed container labels if you have not previously done so. Please provide a side-by-side comparison of your previously submitted package insert labeling with the text provided. All differences should be annotated and explained.

In addition, please be certain that you have addressed U.S. Patent No. 6,339,105 (the '105 patent) and the exclusivity (D-63) listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"). A patent statement provided under Section 505(j)(2)(A)(viii) of the Act indicating that the '105 patent is a method of use patent and that this patent does not claim any of the proposed indications for which you are seeking approval is consistent with the labeling we have presented. Furthermore, you may need to amend appropriate sections of your ANDA to provide for the manufacture of **unscored** tablets. We refer you to the "Reporting Requirements" section of the Office of Pharmaceutical Science's Manual of Policies and Procedures (MAPP) 5223.2 (November 1, 1995) for information on the type of data or pre-approval commitment to provide such data that may be needed prior to approval of your application.

If you have previously received an approvable letter from OGD for the application, please submit the information requested above as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED. This amendment should also provide data to substantiate any minor chemistry, manufacturing, or controls changes that may have been introduced into the application since your receipt of the approvable letter. If none of these changes were made, please provide a confirmatory statement in your cover letter. This amendment will be reviewed and, if appropriate, an approval letter will be issued based upon current OGD policies and procedures. If you have not received an approvable letter on your application, please submit the information as part of your response to an outstanding not approvable letter. If you have already submitted such a response, you may provide the requested information as an addendum to that submission.

If you have questions concerning the content or format of the proposed package insert labeling, please contact the labeling reviewer, Chan Park, Ph.D., (301) 827-5846. Additional questions concerning the approval process for your ANDA should be directed to Robert L. West, Deputy Director (Actg.), Office of Generic Drugs (301) 827-5840 or Peter Rickman, Director (Actg.), Division of Labeling and Program Support (301) 827-5840. Thank you,

trmadol.generic.doc

Tracking:	Recipient	Delivery
	'elengle@watsonpharm.com'	
	Park, Chan H	Delivered: 6/11/02 11:12 AM

APPEARS THIS WAY
ON ORIGINAL

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ORIG AMENDMENT
N/AM

June 13, 2002

Gary Buehler, R. Ph.
Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Tramadol Hydrochloride Tablets, 50 mg
ANDA 75-962
Minor Amendment – Final Approval Requested

Dear Mr. Buehler:

This is in response to Office of Generic Drugs (OGD) e-mail dated June 11, 2002 from Dr. Chan Park concerning the above-referenced ANDA and to Watson Laboratories, Inc. (Watson) Approvable Letter dated January 15, 2002. Watson believes that the issues involving the approved labeling for the reference listed drug product, Ultram® Tablets of R. W. Johnson Pharmaceutical Research Institute, and related exclusivity as described in 21 CFR 314.108(b)(5) have been resolved. Based on this information and in compliance with OGD's e-mail dated June 11, 2002 and our January 15, 2002 Approvable Letter, Watson is submitting this amendment with the following particulars:

1. Revised our July 18, 2001 labeling. We have provided a total of twelve (12) copies of final printed inserts and container labels. Eleven (11) copies are with the Archival Copy of the application and one (1) copy is with the Review Copy of the application (see Exhibit I). In order to facilitate the review of the submission, and in accordance with 21 CFR 314.94(a)(8)(iv), we have provided a side-by-side comparison of our previously submitted labeling and our final printed labeling. All differences have been annotated and explained (see Exhibit II).

Watson commits to routinely monitor the FDA website for any approved labeling changes.

2. Section viii statement is enclosed which addresses U.S. Patent No. 6,339,105 (the '105 patent) and the exclusivity (D-63) listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book")(see Exhibit III).

3. Watson certifies that except for a revision of the description of the drug product (the deletion of "scored" in reference to the tablet) and minor format changes, there have been no significant changes in the conditions outlined in our abbreviated new drug application or changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices since the issuance of the Approvable Letter (see Exhibits IV - XIII).

RECEIVED
JUN 14 2002
OGD / CDER

311 Bonnie Circle, Corona, CA 92880 • Tel: (800) 249-5499 • Fax: (909) 270-1096 • Website: www.watsonpharm.com

We certify that a true copy of the technical sections of this amendment has been provided to the Food and Drug Administration Florida District Office.

We believe the application is complete and request final approval. Please contact me by phone at (909) 493-5446 or by fax at (909) 493-5806 if you have any questions of if I can assist you with the review of this application.

Sincerely,

Joyce Anne Del Gaudio /for

Ernest Lengle, Ph.D.
Executive Director
Regulatory Affairs