CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-986

Name: Tramadol Hydrochloride Tablets, 50 mg

Sponsor: Mylan Pharmaceuticals, Inc.

Approval Date: June 21, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-986

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-986

APPROVAL LETTER

ANDA 75-986

JUN 21 2002

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 3, 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 30, 2002, and to your amendments dated December 7, 2000; April 5, 2001; and June 13, and June 18, 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 FDA-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 FDA-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler

Gary Buehler 6/21/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

cc: ANDA 75-986
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-647/ALangowski/6/18/02;6/20/02
HFD-647/GJSmith/6/20/02
HFD-617/J.Min/6/20/02
HFD-613/C.Park/6/20/02
HFD-613/L.Golson/6/20/02

Robert L. West
6/21/2002

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F/T by: rlw/6/21/02

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-986

APPROVABLE LETTER

ANDA 75-986

JAN 30 2002

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 3, 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 7, 2000; and April 5, April 23, and July 24, 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,

Robert L. West for 1/30/2002

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-986
Division File
Field Copy
GCF-1 Liz Dickinson
GCF-1 Kim Dettelbach
HFD-610/R.West
HFD-330
HFD-205/F.O.I.
HFD-92

Endorsements:
HFD-647/A.Langoski/ For Mahnaz Farahan. 12,28,01
HFD-647/G.Smith/ D. Rosella for 12/27/01
HFD-617/J.Min/ Jean Min 12/27/01
HFD-613/C.Park/12/27/01 C Park 12/27/01
HFD-613/C.Hoppes/ C Park for 12/27/01 (OR per Bob West)

F/t by rad12/27/01
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APPROVABLE

Robert West
1/30/2002

cmc satisfactory.
1/29/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

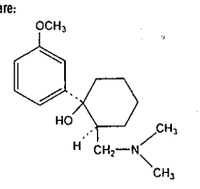
ANDA 75-986

LABELING

TRAMADOL HYDROCHLORIDE TABLETS 50 mg

℞ only

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



$C_{16}H_{25}NO_2 \cdot HCl$

The molecular weight of tramadol hydrochloride is 299.8. 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 tramadol hydrochloride tablet for oral administration contains 50 mg of tramadol hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, glyceryl triacetate, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, polydextrose, polyethylene glycol, sodium lauryl sulfate and titanium dioxide.

CLINICAL PHARMACOLOGY: Pharmacodynamics: Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complimentary 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. 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 has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

Pharmacokinetics: The analgesic activity of tramadol is due to both parent drug and the M1 metabolite (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 2.7 L/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.

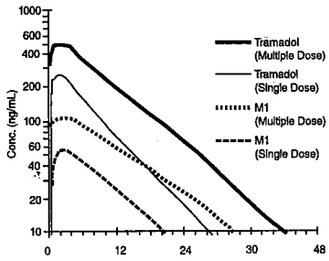


Table 1
Mean (%CV) Pharmacokinetic Parameters for Racemic Tramadol and M1 Metabolite

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)	8.50 (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	18.5 (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, q.i.d. = 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 decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of SEROTONIN re-uptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse events, including seizure (see WARNINGS) and serotonin syndrome.

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).

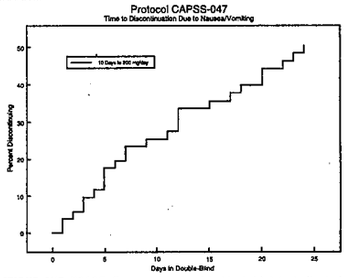
Gender: The absolute bioavailability of tramadol was 73% in males and 79% in females. The plasma clearance was 6.4 mL/min/kg in males and 5.7 mL/min/kg in females following a 100 mg IV dose of tramadol. Following a single oral dose, and after adjusting for body weight, females had a 12% higher peak tramadol 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 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 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 daily.

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.



INDICATIONS AND USAGE: Tramadol hydrochloride tablet is 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 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 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 cautiously in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of tramadol 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 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. (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 with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of tramadol 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.

TRML:R1

APPROVED
JUN 21 2002

Physical Dependence and Abuse: Tramadol hydrochloride may induce psychic and physical dependence of the morphine-type (μ-opioid) (see DRUG ABUSE AND DEPENDENCE). Tramadol should not be used in opioid-dependent patients. Tramadol 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 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 may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- Tramadol hydrochloride should not be taken with alcohol containing beverages.
- Tramadol hydrochloride 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. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of tramadol and carbamazepine is not recommended.

Use with Quinidine: Tramadol is metabolized to M1 by 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/m^2, 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/m^2, respectively.

Pregnancy: ***Teratogenic Effects. Pregnancy Category C:*** Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg or 360 mg/m^2), rats (≥ 25 mg/kg or 150 mg/m^2) and rabbits (≥ 75 mg/kg or 900 mg/m^2) 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/m^2) 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/m^2), rats (up to 80 mg/kg or 480 mg/m^2) or rabbits (up to 300 mg/kg or 3600 mg/m^2) 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/m^2), 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/m^2), 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/m^2 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/m^2 or 1.9 and higher 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, 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 post-dose 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 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 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, acetaminophen 300 mg with codeine phosphate 30 mg, and aspirin 325 mg with codeine phosphate 30 mg, however, the rates of withdrawals due to adverse events appeared to be higher in the tramadol 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	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 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 is associated with craving and tolerance development. Withdrawal symptoms may occur if tramadol 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. 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, 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 tablets 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 to 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 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 Tablet, 50 mg is a white, film-coated, round, biconvex, beveled edge, unscored tablet debossed with **M** on one side of the tablet and **T7** on the other side. They are available as follows:

NDC 0378-4151-01
bottles of 100 tablets
NDC 0378-4151-05
bottles of 500 tablets

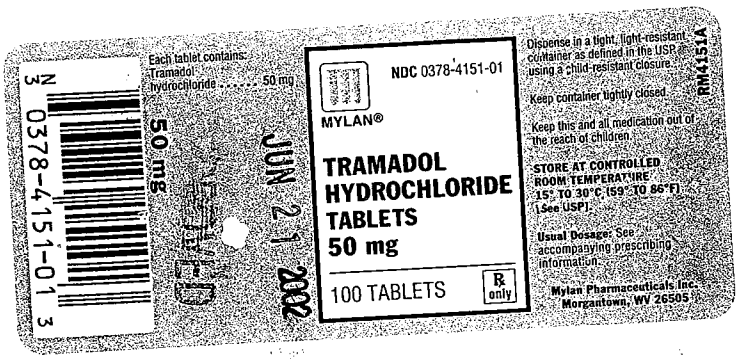
STORE AT CONTROLLED ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F) [see USP].

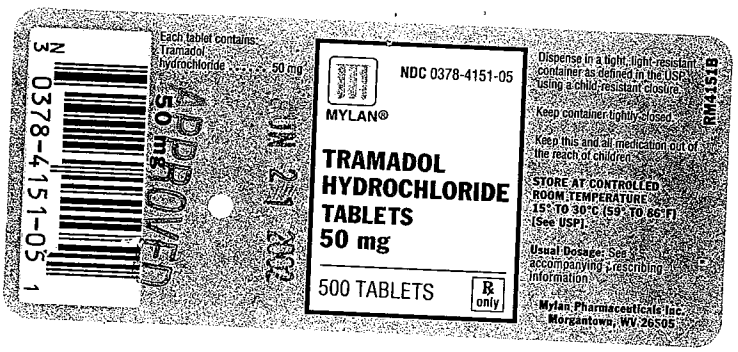
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED JUNE 2002
TRML:R1


Each tablet contains:
Tramadol hydrochloride ..... 50 mg
N 3 0378-4151-01 3
50 mg
APPROVED
JUN 21 2002
NDC 0378-4151-01
MYLAN®
TRAMADOL HYDROCHLORIDE TABLETS 50 mg
100 TABLETS
℞ only
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT CONTROLLED ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F) [See USP].
Usual Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM4151A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N 3 0378-4151-05 1
50 mg
APPROVED
JUN 21 2002
NDC 0378-4151-05
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STORE AT CONTROLLED ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F) [See USP].
Usual Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM4151B

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-986

LABELING REVIEWS

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

ANDA Number: 75-986 Date of Submission: September 3, 2000

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Tramadol Hydrochloride Tablets, 50 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. We acknowledge your Patent Certification and Exclusivity Statements and comments stating that you are not seeking approval for the dosing information protected by the pediatric exclusivity associated with D-44.

   b. We acknowledge that you have included the new titration information under CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections, which was approved on 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 inclusion of this new titration information in your proposed labeling, we defer comment at this time.

   c. Include "[see USP]" to your storage temperature statement.

2. CONTAINER – 100s & 500s

   Refer to the general comment (c) above.

3. INSERT

   a. DESCRIPTION – First paragraph, First sentence:

      Tramadol hydrochloride tablet is a ... [add "tablet"]

   b. INDICATIONS AND USAGE

      See comment under DESCRIPTION.

   c. PRECAUTIONS - Use in the Elderly:

      Revise this subsection heading to read "Geriatric Use".

   d. HOW SUPPLIED

      i. We encourage that you combine the first and second paragraph and revise to read:

         Tramadol hydrochloride tablets, 50 mg is a white, film-coated, round,...

ii. Please note that the innovator has changed the scoring configuration from "unscored" to "scored" for Ultram® tablets, 50 mg. Please change the scoring configuration of your drug product to be same as the innovator's and revise this section accordingly.

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

We will not request final printed insert labeling until we are able to provide adequate guidance regarding resolution of issues associated with the inclusion of this new titration information in your proposed labeling.

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:

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.

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 2987, B.1.2.

4. Exclusivity Data

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. 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.

5. The sponsor's Exclusivity statement is accurate. The firm did not include the titration information protected by D-44, but included the new titration information approved in S-016 to the innovator.

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 general comment (c).

7. DISPENSING STATEMENT

   RLD – Dispense in a tight container.

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

8. PACKAGING CONFIGURATIONS

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

9. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, Page 3403.

10. 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.

11. 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.

12. CLOSURE

Container – HDPE
Closure – 100s & 500s (CRC) [p.3334-3335, B.1.2)

13. Mylan Pharmaceuticals Inc. is the manufacturer of this product. (p.3122, B.1.2)

14. 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,

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Date of Review: 12/12/00 **Date of Submission: 9/3/00**

Primary Reviewer: Chan Park **Date:** 12/13/00

Team Leader: **Date:** 12/13/00

cc:

ANDA: 75-986
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
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Review

(This review is superseded by the one done on 12/12/00)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-986 Date of Submission: September 3, 2000

Applicant's Name: Mylan Pharmaceuticals 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 your Patent Certification and Exclusivity Statements and comments stating that you are not seeking approval for the dosing information protected by the pediatric exclusivity associated with D-44.

   c. We acknowledge that you have included the new titration information under CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections, which was approved on 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 inclusion of this new titration information in your proposed labeling, we defer comment at this time.

   d. Include "[see USP]" to your storage temperature statement.

2. CONTAINER – 100s & 500s

   Refer to the general comment (c) above.

3. INSERT

   a. DESCRIPTION – First paragraph, First sentence:

      Tramadol hydrochloride tablet is a ... [add "tablet"]

   b. INDICATIONS AND USAGE

      See comment under DESCRIPTION.

   c. PRECAUTIONS - Use in the Elderly:

      Revise this subsection heading to read "Geriatric Use".

d. HOW SUPPLIED

i. We encourage that you combine the first and second paragraph and revise to read:

Tramadol hydrochloride tablets, 50 mg is a white, film-coated, round,...

ii. Please note that the innovator has changed the scoring configuration from "unscored" to "scored" for Ultram® tablets, 50 mg. Please change the scoring configuration of your drug product to be same as the innovator's and revise this section accordingly.

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

We will not request final printed insert labeling until we are able to provide adequate guidance regarding resolution of issues associated with the inclusion of this new titration information in your proposed labeling.

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:

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.

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 2987, B.1.2.

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. The sponsor's Exclusivity statement is accurate. The firm did not include the titration information protected by D-44, but included the new titration information approved in S-016 to the innovator.

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 general comment (c).

7. DISPENSING STATEMENT

   RLD – Dispense in a tight container.

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

8. PACKAGING CONFIGURATIONS

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

9. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR

206,et al. See Vol.B.1.2, Page 3403.

10. 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.

11. 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.

12. CLOSURE

Container – HDPE
Closure – 100s & 500s (CRC) [p.3334-3335, B.1.2)

13. Mylan Pharmaceuticals Inc. is the manufacturer of this product. (p.3122, B.1.2)

14. 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: 12/12/00 **Date of Submission: 9/3/00**

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

Team Leader: **Date:** 2/26/01

cc:

ANDA: 75-986
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
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Review

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

ANDA Number: 75-986 Date of Submission: April 23, 2001

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Tramadol Hydrochloride Tablets, 50 mg

Labeling Deficiencies:

1. CONTAINER – 100s & 500s

   Please increase the prominence of expression of strength by increasing the font size when preparing final print.

2. INSERT

   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.

We will not request final printed insert labeling until we are able to provide adequate guidance regarding resolution of issues associated with the inclusion of this new titration information in your proposed labeling.

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. 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 2987, B.1.2.

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

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.

5. 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]

6. DISPENSING STATEMENT

RLD – Dispense in a tight container.

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

7. PACKAGING CONFIGURATIONS

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

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, Page 3403.

9. SCORING

The RLD is scored for both 50 mg & 100 mg strengths.
The ANDA proposes scored 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. The sponsor has changed "unscored" to "scored" in this submission.

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 (CRC) [p.3334-3335, B.1.2)

12. Mylan Pharmaceuticals Inc. is the manufacturer of this product. (p.3122, B.1.2)

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: 8/29/01 **Date of Submission: 4/23/01**

Primary Reviewer: Chan Park **Date:** 8/30/01

Team Leader: **Date:** 8/30/01

cc:

ANDA: 75-986
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: 75-986 Date of Submission: June 13, 2002

Applicant's Name: Mylan Pharmaceuticals 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

Satisfactory in FPL as of 6/13/02 submission (100s - RM4151A; 500s - RM4151B, vol. 3.1)

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of 6/13/02 submission (Rev. June 2002, Code# - TRML:R1, vol.3.1)

REVISIONS NEEDED POST-APPROVAL - INSERT

1. CLINICAL PHARMACOLOGY (Titration Trials, Figure 2)

   Increase the prominence, the legends in particular.

2. PRECUATIONS (Pregnancy, Non-teratogenic Effects) - Last sentence:

   ...1.9 times higher than the... [rather than-"1.9 and higher the"...]

3. DOSAGE AND ADMINISTRATION - First paragraph:

   a. First sentence:

      ...regimen: The total... ["The" rather than "the"]

   b. Last sentence:

      ...6 hours **not to exceed 400 mg/day.** [bold face type]

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 2987, B.1.2.

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 (submitted 6/13/02) and Exclusivity statement (submitted 4/13/01) 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]

7. DISPENSING STATEMENT

RLD – Dispense in a tight container.

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

8. PACKAGING CONFIGURATIONS

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

9. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, Page 3403.

10. 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.

11. CLOSURE

Container – HDPE
Closure – 100s & 500s (CRC) [p.3334-3335, B.1.2)

12. Mylan Pharmaceuticals Inc. is the manufacturer of this product. (p.3122, B.1.2)

13. 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 **Date:** 6/20/02

Acting Team Leader: Lillie Golson **Date:** 6/20/02

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cc:

ANDA: 75-986
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-986

MEDICAL REVIEW

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 1 out 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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-986

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-986

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Ultram. The holder of the approved application is R.W. Johnson. The product is covered by a new dosing exclusivity which expires 8/21/01 and a related PED which expires 2/21/02;however, the applicant is not seeking approval for these dosing schedules.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Tramadol Hydrochloride

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

9. AMENDMENTS AND OTHER DATES:
Original Submission - 9/3/00

10. PHARMACOLOGICAL CATEGORY
Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
[redacted]

13. DOSAGE FORM
Tablet

14. POTENCIES
50 mg

15. CHEMICAL NAME AND STRUCTURE
cis-2-[Dimethylaminomethyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride
cis-2-[Dimethylaminomethyl]-1-(m-methoxyphenyl)cyclohexanol hydrochloride

$C_{16}H_{25}O_2.HCl$ CAS No.3682-47-0 M.W. 299.84

17. COMMENTS

Note: The tablet scoring configuration of the RLD has been changed from non-scored to scored. Comment has been included in deficiency letter.

18. CONCLUSIONS AND RECOMMENDATIONS

Not approvable.

19. REVIEWER: Andrew J. Langowski

DATE COMPLETED: 02/25/01

APPEARS THIS WAY
ON ORIGINAL

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information from

CHEMISTRY REVIEW #1

cc: ANDA 75-986
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-647/ALangowski/02/25/01 3/5/01
HFD-647/GSmith/3/5/01 3/7/01
HFD-617/JMin/3/5/01

F/T by jsm/3/5/01

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TYPE OF LETTER: NOT APPROVABLE - MINOR

1. CHEMISTRY REVIEW NO. 3A

2. ANDA # 75-986

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Ultram. The holder of the approved application is R.W. Johnson. The product is covered by a new dosing exclusivity which expires 8/21/01 and a related PED which expires 2/21/02;however, the applicant is not seeking approval for these dosing schedules.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Tramadol Hydrochloride

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

9. AMENDMENTS AND OTHER DATES:

Original Submission -	9/3/00
Amendment	4/5/01
Amendment	4/23/01
Amendment	7/24/01

10. PHARMACOLOGICAL CATEGORY
Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
C

3

13. DOSAGE FORM
Tablet

14. POTENCIES
50 mg

15. CHEMICAL NAME AND STRUCTURE
cis-2-[Dimethylaminomethyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride
cis-2-[Dimethylaminomethyl]-1-(m-methoxyphenyl)cyclohexanol hydrochloride

$C_{16}H_{25}O_2.HCl$ CAS No.3682-47-0 M.W. 299.84

17. COMMENTS
Methods validation pending.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable pending labeling.

19. REVIEWER: Andrew J. Langowski

DATE COMPLETED: 05/01/01

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CHEMISTRY REVIEW #2 ("3A")

cc: ANDA 75-986
DIV FILE
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Endorsements (Draft and Final with Dates):

HFD-647/ALangowski/6/13/01
HFD-647/GSmith/6/13/01
HFD-617/JMin/6/18/01

1/29/02

F/T by: rad12/27/01

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TYPE OF LETTER:

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-986

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Ultram. The holder of the approved application is R.W. Johnson. The product is covered by a new dosing exclusivity which expires 8/21/01 and a related PED which expires 2/21/02;however, the applicant is not seeking approval for these dosing schedules.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Tramadol Hydrochloride

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

9. AMENDMENTS AND OTHER DATES:

Original Submission -	9/3/00
Amendment	4/5/01
Amendment	4/23/01
Amendment	7/24/01
Amendment	6/13/02

10. PHARMACOLOGICAL CATEGORY
Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
c

13. DOSAGE FORM
Tablet

14. POTENCIES
50 mg

15. CHEMICAL NAME AND STRUCTURE
cis-2-[Dimethylaminomethyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride
cis-2-[Dimethylaminomethyl]-1-(m-methoxyphenyl)cyclohexanol hydrochloride

$C_{16}H_{25}O_2.HCl$ CAS No.3682-47-0 M.W. 299.84

17. COMMENTS
Methods validation acceptable. See comments in addendum dated 06/18/02.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER: Andrew J. Langowski

DATE COMPLETED: 06/18/02

APPEARS THIS WAY
ON ORIGINAL

Addendum Date: 06/18/02

The firm submitted a minor amendment dated June 13, 2002 addressing CMC, Patent and Labeling concerns. The firm submitted a patent certification as provided under Section 505(j)(2)(A)(viii) of the Act that US Patent 6339105 is a method of use patent and that this patent does not claim any of the proposed indications for which the firm seeking approval.

Regarding CMC issues, the applicant states that the application contains information for both a scored and unscored 50 mg tablet. The firm now wishes to withdraw its request for approval of a scored tablet. The amendment provides no changes to CMC controls and that with exception to the tablet description, all of the CMC information in the ANDA pertaining to the manufacture and testing of the scored tablet is also applicable to the unscored tablet.

Regarding the methods validation, notification was received from the FDA District Laboratory in Philadelphia indicating that the methods were suitable for regulatory purpose. It was recommended, however, that the firm revise its resolution calculation for one the related compounds so as to ensure that its calculation was made on the two components, chromatographed in a single chromatogram.

In addition, the applicant must employ a reference standard for ———— and not that of the active ingredient for the determination of the ———— impurity. The firm submitted general correspondence on June 18, 2002 containing a commitment to make the requested revisions with subsequent filing in the first annual report.

APPEARS THIS WAY
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CHEMISTRY REVIEW #3

cc: ANDA 75-986
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Endorsements (Draft and Final with Dates):

HFD-647/ALangowski/6/13/01:06/18/02 A. Langowski 6/20/02
HFD-647/GSmith/6/20/02 6/20/02
HFD-617/JMin/6/20/02 Jean Min 6/20/02

F/T by: jsm/6/20/02

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TYPE OF LETTER: Approval

DIVISION REVIEW SUMMARY

ANDA: 75-986

FIRM: Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown, WV 26504-4310

DOSAGE FORM: Tablet STRENGTH: 50 mg

DRUG: Tramadol Hydrochloride

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable 11/13/00.

BIO STUDY INFORMATION:

METHODS VALIDATION: The field will be requested to conduct the methods validation after the firm's responses have been found satisfactory. Methods validation requested 5/01. Found acceptable 04/25/02; minor revisions requested.

STABILITY:

Note: Stability data were obtained on a container closure configuration used for the exhibit batch that will be unavailable for future production batches. The firm has since submitted some stability data for the product packaged in the proposed configuration and the results are acceptable. In addition, the stability protocol has been revised to include the commitment regarding testing of annual batches of the product packaged in the configuration using [redacted].

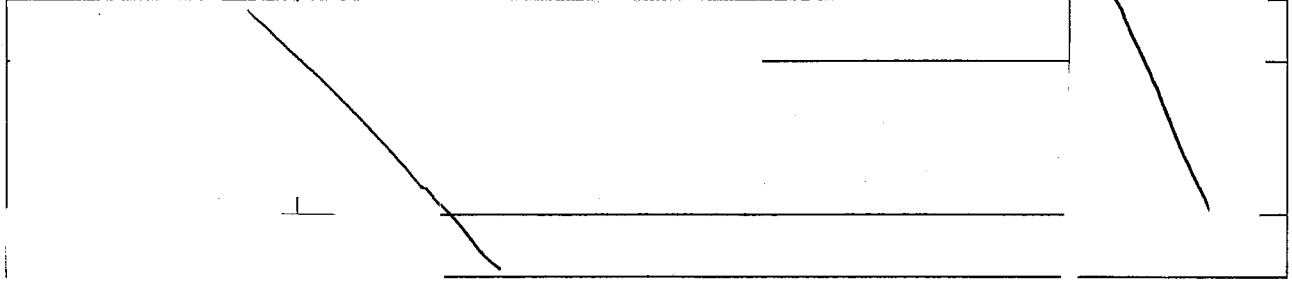
The firm requests an expiration date of 24 months based on the data submitted.

The stability tests and specifications are indicated in the following table:

The stability tests and specification are as follows:

TEST	SPECIFCATION	METHOD
Appearance	White film-coated, round, biconvex, beveled edge tablets debossed with M on one side of the tablet and T7 on the other side	Visual

Dissolution	Media: 900 ml, 0.1N HCl @37 C ± 5C; 2 paddles @ 50 rpm; Q = NLT — % in 30 min



LABELING: Acceptable.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH: See below.

SIZE OF STABILITY BATCHES:

The executed batch record for exhibit lot #2E004G (— tablets) begins on p. 3231.

[ ]

PROPOSED PRODUCTION BATCH:

The intended production batch sizes are — and — tablets. The master batch record for the — tablet batch begins on p. 3166.

The differences between the exhibit batch record and the intended production batch record are outlined on p. 3163. The majority of the changes are minor format changes. The

[ ]

RECOMMENDATION: Approve;

SIGNATURE: Andrew Langowski DATE:6/19/02

Andrew Langowski
6/20/02

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CHEMISTRY DIVISION REVIEW SUMMARY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-986

BIOEQUIVALENCE REVIEWS

TRAMADOL HYDROCHLORIDE
50 mg Tablets
ANDA #75-986
Reviewer: Sikta Pradhan
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Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission Dates:
~~September 9, 2000~~ September 3, 2000
December 7, 2000
~~December 14, 2000~~

REVIEW OF TWO BIOEQUIVALENCE STUDIES AND DISSOLUTION DATA (Electronic Submission)

INTRODUCTION

Tramadol Hydrochloride is a centrally acting synthetic analgesic available as tablets for oral administration.

Type of Submission: Original

Contents of Submission: **Single-dose fasting and non-fasting bioequivalence studies, and dissolution data.**

RLD: Ultram® 50-mg tablets manufactured by Ortho-McNeil . (NDA 20-281).

Indication: For the management of moderate to moderately severe pain.

Recommended Dose: The usual dose is 25 mg daily initially to 50 mg four time a day. A dose of 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day (Electronic PDR, 2000).

Background

A. Pharmacokinetics/Metabolism:

The analgesic activity of Ultram® is due to both parent drug and the O-demethylated M1 metabolite. Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 metabolite are detected in the circulation. Tramadol is well absorbed orally with an absolute bioavailability of 75%. 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. The mean peak plasma concentration of racemic tramadol and M1 occurs at two and three hours, respectively, after administration in healthy adults.

Food Effects: Oral administration of Ultram® with food does not significantly affect its rate or extent of absorption, therefore, Ultram® can be administered without regard to food (Electronic PDR, 2000).

Protocol No.: **TRAM-9813, Single-Dose Fasting Bioequivalence Study Report for Mylan Tramadol HCl Tablets**

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	———
Medical Director:	——— M.D. and ——— M.D.
Scientific Director:	——— Ph.D.
Clinical Study Dates:	07/31/98 to 08/09/98
Analytical Facility	MYLAN PHARMACEUTICALS INC.
Principal Investigator:	Walt Owens, Ph.D.
Analytical Study Dates:	09/16/98 to 10/13/98
Storage Period:	About ten weeks

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	R	T
Product Name:	Ultram	Tramadol hydrochloride tablets
Manufacturer:	Ortho-McNeil	Mylan Pharmaceuticals Inc.
Manufacture Date:	N/A	6/29/98
Expiration Date:	N/A	N/A
Bio Batch Size:		——— tablets
Batch/Lot Number:	BAA1226	2E004G
Potency:	102.2	100.2
Strength:	50 mg	50 mg
Dosage Form:	tablet	tablet
Dose Administered:	100 mg	100 mg
Study Condition:	fasting	fasting
Length of Fasting:	10 hours	10 hours

RANDOMIZATION		DESIGN	
Randomized:	Y	Design Type:	crossover
No. of Sequences:	2	Replicated Treatment Design:	N
No. of Periods:	2	Balanced:	Y
No. of Treatments:	2	Washout Period:	7 days

DOSING		SUBJECTS	
		IRB Approval:	Y
Single or Multiple Dose:	Single	Informed Consent Obtained:	Y
Steady State:	N	No. of Subjects Enrolled:	28
Volume of Liquid Intake:	240 mL	Healthy Volunteers	Y
Route of Administration:	Oral	Sex(es)	Male
		No. of Subjects Completing:	24
Number of Doses:	N/A	No. of Dropouts:	4

Dietary Restrictions: No ingestion of any alcoholic, caffeine- or xanthine-containing food or beverage within 48 hours prior to the initial dose of study medication. Any change in dietary or exercise habits throughout the duration of the study.

Activity Restrictions: Subjects engaged in normal activity for the first 12 hours after drug administration, avoiding both vigorous exertion and complete rest. Subjects did not lie flat except for ECG measurements.

Drug Restrictions: No vitamins within 48 hours prior to the initial dose of study medication. No medication within the last 14 days prior to the initial dose of study medication. No use of any medication known to alter hepatic enzyme activity within 28 days of dosing.

Blood Sampling: At 0 time (pre-dose) and at 0.25, 0.5, 1.0, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12, 16, 20, 24, 30, and 36 hours post-dose.

Study Results

1) Clinical

Adverse Events: Adverse Events: During the study, 19 adverse events (12 events with reference product and 7 events with test product) were reported by 9 of the 28 subjects.

Dropouts:

SUBJECT NO.:	18	4	6	7
REASON:	did not report for Period 2 due to personal reasons that were not study related	discontinued from Period 2 due to an adverse experience	withdrew from the study during Period 2 due to personal reasons that were not study related	Discontinued from Period 1 due to an adverse experience.
PERIOD:	2	2	2	1
REPLACEMENT:	N	N	N	N

Protocol Deviations: None other than minor sampling deviations.

2) Analytical (Not to be released under FOI)

Analytes: Tramadol and O-desmethyl tramadol
Assay Method: HPLC with Fluorescence detection

ANALYTE:	O-DESMETHYLTRAMADOL	TRAMADOL
ASSAY METHOD:	HPLC	HPLC
MATRIX:	plasma	Plasma
INTERNAL STANDARD:	[redacted]	[redacted]

The during study assay validations are presented in Table 1 below:

Table 1. During study Assay Validation for Fasting Study

Parameters	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	a) 12.0, 80.0, 240.0 for tramadol; b) 4.50, 30.0, 90.0 for O-desmethyltramadol	a) 4.0, 8.0, 12.0, 20.0, 40.0, 80.0, 120.0, 160.0, 240.0, 320.0, 400.0 for tramadol; b) 1.50, 3.0, 4.5, 7.5, 15.0, 30.0, 45.0, 60.0, 90.0, 120, 150 for O-desmethyltramadol
Inter-day Precision (% CV)	a) 2.8 - 4.7% for tramadol b) 3.7-5.8% for O-desmethyltramadol	a) 2.4 – 6.9% for tramadol, b) 2.4 - 6.9% for O-desmethyltramadol
Accuracy(%)	a) 90.6 - 92.5% for tramadol b) 95.6 - 97.7% for O-desmethyltramadol	a) 96.3 - 103.0% for tramadol b) 96.5 - 103.2% for O-desmethyltramadol
Linearity (R values)	Greater than 0.98 for both analytes	
Linear Range (ng/mL)	4.0 ng/mL to 400.0 ng/mL for tramadol and, 1.50 ng/mL to 150 .0 ng/mL for O-desmethyltramadol	
Sensitivity/LOQ (ng/mL)	4.00 ng/mL for tramadol and, 1.50 ng/mL for O-desmethyltramadol	
Stability in Plasma at room temperature:	Both analytes stable for 4 hours	
Long-term Frozen stability of plasma	Both analytes stable for 110 days at –70°C	
Extracted analytes (both)	Stable at 20°C for 96 hours	
Freeze/Thaw	Stable at least three cycles	
Specificity	Specific; no interference from endogenous compounds noted in serum blanks or pre-dose subject serum samples.	
Repeat assay:	There were some repeat analyses, but none were because of pharmacokinetic anomaly and against the firm's SOP.	

Comments: Analytical method is acceptable.

3) Pharmacokinetic and Statistical Analysis:

Mean Plasma Concentration: Table 2 (tramadol) and Table 5 (O-desmethyl tramadol), Figure 1

Pharmacokinetic Measures: Tables 3 & 4 (tramadol) and Tables 6 & 7 (O-desmethyl tramadol)

Table 2. Mean Plasma Tramadol Concentrations (ng/mL)
Mean Plasma Concentrations of TRAMADOL (N=24)
Treatment A = Ultram, 50 mg tablet, Dose Administered = 100 mg, fasting
Treatment B = tramadol hydrochloride tablets, 50 mg tablet, Dose Administered = 100 mg, fasting

Time(hours)	Test Mean (B)	Test %CV (B)	Ref Mean (A)	Ref %CV (A)	T/R Ratio (B)/(A)
0	0.	0.	0.	0.	**
0.25	1.44	261.89	0.	0.	**
0.50	53.59	110.06	27.58	83.77	1.944
1.0	202.89	32.16	188.31	31.46	1.077
1.5	251.44	21.86	249.2	23.1	1.009
1.75	253.55	21.13	255.52	21.61	0.992
2.0	247.45	21.75	248.21	21.82	0.997
2.5	227.02	21.38	238.72	24.15	0.951
3.0	216.16	23.53	220.77	23.	0.979
3.5	197.99	24.71	204.24	25.68	0.969
4.0	185.29	25.53	191.07	28.49	0.97
5.0	163.65	27.32	168.73	30.54	0.97
6.0	139.12	32.93	144.22	32.12	0.965
8.0	110.32	34.14	111.93	35.92	0.986
12	65.69	42.71	68.82	46.77	0.955
16	44.85	51.53	45.89	54.1	0.977
20	28.37	57.69	29.21	62.25	0.971
24	18.37	60.55	19.14	67.41	0.959
30	9.71	69.23	10.36	85.46	0.938
36	4.16	104.34	4.88	115.47	0.853

Table 5. Mean Plasma Concentrations of O-DESMETHYLTRAMADOL (N=24)
Treatment A = Ultram, 50 mg tablet, Dose Administered = 100 mg, fasting
Treatment B = tramadol hydrochloride tablets, 50 mg tablet, Dose Administered = 100 mg, fasting

Time(hours)	Test Mean (B)	Test %CV (B)	Ref Mean (A)	Ref %CV (A)	T/R Ratio (B)/(A)
0	0.	0.	0.	0.	**
0.25	1.11	230.32	0.19	350.39	5.836
0.5	16.85	115.08	10.45	104.85	1.612
1.0	45.88	46.24	44.57	49.81	1.029
1.5	59.71	39.36	58.84	40.06	1.015
1.75	61.46	36.12	60.89	39.3	1.009
2.0	61.29	37.36	60.19	37.11	1.018
2.5	58.82	35.39	59.87	36.75	0.982
3.0	57.76	36.11	57.93	34.77	0.997
3.5	55.3	35.31	54.95	34.27	1.006
4.0	52.94	34.53	52.6	33.42	1.006
5.0	47.47	35.79	48.01	33.47	0.989
6.0	43.7	33.71	44.13	32.98	0.99
8.0	36.19	33.44	36.07	31.79	1.003
12	23.89	32.58	24.51	33.47	0.975
16	17.31	31.35	17.42	33.09	0.994
20	11.52	30.35	11.69	34.07	0.986
24	8.02	31.01	8.12	36.45	0.987
30	4.23	37.87	4.39	39.38	0.965
36	1.96	61.19	2.07	66.49	0.946

Table 6. O-DESMETHYLTRAMADOL Pharmacokinetic Parameters
Treatment A = Ultram, 50 mg tablet, Dose Administered = 100 mg, fasting
Treatment B = tramadol hydrochloride tablets, 50 mg tablet, Dose Administered = 100 mg, fasting

Parameter	Test Mean (B)	Test %CV (B)	Ref Mean (A)	Ref %CV (A)	T/R Ratio (B)/(A)
AUCT	718.468	29.882	720.467	30.894	0.997
AUCI	743.402	28.96	746.391	30.036	0.996
CMAX	64.793	35.838	64.932	36.502	0.998
TMAX	2.167	48.677	2.052	32.725	1.056
KEL	0.108	17.575	0.105	16.028	1.024
THALF	6.62	18.001	6.748	16.899	0.981

Table 3. TRAMADOL Pharmacokinetic Parameters
Treatment A = Ultram, 50 mg tablet, Dose Administered = 100 mg, fasting
Treatment B = tramadol hydrochloride tablets, 50 mg tablet, Dose Administered = 100 mg, fasting

Parameter	Test Mean (B)	Test %CV (B)	Ref Mean (A)	Ref %CV (A)	T/R Ratio (B)/(A)
AUCT	2243.773	33.185	2291.99	35.917	0.979
AUCI	2308.778	33.23	2365.701	36.864	0.976
CMAX	269.216	19.973	273.031	20.627	0.986
TMAX	1.635	23.844	1.76	25.293	0.929
KEL	0.11	19.134	0.112	19.026	0.989
THALF	6.494	18.153	6.47	23.169	1.004
Geometric Means:					
AUCT	2125.304		2160.582		0.984
AUCI	2187.077		2225.952		0.983
CMAX	264.365		267.658		0.988

Table 4. Summary Statistics for TRAMADOL
Treatment A = Ultram, 50 mg tablet, Dose Administered = 100 mg, fasting
Treatment B = tramadol hydrochloride tablets, 50 mg tablet, Dose Administered = 100 mg, fasting

B vs A Arithmetic & Geometric Means

Parameter	B	A	Ratio	90% C.I.
AUCI	2309	2366		
AUCT	2244	2292		
CMAX	269	273		
HALF	6.49	6.47		
KEL	0.1103	0.1116		
LNAUCI	7.69	7.71	0.99	95; 103
LNAUCT	7.66	7.68	0.99	95; 104
LNCMAX	5.58	5.59	0.99	95; 103
TMAX	1.64	1.76		

Geometric Means:			
AUCT	684.105	683.555	1.001
AUCI	709.955	710.814	0.999
CMAX	59.584	59.62	0.999

Table 7. Summary Statistics for O-DESMETHYLTRAMADOL
Treatment A = Ultram, 50 mg tablet, Dose Administered = 100 mg, fasting
Treatment B = tramadol hydrochloride tablets, 50 mg tablet, Dose Administered = 100 mg, fasting

B vs A Arithmetic & Geometric Means				90% C.I.
Parameter	B	A	Ratio	
AUCI	743	746		
AUCT	718	720		
CMAX	64.8	64.9		
HALF	6.62	6.75		
KEL	0.1079	0.1054		
LNAUCI	6.57	6.57	1	97; 104
LNAUCT	6.53	6.53	1.01	97; 104
LNCMAX	4.09	4.09	0.99	95; 103
TMAX	2.17	2.05		

Comments: On pharmacokinetic data

1. The pharmacokinetic measures (AUC_t, AUC_i, C_{max}, t_{max} *and* $t_{1/2}$) and confidence intervals of AUC_t, AUC_i *and* C_{max} for tramadol and its O-desmethyl metabolite reported by the firm are found acceptable by the reviewer.

2. The 90% confidence intervals for ln-transformed AUC_t, AUC_i, and C_{max} ratios are within the acceptable limits of 80-125%.

Protocol No.: TRAM-9827, Single-Dose Food Bioequivalence Study Report for Mylan Tramadol HCl Tablets

Study Information

STUDY FACILITY INFORMATION
Clinical Facility: [ ]

Medical Director:	———— M.D. and ———— M.D.
Scientific Director:	———— Ph.D.
Clinical Study Dates:	08/05/98 to 08/21/98
Analytical Facility	MYLAN PHARMACEUTICALS INC.
Principal Investigator:	Walt Owens, Ph.D.
Analytical Study Dates:	10/14/98 to 11/06/98
Storage Period:	About 3 months

TREATMENT INFORMATION

Treatment ID:	A	B	C
Test or Reference:	T	R	T
Product Name:	tramadol hydrochloride tablets	Ultram	Tramadol hydrochloride tablets
Manufacturer:	Mylan Pharmaceuticals Inc.	Ortho-McNeil	Mylan Pharmaceuticals Inc.
Manufacture Date:	6/29/98	N/A	6/29/98
Expiration Date:	N/A	Jan 00	N/A
ANDA Batch Size:	———— Tabs	N/A	———— Tabs
Batch/Lot Number:	2E004G	BAA1226	2E004G
Content Uniformity:	100.2	102.2	100.2
Strength:	50 mg	50 mg	50 mg
Dosage Form:	Tab	Tab	Tab
Dose Administered:	100 mg	100 mg	100 mg
Study Condition:	Fed	Fed	Fasting
Length of Fasting:	N/A	N/A	10 hours
Standardized Breakfast:	Y	Y	N
Breakfast Specifics:	1 buttered English muffin, 1 fried egg, 1 slice of Canadian bacon, 1 slice of American cheese, one serving hashed brown potatoes, 6 ounces of orange juice and 8 ounces of whole milk	1 buttered English muffin, 1 fried egg, 1 slice of Canadian bacon, 1 slice of American cheese, one serving of hashed brown potatoes, 6 ounces of orange juice and 8 ounces whole milk	N/A

RANDOMIZATION		DESIGN	
Randomized:	Y	Design Type:	crossover
No. of Sequences:	6	Replicated Treatment Design:	N
No. of Periods:	3	Balanced:	Y
No. of Treatments:	3	Washout Period:	7 days

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:	N/A	No. of Subjects Plasma Analyzed:	24
Number of Doses:	N/A	No. of Dropouts:	0
Loading Dose:	N/A	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 ingestion of any alcoholic, caffeine- or xanthine-containing food or beverage within 48 hours prior to the initial dose of study medication. Any change in dietary or exercise habits throughout the duration of the study.
Activity Restrictions:	Subjects engaged in normal activity for the first 12 hours after drug administration, avoiding both vigorous exertion and complete rest. Subjects did not lie flat except for ECG measurements.
Drug Restrictions:	No vitamins within 48 hours prior to the initial dose of study medication. No medication within the last 14 days prior to the initial dose of study medication. No use of any medication known to alter hepatic enzyme activity within 28 days of dosing.

Blood Sampling: At 0 time (pre-dose) and at 0.25, 0.5, 1.0, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12, 16, 20, 24, 30, and 36 hours post-dose.

Study Results

Clinical

Adverse Events: There were 10 mild adverse effects (7 events were due to reference product and 3 events were due test product) observed in 5 subjects. However, there was no serious adverse event, which required terminating any subject from the study.

Dropouts: No Dropouts Reported

Analytical (Not to be Released Under FOI)

Within-Study Method Validation

The during study assay validations are presented in Table 8 below:

Table 8. During study Assay Validation for Fasting Study

Parameters	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	**a)** 12.0, 80.0, 240.0 for tramadol; **b)** 4.50, 30.0, 90.0 for O-desmethyltramadol	**b)** 4.0, 8.0, 12.0, 20.0, 40.0, 80.0, 120.0, 160.0, 240.0, 320.0, 400.0 for tramadol; **b)** 1.50, 3.0, 4.5, 7.5, 15.0, 30.0, 45.0, 60.0, 90.0, 120, 150 for O-desmethyltramadol
Inter-day Precision (% CV)	a) 2.7 - 4.3% for tramadol b) 3.1 - 6.7% for O-desmethyltramadol	a) 1.6 – 4.2% for tramadol b) b) 2.3 - 6.2% for O-desmethyltramadol
Accuracy(%)	a) 93.5 - 94.1% for tramadol b) 96.9 - 97.6 for O-desmethyltramadol	c) 96.0 - 102.7% for tramadol d) 94.5 - 102.5% for O-desmethyltramadol
Linearity (R values)	Greater than 0.98 for both analytes	
Linear Range (ng/mL)	4.0 ng/mL to 400.0 ng/mL for tramadol and, 1.50 ng/mL to 150 .0 ng/mL for O-desmethyltramadol	
Sensitivity/LOQ (ng/mL)	4.00 ng/mL for tramadol and, 1.50 ng/mL for O-desmethyltramadol	

Stability in Plasma at room temperature:	Both analytes stable for 4 hours
Long-term Frozen stability of plasma	Both analytes stable for 110 days at –70°C
Extracted analytes (both)	Stable at 20°C for 96 hours
Freeze/Thaw	Stable at least three cycles
Specificity	Specific; no interference from endogenous compounds noted in serum blanks or pre-dose subject serum samples.

Comment: No sample analysis was rejected because of pharmacokinetic anomaly. Analytical method is acceptable.

Pharmacokinetic and Statistical Analysis:

TABLE 9. Post-prandial Single-dose in vivo Bioequivalence of Tramadol Plasma (mean) Concentrations [ng/ml] Versus Time (CV%) in 24 Subjects

	Treatment						
	A (Tramadol HCl #2E004G fed)		B (Utram #BAA1226 fed)		C(Tramadol HCl #2E004G fast)		
	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	A VS B P(|T|>t)
Draw Time							
0.00 hours	0.00	.	0.00	.	0.00	.	----
0.25 hours	0.68	285.27	0.96	369.62	0.45	340.13	0.6783
0.50 hours	39.61	110.92	21.37	167.87	0.07	73.95	0.0837
1.00 hours	169.50	56.13	110.51	89.12	216.84	30.54	0.0107
1.50 hours	232.56	25.47	198.59	45.73	233.95	20.90	0.0685
1.75 hours	248.69	21.50	220.48	36.40	233.68	18.79	0.0718
2.00 hours	246.68	20.25	231.65	27.16	232.61	16.37	0.1938
2.50 hours	239.93	20.81	238.24	19.04	221.97	18.61	0.7978
3.00 hours	229.04	21.77	234.52	18.79	208.54	17.99	0.4231
3.50 hours	210.03	23.35	219.34	20.22	192.29	17.94	0.1096
4.00 hours	194.43	23.65	205.38	21.62	180.57	19.31	0.0858
5.00 hours	168.65	24.65	178.64	24.84	159.18	21.67	0.0461
6.00 hours	141.57	29.47	148.95	27.81	137.06	22.73	0.1089
8.00 hours	114.00	32.58	118.30	30.01	107.73	27.53	0.1725
12.00 hours	68.13	44.44	71.36	40.96	65.36	35.32	0.2429
16.00 hours	45.43	53.20	47.05	49.36	43.49	44.04	0.3826

20.00 hours	29.44	57.60	29.92	53.56	28.23	53.74	0.7335
24.00 hours	21.11	69.69	21.15	60.17	20.08	54.00	0.9748
30.00 hours	10.08	89.59	10.13	81.60	9.56	83.84	0.9366
36.00 hours	4.99	126.56	4.56	130.04	4.54	123.38	0.4338

TABLE 10. Post-prandial Single-dose in vivo Bioequivalence of O-Desmethyltramadol Plasma (mean) Concentrations [ng/ml] Versus Time (cv%) in 24 Subjects

	Treatment						
	A (Tramadol HCl #2E004G fed)		B (Utram #BAA1226 --fed)		C (Tramadol HCl #2E004G fast)		f
	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	A VS B P(|T|>t)
Draw Time							
0.00 hours	0.00	.	0.00	.	0.00	.	----
0.25 hours	0.00	.	0.34	489.90	0.42	201.08	0.2927
0.50 hours	6.32	93.99	4.01	193.82	14.38	78.11	0.2929
1.00 hours	28.42	60.09	21.17	99.47	40.54	37.49	0.0560
1.50 hours	41.91	40.59	36.95	60.33	46.93	31.27	0.1335
1.75 hours	46.82	41.56	42.11	50.22	48.27	30.91	0.1285
2.00 hours	47.36	38.90	46.07	43.94	50.17	33.64	0.5335
2.50 hours	48.99	36.67	50.05	37.52	50.40	32.83	0.4133
3.00 hours	49.64	35.03	52.22	35.78	49.44	32.47	0.0830
3.50 hours	48.60	35.22	51.82	33.65	48.08	31.98	0.0073
4.00 hours	47.39	35.39	50.52	33.81	46.78	32.40	0.0144
5.00 hours	44.00	33.04	47.73	36.28	42.70	32.24	0.0145
6.00 hours	40.41	32.38	43.59	32.18	39.99	32.20	0.0015
8.00 hours	34.24	29.48	36.58	31.43	33.36	32.74	0.0053
12.00 hours	23.64	27.85	25.75	28.74	23.43	29.35	0.0070
16.00 hours	16.75	26.45	18.31	25.33	17.02	28.62	0.0071
20.00 hours	11.52	26.19	12.25	24.23	11.74	25.21	0.1029
24.00 hours	7.99	26.14	8.51	26.19	8.27	24.26	0.1209
30.00 hours	3.86	36.65	4.20	35.57	4.07	30.78	0.1928
36.00 hours	1.67	79.30	1.90	54.90	1.66	70.88	0.3581

TABLE 11. MEAN (%CV) TRAMADOL PHARMACOKINETIC PARAMETERS IN TWENTY-FOUR HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 100 MG (2 x 50 MG) DOSE OF TRAMADOL HCL TABLETS IN A FOOD STUDY
(Protocol TRAM-9827)

Parameter	Arithmetic Mean A = Mylan (Fed)	Arithmetic Mean B = Ultram® (Fed)	Arithmetic Mean C =Mylan (Fast)	Ratio (A/B)	Ratio (A/C)	LSMEAN Ratio (A/B)
AUCL (ng x hr/mL)	2295 (33.1)	2301 (29.6)	2210 (28.5)	1.00	1.04	1.00
AUCI (ng x hr/mL)	2368 (34.2)	2374 (30.6)	2282 (29.6)	1.00	1.04	1.00
CPEAK (ng/mL)	276 (22.7)	273 (22.0)	255 (17.9)	1.01	1.08	1.03
KEL (hr^{-1})	0.1135 (13.1)	0.1155 (15.2)	0.1143 (15.5)			
HALF (hr)	6.21 (13.5)	6.15 (16.5)	6.22 (17.9)			
TPEAK (hr)	2.03 (29.1)	2.33 (33.5)	1.63 (29.7)			

*Ratio (A/B) = $e^{[\text{LSMEAN of LNA - LSMEAN of LNB}]}$

TABLE 12. MEAN (%CV) *O*-DESMETHYLTRAMADOL PHARMACOKINETIC PARAMETERS IN TWENTY-FOUR HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 100 MG (2 x 50 MG) DOSE OF TRAMADOL HCL TABLETS IN A FOOD STUDY
(Protocol TRAM-9827)

Parameter	Arithmetic Mean A = Mylan (Fed)	Arithmetic Mean B = Ultram® (Fed)	Arithmetic Mean C =Mylan (Fast)	Ratio (A/B)	Ratio (A/C)	LSMEAN Ratio (A/B)
AUCL (ng x hr/mL)	651 (27.1)	688 (26.6)	663 (27.5)	0.95	0.99	0.95
AUCI (ng x hr/mL)	676 (25.8)	713 (25.5)	686 (26.4)	0.95	0.98	0.96
CPEAK (ng/mL)	53.4 (35.1)	56.0 (36.0)	53.6 (33.3)	0.95	1.00	0.96
KEL (hr^{-1})	0.1108 (16.2)	0.1106 (16.3)	0.1147 (15.4)			
HALF (hr)	6.42 (16.8)	6.43 (16.8)	6.19 (16.5)			
TPEAK (hr)	2.66 (39.2)	3.00 (42.6)	2.22 (31.9)			

*Ratio (A/B) = $e^{[\text{LSMEAN of LNA - LSMEAN of LNB}]}$

TABLE 13. QUANTITATIVE COMPOSITION OF TRAMADOL HYDROCHLORIDE TABLETS, 50MG

ACTIVE COMPONENT	MG PER UNIT
Tramadol Hydrochloride	50.0
INACTIVE COMPONENTS:	
Colloidal Silicon Dioxide, NF	
Mannitol, USP,	
Microcrystalline Cellulose,	
Croscarmellose Sodium, NF	

Dissolution

The firm has conducted dissolution testing using the following dissolution conditions:

CONDITIONS: Dissolution Medium: 0.1 N HCl, 900 mL @ 37 C^0

Apparatus : 2 (paddles)

Speed: 50 rpm

Sample Times: 10, 20, and 30 minutes

Limits: NLT — % (*Q*) in 30 minutes

The results of the dissolution testing are presented below in Table 14:

Table 14. Dissolution Profile Summary of Tramadol Hydrochloride Tablets, 50mg

	10 minutes	20 minutes	30 minutes
Mylan, Lot 2E004G			
UNnSCORED TABLETS			
Mean	92%	95%	97%
Range			
RSD	9.5%	7.4%	5.0%
Ultram®, Lot BAA1226			
SCORED TABLETS			
Mean	70%	100%	101%
Range			
RSD	4.9%	1.2%	0.9%

The dissolution conditions used by the company were not acceptable to the Agency. Upon the Division's request, the firm provided additional dissolution testing data (see Table 15) on the test and reference products as a telephone amendment dated December 7, 2000, using the following recommended method:

Apparatus: USP I (basket), 100 rpm
Medium: 900 mL of 0.1 N HCl at 37 °C
Sampling Times: 10, 20, 30 and 45 minutes

Furthermore, the test product is unscored tablet but the reference drug is now supplied as a scored tablet. Therefore, the firm was advised (by telephone communication) to manufacture scored tablets and conduct the comparative dissolution testing on the scored test tablets versus the unscored test tablets using the Agency recommended dissolution conditions.

On December 14, 2000, the firm has provided additional dissolution testing data (see Table 15) on the test (scored) and reference (scored) products as an addendum to amendment dated December 7, 2000.

Table 15

Test Products: Tramadol Hydrochloride, 50 mg Tablets, Lot # 2E004G (Unscored) and Lot# R1H3992 (Scored) Reference Products: Ultram® 50 mg Tablets, Lot #BAA1226 (Uscored) and Lot #CPA2848 (Scored)						
Assay methodology: HPLC						
Results of dissolution testing (percentage dissolved in minutes):						
Sampling time (min)	Test product Tramadol Hydrochloride Lot # 2E004G Unscored Tablets			Reference Product Ultram® Lot #BAA1226 Unscored Tablets		
	Mean %	Range %	%CV	Mean %	Range %	%CV
10	99		1.5	78		5.6
20	100		1.5	103		2.2
30	100		1.6	103		2.1
45	100		1.7	103		2.2
Results of dissolution testing (percentage dissolved in minutes):						
Sampling time (min)	Test product Tramadol Hydrochloride Scored Tablets Lot #R1H3992			Reference Product Ultram® Scored Tablets Lot #CPA2848		
	Mean %	Range %	%CV	Mean %	Range %	%CV
10	102		1.9	71		7.0
20	102		1.6	103		1.6
30	103		1.8	101		2.0
45	103		1.7	103		1.5

Comments:

1. The single-dose fasting and non-fasting bioequivalence studies conducted by Mylan Pharmaceuticals Inc. on its Tramadol Hydrochloride, 50 mg, Lot # 2E004G, comparing it to Ultram® 50-mg Tablets, Lot # BAA1226 have been found acceptable by the Division of Bioequivalence.

2. **Dissolution testing using the Agency recommended dissolution method** (Specifications: NLT —% (Q) in 30 minutes) **is acceptable.**

RECOMMENDATIONS

1. The single-dose fasting and non-fasting bioequivalence studies conducted by Mylan Pharmaceuticals Inc. on its Tramadol Hydrochloride, 50 mg, Lot #2E004G, comparing it to Ultram® 50-mg Tablets, Lot # BAA1226 have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Mylan's Tramadol Hydrochloride 50-mg tablets are bioequivalent to the reference product Ultram® 50-mg tablets manufactured by Ortho-McNeil.

2. The firm has conducted an acceptable dissolution testing on its Tramadol Hydrochloride 50-mg Tablets, Lot # 2E004G (unscored) and Lot #R1H3992 (scored).

3. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The 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 products should meet the following interim specifications:

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

4. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing, and the application is approvable.

Sikta Pradhan

Sikta Pradhan, Ph.D.
Review Branch I
Division of Bioequivalence

RD INITIALED YHUANG
FT INITIALED YHUANG Date: 12/18/2000

Concur: Barbara M. Davit Date: 12/22/00
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75986S2D.900(original, duplicate), HFD-652 (Huang, Pradhan), HFD-650 (Director), Drug File, Division File
Draft: 11/29/00; Final: 12/18/00

FIGURE 1

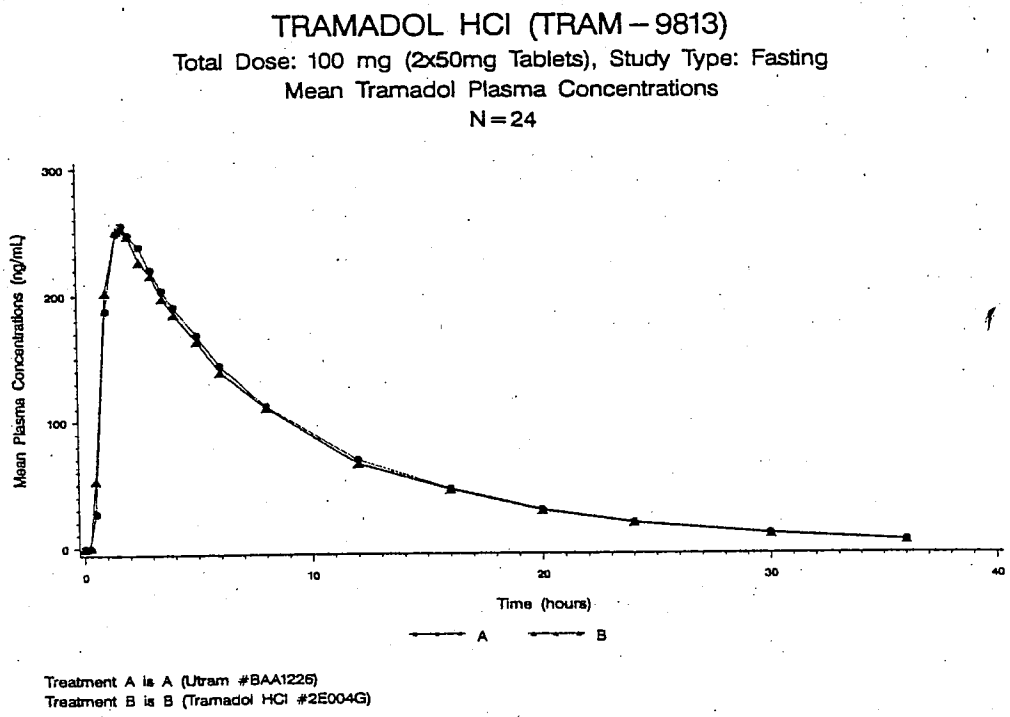
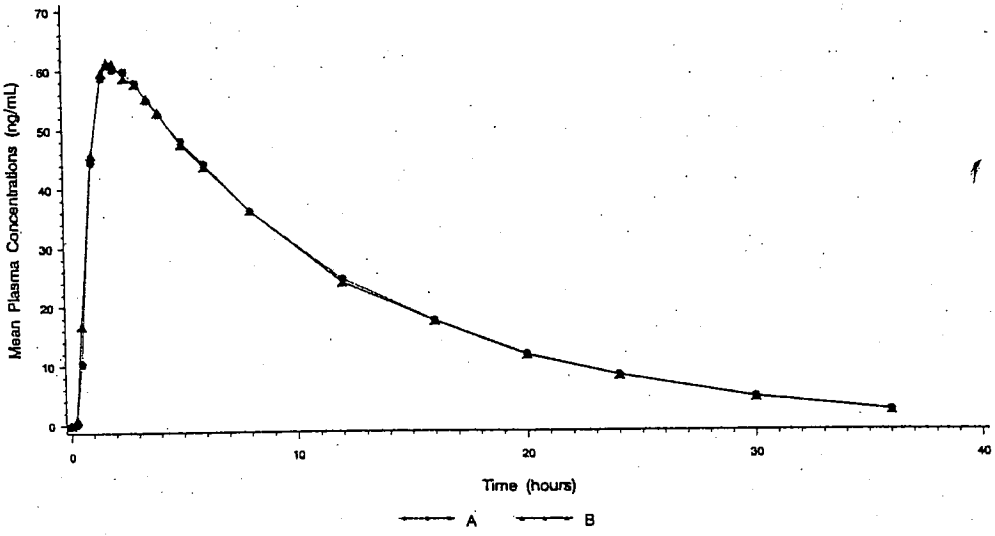

TRAMADOL HCl (TRAM – 9813)
Total Dose: 100 mg (2x50mg Tablets), Study Type: Fasting
Mean Tramadol Plasma Concentrations
N = 24
Mean Plasma Concentrations (ng/mL)
300
200
100
0
0
10
20
30
40
Time (hours)
A
B
Treatment A is A (Utram #BAA1226)
Treatment B is B (Tramadol HCl #2E004G)

FIGURE 2

TRAMADOL HCl (TRAM – 9813)
Total Dose: 100 mg (2x50mg Tablets), Study Type: Fasting
Mean 0 – desmethyltramadol Plasma Concentrations
N = 24



Treatment A is A (Utram #BAA1226)
Treatment B is B (Tramadol HCl #2E004G)

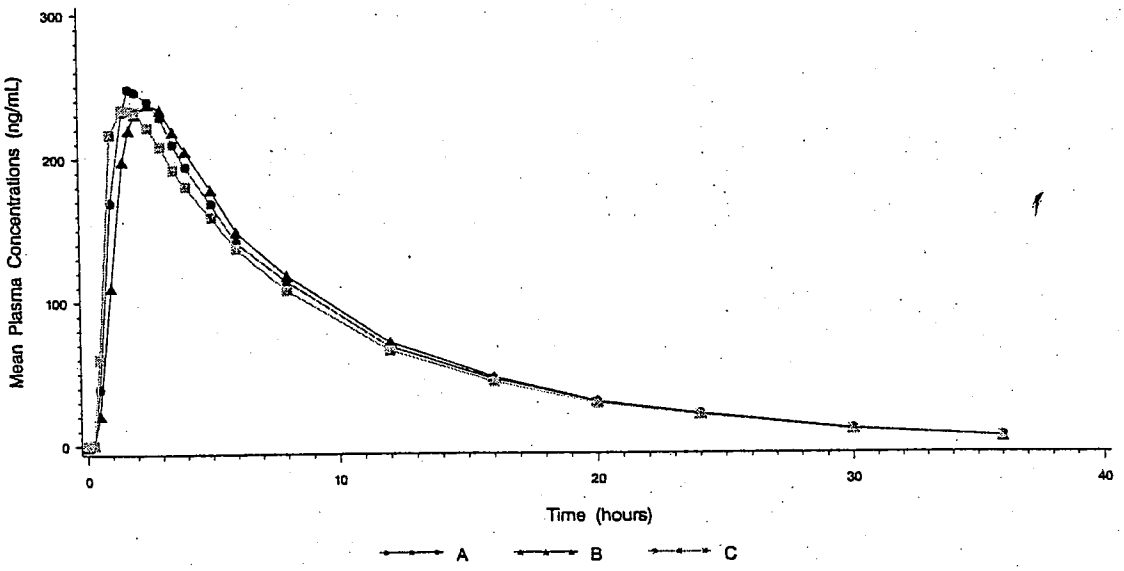
FIGURE 3

TRAMADOL HCl (TRAM – 9827)

Total Dose: 100 mg (2x50mg Tablets), Study Type: Fed

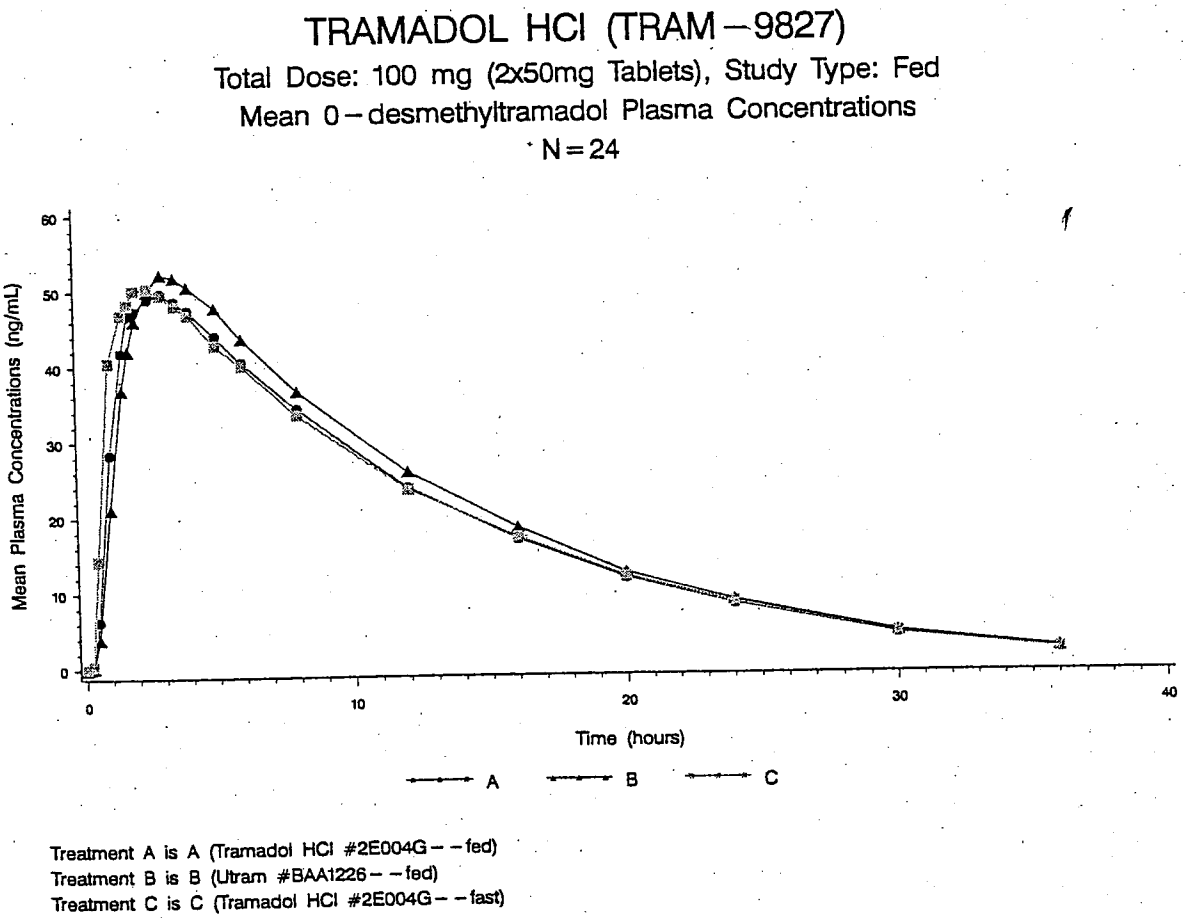
Mean Tramadol Plasma Concentrations

N = 24



Treatment A is A (Tramadol HCl #2E004G – – fed)
Treatment B is B (Utram #BAA1226 – – fed)
Treatment C is C (Tramadol HCl #2E004G – – fast)

FIGURE 4



Treatment A is A (Tramadol HCl #2E004G--fed)
Treatment B is B (Utram #BAA1226--fed)
Treatment C is C (Tramadol HCl #2E004G--fast)

2.1 Pradhan, S.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:75-986 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Tramadol Hydrochloride Tablets, 50 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

We acknowledge that the following dissolution testing method has been incorporated into your manufacturing controls and stability program:

The 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 products should meet the following interim specifications:

Not less than — % (Q) of the labeled amount of tramadol 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 regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation in not approvable.

Sincerely yours,

Barbara Myers Saint

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

CC: ANDA 75-986
ANDA DUPLICATE
DIVISION FILE
S. Pradhan

Endorsements: (Draft and Final with Dates)
HFD-652/S Pradhan
HFD-652/YC Huang 12/18/2000
HFD-617/K Scardina
for HFD-650/Dale Conner 12/22/00
V:\firmsam\Mylan\ltrs&rev\75986SDA.900

Printed in Final on 12/18/00

BIOEQUIVALENCY – **Acceptable** Submission Dates: 09/03/2000

1. **FASTING STUDY** (STF) oic **Strength: 50 mg**

Outcome: **AC**

2. **FOOD STUDY** (STP) oic **Strength: 50 mg**

Outcome: **AC**

3. **STUDY AMENDMENT** (STA) oic Strength: **50 mg**
(Amendment dated 12/7/00 on dissolution testing)

Outcome: **AC**

4. **STUDY AMENDMENT** (STA) oic Strength: **50 mg**
(Addendum to amendment, dated 12/14/00 on dissolution testing)

changed to "new correspondence", 12/14/00 no credit assigned BMD 12/22/00

Outcome: **AC**

Outcome Decisions:
AC - Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-986 SPONSOR : Mylan
DRUG AND DOSAGE FORM : Tramadol HCl Tablets
STRENGTH(S) : 50 mg
TYPES OF STUDIES : Fasting Study & Non-Fasting Study
CINICAL STUDY SITE(S) : See Review
ANALYTICAL SITE(S) : See Review

STUDY SUMMARY : 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 : Sikta Pradhan BRANCH : I
INITIAL : Sikta Pradhan DATE : 12-18-00

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : DATE : 12/18/2000

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

INITIAL : Barbara M Davit DATE : 12/22/00

3.1
P. Chan

TRAMADOL HYDROCHLORIDE
50 mg Tablets
ANDA #75-986
Reviewer: Sikta Pradhan
V:\firmsam\Mylan\ltrs&rev\75986A.401

Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission Dates:
April 5, 2001

REVIEW OF AN AMENDMENT

INTRODUCTION

This submission contains the dissolution data on the test scored and unscored tablets and on the reference scored tablets. The dissolution testing was conducted using the Agency recommended dissolution conditions presented below:

Apparatus: USP I (basket), 100 rpm
Medium: 900 mL of 0.1 N HCl at 37 °C
Sampling Times: 10, 20, 30 and 45 minutes

The firm originally conducted the in vivo bioequivalence study and the in vitro dissolution testing on its unscored test product comparing it with the unscored reference product. However, recently the reference drug is being marketed as scored tablets. Therefore, the firm was advised by telephone communication to manufacture scored test tablets and conduct the comparative dissolution testing on scored test tablets, unscored test tablets and scored reference tablets using the Agency recommended dissolution conditions.

The firm had provided the Agency requested dissolution testing data as an amendment (dated 12/14/00) on the test (scored & unscored) and reference (scored and unscored) products. The dissolution data are presented below:

2E004G (unscored) and Lot #R1H3992 (scored), comparing them with the scored reference tablets.

2. The bioequivalence study had previously been found acceptable (review dated 12/22/00).

3. Therefore, no further action is needed on this submission.

Sikta Pradhan

Sikta Pradhan, Ph.D.
Review Branch I
Division of Bioequivalence

RD INITIALED YHUANG
FT INITIALED YHUANG Date: 4/24/2001

Concur: Date: 4/24/2001
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75986A.401(original, duplicate), HFD-652 (Huang, Pradhan), HFD-650 (Director), Drug File, Division File

Draft: 4/16/01 Final: 4/18/01

Test Products: Tramadol Hydrochloride, 50 mg Tablets, Lot # 2E004G (Unscored) and Lot# R1H3992 (Scored) Reference Products: Ultram® 50 mg Tablets, Lot #BAA1226 (Uscored) and Lot #CPA2848 (Scored)						
Assay methodology: HPLC						
Results of dissolution testing (percentage dissolved in minutes):						
Sampling time (min)	Test product Tramadol Hydrochloride Lot # 2E004G Unscored Tablets			Reference Product Ultram® Lot #BAA1226 Unscored Tablets		
	Mean %	Range %	%CV	Mean %	Range %	%CV
10	99		1.5	78		5.6
20	100		1.5	103		2.2
30	100		1.6	103		2.1
45	100		1.7	103		2.2
Results of dissolution testing (percentage dissolved in minutes):						
Sampling time (min)	Test product Tramadol Hydrochloride Scored Tablets Lot #R1H3992			Reference Product Ultram® Scored Tablets Lot #CPA2848		
	Mean %	Range %	%CV	Mean %	Range %	%CV
10	102		1.9	71		7.0
20	102		1.6	103		1.6
30	103		1.8	101		2.0
45	103		1.7	103		1.5

COMMENTS:

1. The firm had already conducted acceptable dissolution testing (as currently requested by the Agency, see FDA Comment #6 of the current submission) on its Tramadol Hydrochloride 50-mg Tablets, Lot #

CC: ANDA 75-986
ANDA DUPLICATE
DIVISION FILE
S. Pradhan

Endorsements: (Draft and Final with Dates)
HFD-652/S Pradhan
HFD-652/YC Huang 4/18/2001
HFD-617/K Scardina 4/25/01
HFD-650/Dale Conner
V:\firmsam\Mylan\ltrs&rev\75986A.401

Printed in Final on

BIOEQUIVALENCY – **Acceptable** Submission Dates: 4/5/01

STUDY AMENDMENT (STA) OIC Strength: **50 mg**
(Amendment dated 4/5/01 on dissolution testing)

Outcome: **AC**

Outcome Decisions:
AC - Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-986 SPONSOR: Mylan Pharmaceuticals, Inc

DRUG AND DOSAGE FORM: Tramadol Hcl Tablets

STRENGTH(S): 50 mg

TYPES OF STUDIES:

CLINICAL STUDY SITE(S):

ANALYTICAL SITE(S):

STUDY SUMMARY: previously found acceptable (see review)

DISSOLUTION: Acceptable (scored vs unscored) tablets

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic ____	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	
For cause ____		
other ____		

PRIMARY REVIEWER: (NAME) BRANCH:

INITIAL: Sirisha Radhakrishnan DATE: 4/24/01

TEAM LEADER: (NAME) BRANCH:

INITIAL: [illegible] DATE: 4/24/2001

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

for INITIAL: [signature] DATE: 4/24/2001

V:\division\bio\signoff.doc

Dissolution data presented in this review have already been reviewed earlier. (Review date 12/22/2000)

[signature] 4/24/2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-986

ADMINISTRATIVE DOCUMENTS

75986

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.

APPEARS THIS WAY
ON ORIGINAL

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

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Record of Telephone Conversations
For Tramadol

4.1

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

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OGD APPROVAL ROUTING SUMMARY

ANDA # 75-986 Applicant Mylan
Drug Tramadol Hydrochloride Tablets Strength 50 mg

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

REVIEWER:

1. Project Manager Jeen Min
Review Support Branch 9

DRAFT RECEIPT
Date 12/26/01
Initials JM

FINAL ACTION
Date 12/28/01
Initials JM

Application Summary:

Original Rec'd date 9/3/00
Date Acceptable for Filing 9/8/00 ✓
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 11/13/00
Date of Office Bio Review 4/24/01
Date of Labeling Approv. Sum
Date of Sterility Assur. App. 2/PA
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 12/29/02
Initials [illegible]

Date 1/29/02
Initials [illegible]

Revised review. 1/29/02
CMC satisfactory.

3. Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review)

Date
Initials

Date
Initials

Refer to ANDA for the first generic CMC audit.

4. Pat Beers Block
Supv., Review Support Branch
EER Status: Refer to DLPS review below.

Date
Initials

Date
Initials

Bioequivalence sites:
Clinical site:
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐ pending
Date of status:
Reason:

Analytical site:
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐pending
Date of status:
Reason:

Bioequivalence office level sign off:

Labeling Status:

Microbiology status:

Patent Certification:
Controlled Correspondence/Cit.Pet:
Comments: RLD =

REVIEWER:	DRAFT RECEIPT	FINAL ACTION
5. Gregory Davis Supv., Reg. Support Branch	Date 1/30/02 Initials RW	Date 1/30/02 Initials RW for

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐ Pediatric Exclusivity System
If Para. IV Certification- did applicant No Relevant Patents Date Checked Previously granted
Notify patent holder/NDA holder Yes ☐ No ☐ Nothing Submitted ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Written request issued ☐
Has case been settled: Yes ☐ No ☐ N/A Study Submitted ☐
Date settled:
Is applicant eligible for 180 day N/A RLD Ultram tablets 50mg NDA 20-281
Generic Drugs Exclusivity for each strength: RLD Johnson Pharmaceutical Research Institute
Yes ☐ No ☒
Comments: There are no unexpired patents on this drug product. There are two unexpired exclusivities (D-44 and D-63) expiring on 2/21/02 and 6/23/03. Hyban has addressed the D-44 exclusivity and the D-63 exclusivity.

6. Peter Rickman Acting Director, DLPS	Date 1/30/02 Initials RW	Date 1/30/02 Initials RW for

Comments: Acceptable ES dated 11/13/00 (Verified 1/30/02). No O.A.I. alerts noted. Bioequivalence studies (fasting; fed) on unscored tablets found acceptable 12/18/00. Dissolution studies also acceptable. Clinical studies performed by Analytical Methods validation is pending. Labeling remains under review.
Data found acceptable 4/24/01. Office-level bio endorsed 12/29/00. Scored vs unscored tablet dissolution
Office-level bio endorsed 4/24/01. CMC acceptable 1/29/02.

7. Robert L. West Acting Deputy Director, OGD	Date 1/30/02 Initials RW	Date 1/30/2002 Initials Robert West

Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☒
Comments: Documentation has been received from the review division stating that the D-44 exclusivity should be included in the generic labeling, but that the D-63 exclusivity may be "carved out." We are currently awaiting publication of the "Discontinued Labeling Guidance" in final format. Once that occurs, we will request FPL (package insert) for unscored tablets.
Recommend: ISSUE an approvable letter at this time

8. Gary Buehler Acting Director, OGD	Date 1/30/02 Initials RW	Date 1/30/2002 Initials RW for

Comments:

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 1/30/02 Initials JM	Date 1/30/02 Initials JM

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

Applicant notification:
2:50 pm Time notified of approval by phone 2:55 pm Time approval letter faxed

FDA Notification:
N/A Date e-mail message sent to "OGD approvals" account
1/30/02 Date Approval letter copied to "//cder/drugapp" directory

v:\reports\approval\approvrou

Unscored revised to scored tablets

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

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, unlike 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.

APPEARS THIS WAY
ON ORIGINAL

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: 75-986

APPLICANT: Mylan Pharmaceuticals Inc.

Date of Issuance of Approvable Letter: January 30, 2002

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

Final-printed Labeling (FPL) Reviewed and Found Acceptable On: June 20, 2002

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

Methods Validation Status: Completed and acceptable.

Has Applicant Initiated Changes to the CMC Section of the Application Since Issuance of the Approvable Letter? Minor Changes which were reviewed and found satisfactory in Chemistry Review #3.

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 6/21/200

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:

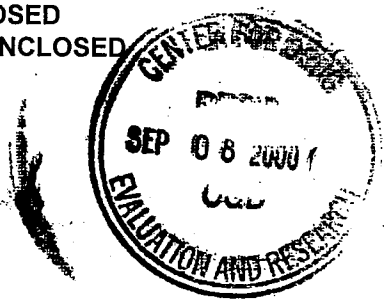
ANDA 75-986

CORRESPONDENCE

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

September 3, 2000

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED



Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: TRAMADOL HYDROCHLORIDE TABLETS, 50mg

Dear Mr. Buehler:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None
Established Name: Tramadol Hydrochloride
This application consists of a total of 19 volumes.
Archival Copy - 8 volumes.
Review Copy - 9 volumes.
Technical Section For Chemistry - 2 volumes.
Technical Section For Pharmacokinetics - 7 volumes.
Analytical Methods - 2 extra copies; 1 volume each.

NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a set of data diskettes for the bioequivalence studies conducted in support of this application. In addition, the diskettes providing the Bioequivalence Electronic Submission ESD (BA/BE) EVA will be forwarded to the Agency within the 30 day grace period.

It should be noted that this Abbreviated New Drug Application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. Pursuant to this guidance, Mylan commits to resolve any issues identified in the methods validation process after approval.

This application provides for the manufacture of Tramadol Hydrochloride Tablets, 50mg. All operations in the manufacture, packaging, and labeling of the drug product are performed by Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

As required by 21 CFR 314.94(d)(5), we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310, or via facsimile at (304) 285-6407.

Sincerely,

for

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

CENTER FOR DRUG EVALUATION AND RESEARCH
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SEP 0 8 2000
OGD

ANDA 75-986

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

OCT 25

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 3, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 8, 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:

Jeen Min
Project Manager
(301) 827-5849

Sincerely yours,

for

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

ANDA 75-986
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 _____ date 10/24/00
HFD-615/PPatel, CSO _____ date 10/23/00
Word File V:\Firmsam\Mylan\ltrs&rev\75986.ACK
F/T PMP 10/23/00
ANDA Acknowledgment Letter!

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

ORIG AMENDMENT
N/AB
BIOAVAILABILITY

December 7, 2000

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT
(in-vitro dissolution data enclosed)

RE: TRAMADOL HYDROCHLORIDE TABLETS, 50MG
ANDA 75-986
(RESPONSE TO NOVEMBER 27, 2000 TELEPHONE REQUEST)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to a request for additional information pertaining to this application which was conveyed to Mylan by telephone on November 27, 2000.

In the November 27 telephone call, Ms. Krista Scardina from the Division of Bioequivalence requested that we provide additional dissolution profile data on Mylan's Tramadol Tablets, 50mg and the referenced listed drug (Ultram® Tablets, 50mg), using the following dissolution conditions:

Dissolution Medium:	900mL of 01.N HCl @ 37°C
USP Apparatus:	1 (basket) @ 100rpm
Sample Times:	10, 20, 30, and 45 minutes

As the bioequivalence studies were conducted with unscored tablets and the reference listed drug is now supplied as a scored tablet we were asked to provide the requested dissolution profile data on both unscored and scored tablets.

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Enclosed is the requested dissolution profile data which has been obtained on the following finished product lots:

- Tramadol Hydrochloride Tablets, 50mg – Mylan Lot 2E046 (unscored) (biolot)
- Ultram® Tablets, 50mg – McNeil Lot BAA1226 (unscored) (biolot)
- Ultram® Tablets, 50mg – McNeil Lot CPA2848 (scored)

Mylan is currently completing the manufacture and testing of an additional lot of Tramadol Hydrochloride Tablets, 50mg, which will be scored. Except for the score this lot is identical, both in composition and manufacturing process, to the exhibit lot provided in the ANDA (Lot 2E046). Dissolution profile data on this lot, obtained in accordance with the conditions requested by the Division of Bioequivalence, will be forwarded to the Agency in the next 7 to 10 days.

This amendment is submitted in duplicate. Should you have any questions or require additional information, please contact the undersigned by telephone at (304) 599-2595, ext. 6600 or by facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

Enclosures

cc: Ms. Krista Scardina (via facsimile)

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

75-986

October 2, 2000

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

RE: TRAMADOL HYDROCHLORIDE TABLETS
50 mg

BIOEQUIVALENCE ELECTRONIC SUBMISSION ESD

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) for the referenced product that was submitted to the Agency on September 3, 2000. Please find enclosed a diskette providing the electronic submission, ESD, for the bioequivalence studies (fasting study TRAM-9813 and post-prandial study TRAM-9827) that were submitted in the ANDA. A copy of Mylan's declaration that the data contained on the electronic bioequivalence diskette is identical to the paper submission except as noted in the companion document is presented in Attachment 1.

Should you have any questions or require additional information, please contact the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

CAM/Enclosures

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Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5454
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
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Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

NEW CORRESP

BIOAVAILABILITY

December 14, 2000

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT (ADDENDUM)
(in-vitro dissolution data enclosed)

RE: TRAMADOL HYDROCHLORIDE TABLETS, 50MG
ANDA 75-986
(Addendum to December 7, 2000 Bioequivalence Amendment)

Dear Mr. Buehler:

Reference is made to the ANDA identified above and to our December 7, 2000 Bioequivalence Amendment to this application in which we provided additional information in response to a telephone request of November 27, 2000.

In our amendment of December 7, 2000 we provided dissolution profile data for Tramadol HCl Tablets, 50mg, using the revised dissolution conditions specified in the Agency's November 27, 2000 telephone request. Data was provided for Mylan tablets without a score and for the reference listed drug, Ultram® Tablets, with and without a score. In the cover letter to the December 7 amendment it was noted that Mylan was in the process of completing the manufacture and testing of a lot of 50mg Tramadol HCl Tablets containing a score, and that the requested dissolution data from this lot would be forwarded to the Agency within the next 7 to 10 days.

Enclosed, as noted, is dissolution profile data on Lot R1H3992 of Mylan 50mg Tramadol HCl Tablets, manufactured with a score. Except for the score, this lot is identical, both in composition and manufacturing process, to the exhibit lot provided in the ANDA (Lot 2E046). The enclosed data provides results of dissolution testing conducted using the conditions indicated in the November 27, 2000 telephone request. For completeness and comparative purposes we have also provided the results of dissolution testing conducted using the conditions provided for in the original ANDA submission.

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Department—Fax Numbers
Accounting (304) 285-6403
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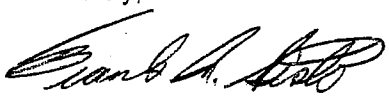
Business Development (304) 599-7284
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

This addendum to our December 7, 2000 amendment is submitted in duplicate. Should you have any questions or require additional information, please contact the undersigned by telephone at (304) 599-2595, ext. 6600 or by facsimile at (304) 285-6407.

Sincerely,



Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

Enclosures

cc: Ms. Krista Scardina (via facsimile)

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

April 5, 2001

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT

ORIG AMENDMENT
N/AB

RE: TRAMADOL HYDROCHLORIDE TABLETS, 50MG
ANDA 75-986
RESPONSE TO AGENCY CORRESPONDENCE DATED MARCH 8, 2001

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to the comments pertaining to this application from the Division of Bioequivalence, which were included in the facsimile from the Agency, dated March 8, 2001. In response to the March 8th comments from the Division of Bioequivalence, Mylan wishes to amend this application as follows:

FDA COMMENT 1. The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

We acknowledge that the following dissolution testing method has been incorporated into your manufacturing controls and stability program:

The 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 products should meet the following interim specifications:

> Not less than – % (Q) of the labeled amount of tramadol 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.

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APR 06 2001
EVALUATION

Department—Fax Numbers		Information	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

MYLAN RESPONSE: As acknowledged by the Division of Bioequivalence, the dissolution testing requirements for Tramadol Hydrochloride Tablets, 50mg have already been incorporated into Mylan's manufacturing controls and stability program. No further action is, therefore, considered necessary.

Mylan also acknowledges that the bioequivalence comments provided in the March 8, 2001 communication are preliminary and that these comments may be revised after review of the entire application.

For your reference, a copy of the Division of Bioequivalence comments contained in the Agency correspondence, dated March 8, 2001 is provided in Attachment A. Responses to the chemistry comments contained in this correspondence have been forwarded in a separate amendment to this application, also submitted on April 5, 2001.

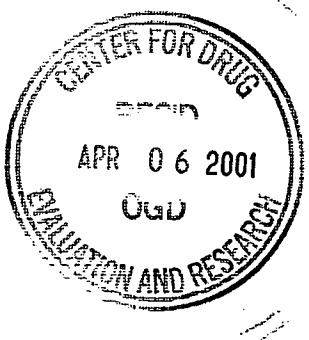
This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosures



MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

April 5, 2001

ORIG AMENDMENT
N/AM

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT
(CMC AND LABELING INFORMATION ENCLOSED)

RE: TRAMADOL HYDROCHLORIDE TABLETS, 50MG
ANDA 75-986
RESPONSE TO AGENCY CORRESPONDENCE DATED MARCH 8, 2001

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review and to the Agency's comments which were provided to Mylan by facsimile in a correspondence dated March 8, 2001. Reference is also made to a March 21, 2001 telephone conversation between Mr. Jeen Min of your Office and representatives from Mylan, and a March 22, 2001 follow-up telephone call from Mr. Jeen Min in which we clarified one of the comments outlined in the March 8, 2001 letter. In response to the Agency's comments of March 8th, which are provided in Attachment Q, and our telephone discussions of March 21 and 22, Mylan wishes to amend this application as follows.

A. CHEMISTRY DEFICIENCIES

FDA COMMENT 1:

MYLAN RESPONSE:

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Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

4-10-01

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of trade secret and/or

confidential commercial

information from

4/5/2001 MYLAN LETTER

(CMC + LABELING AMENDMENT)

B. REGARDING LABELING DEFICIENCIES

MYLAN RESPONSE: Mylan acknowledges the labeling comments contained in the Agency's March 8, 2001 correspondence and the Agency's current position with regard to the inclusion of titration information in the labeling. Based on the Agency's current position Mylan would like to defer responding to the labeling comments until final resolution has been reached regarding the inclusion of the new titration information in the product labeling.

Mylan would like to request that this current amendment, responding to the Agency's CMC comments, be entered into the review queue so that the review clock can be reactivated.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

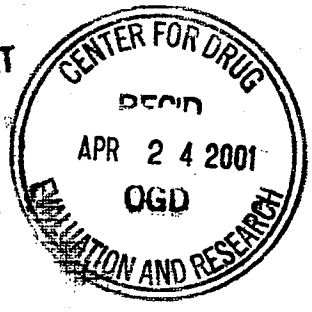
Enclosure

NAI 5/7/01

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

N/AF

ORIG AMENDMENT



April 23, 2001

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT
PATENT/EXCLUSIVITY AMENDMENT

RE: ANDA 75-986; TRAMADOL HYDROCHLORIDE TABLETS, 50MG
Response to Agency Correspondence Dated March 8, 2001

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review and to the Agency's comments which were provided to Mylan by facsimile in a correspondence dated March 8, 2001. Reference is also made to Mylan's April 5, 2001 "Minor Amendment" that provided Mylan's responses to the CMC issues raised in the Agency's March 8th correspondence. However, in the April 5th Minor Amendment, Mylan deferred response to the Agency's comments on labeling and exclusivity statements based upon the Agency's comments in the March 8, 2001 letter which implied that no formal resolution had been reached with regard to the Agency's position on the inclusion of titration information in the labeling. At this time, Mylan is amending the referenced application with an updated Patent Certification and Exclusivity Statement and revised labeling that address the Agency's comments and the dose titration information.

Mylan filed its first patent certification and exclusivity information on September 3, 2000 in the original application. The information provided in the original patent certification and exclusivity information was correct at the time of filing. Subsequent to the filing of Mylan's original submission, the holder of the referenced drug obtained an additional dosing exclusivity. Accordingly, an amended patent certification and exclusivity statement is provided in Attachment 1 that certifies that the referenced product is now covered by a New Dosing Schedule exclusivity (D-63) which expires December 23, 2002 and a related PED exclusivity which expires June 23, 2003. The amended certification further notes that both exclusivities are for a dosing schedule for which Mylan is not currently seeking approval.

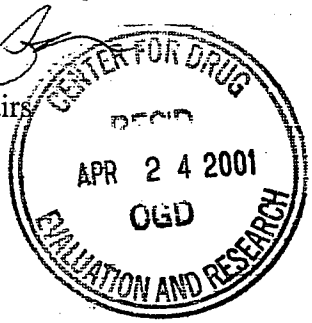
MW 4/23/01

Mylan revised the product labeling to remove references to the dosing schedules covered by exclusivities (D-44 and D-63) for which Mylan is not currently seeking approval. In addition, the enclosed labeling incorporates the revisions requested in the Agency's correspondence of March 8, 2001. A copy of this correspondence is provided in Attachment 2 for the convenience of the reviewer. Four copies of the revised draft bottle labels and outsert are provided in Attachment 5. In order to facilitate the review of this labeling, Attachment 3 contains a side-by-side comparison of the revised bottle labels to those previously submitted and Attachment 4 contains a side-by-side comparison of the revised outsert (TRML:RX2) to the outsert that was previously submitted (TRML:RX1). It is noted that prior to approval of this application, the Agency may find the color or other factors in the final printed labeling unacceptable and may request further changes to the labeling. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs



Enclosures

ABM/tlr

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

APR 23 2001

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: TRAMADOL HYDROCHLORIDE TABLETS, 50mg
ANDA #75-986
PATENT AMENDMENT

Dear Mr. Buehler:

Mylan previously filed its original patent certification and exclusivity information, which was correct as of the date of filing. This current amendment is submitted to address exclusivity filings by the holder of the referenced drug which were filed subsequent to Mylan's original submission. The exclusivity information identified herein is in addition to that set forth in the original submission. All patent and exclusivity information set forth in the original submission remains intact and this letter is merely an update to reflect newly filed exclusivity data.

Mylan certifies that according to the exclusivity information published by the FDA in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (20th Edition through Cumulative Supplement 12), the referenced product is covered by a New Dosing Schedule exclusivity (D-63) which expires December 23, 2002 and a related PED which expires June 23, 2003. Both exclusivities are for a dosing schedule for which Mylan is not currently seeking approval.

Mylan will market its Tramadol Hydrochloride Tablets, 50 mg upon approval of this application.

Sincerely,

Dawn Beto

Dawn J. Beto, Esq.
Corporate Counsel

DJB/pp

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

N/AA

July 24, 2001

ORIG AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

GRATUITOUS AMENDMENT
(CMC INFORMATION ENCLOSED)

RE: TRAMADOL HYDROCHLORIDE TABLETS, 50MG
ANDA 75-986

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review. Mylan wishes to amend the application to provide a revised Limit of ——— for the drug substance, Tramadol Hydrochloride (Attachment A). The revisions to the procedure are as follows:

1. [redacted]

2. [redacted]

3. [redacted]

Prior to submission of the original ANDA, the procedure was inadvertently not corrected to provide the above revisions. The procedure was subsequently revised to provide an accurate procedure for the Method Validation requested by the Agency on May 25, 2001. Mylan acknowledged in the Method Validation submitted on June 5, 2001, that the procedure was revised and would be submitted as an amendment to the application.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECEIVED
JUL 26 2001
OGD

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Vincent Mancinelli II for

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosures

APPEARS THIS WAY
ON ORIGINAL

Park, Chan H

From: Park, Chan H
Sent: Tuesday, June 11, 2002 11:12 AM
To: 'Amiller@mylanlabs.com'
Subject: 75-986 (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
	'Amiller@mylanlabs.com'	
	Park, Chan H	Delivered: 6/11/02 11:12 AM

APPEARS THIS WAY
ON ORIGINAL

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 13, 2002

MINOR AMENDMENT –
REQUEST FOR FINAL APPROVAL
(CMC, Labeling and Patent Information Enclosed)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

RE: TRAMADOL HYDROCHLORIDE TABLETS, 50MG
ANDA 75-986

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above and to the Agency's letter dated January 30, 2002, which indicated that this application was Approvable (see Attachment 1). As indicated in the January 20, 2002 letter, final ANDA approval could not be granted until issues involving the approved labeling for the reference listed drug, Ultram® Tablets, and related exclusivity were resolved. Reference is also made to Agency correspondence received by electronic mail on June 11, 2002 indicating that resolution had been reached on the content of a package insert that represents safe and effective labeling for generic Tramadol Hydrochloride Tablets (see Attachment 2).

As requested in the June 11, 2002 correspondence, provided in Attachment 3 is a patent certification as provided under Section 505(j)(2)(A)(viii) of the Act indicating that U.S. Patent No. 6,339,105 is a method of use patent and that this patent does not claim any of the proposed indications for which we are seeking approval. Accordingly, this certification is consistent with the product labeling presented herein. Please note that Mylan previously addressed the exclusivity (D-63) associated with this patent on April 23, 2001 (Attachment 4).

In regards to Chemistry, Manufacturing, and Controls, Mylan's ANDA contains information for both a scored and unscored presentation of Tramadol Hydrochloride Tablets, 50mg. The original bioequivalence studies were conducted using unscored tablets. With this amendment, Mylan wishes to withdraw our request for approval of a scored tablet without prejudice to future refiling. This amendment provides notification that no changes to the Chemistry, Manufacturing, and Controls have been made since the application received Approvable status. Except for the tablet description, all of the CMC information in the ANDA pertaining to the manufacture and testing of the scored tablet is also applicable to the unscored tablet. Mylan commits to update all applicable documentation to reflect the change in product description (i.e., unscored) prior to release and distribution of commercial product and to submit this revised documentation in the product's first post approval Annual Report. Provided in Attachment 5 is updated drug product stability data for unscored Tramadol Tablets stored at 25°C/60%RH for 36 months.

RECEIVED
JUN 14 2002
OGD / CDER

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Regulatory Affairs	(304) 285-6407
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Sales & Marketing	(304) 598-3232

As requested, Mylan has revised its prescribing information pursuant to the labeling for the reference listed drug provided in the Agency's June 11, 2002 correspondence (Attachment 2). Enclosed in Attachment 8 are twelve (12) copies of the revised final printed outsert (Code TRML:R1; revised June 2002) and of the following final printed bottle labels:

50mg	100 tablets	Code RM4151A
	500 tablets	Code RM4151B

Attachment 6 contains a side-by-side comparison of Mylan's final printed outsert (Code TRML:R1) with Mylan's previously submitted draft outsert (Code TRML:RX2). A side-by-side comparison of the final printed bottle labels to Mylan's previously submitted draft bottle labels are provided in Attachment 7.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Tal for

Frank R. Sisto
Executive Vice President
Regulatory Affairs and Generic Drug Development

FRS/dn

Enclosure

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 18, 2002

GENERAL CORRESPONDENCE

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

RE: TRAMADOL HYDROCHLORIDE TABLETS, 50MG
ANDA 75-986

Dear Mr. Buehler:

Reference is made to our pending Abbreviated New Drug Application (ANDA) identified above and to a telephone call received on June 18, 2002, from Mr. Andrew Langowski, of your Office regarding our Methods Validation documentation submitted in support of this application.

In response to Mr. Langowski's telephone call, Mylan would like to commit to evaluate the following proposed changes to the drug substance analytical methods for ——————— — and ———————. Upon completion of the evaluation, Mylan commits to revise the methods accordingly and submit the revised methods in the first post approval Annual Report.

1. [
2. [ ]

This correspondence is submitted in duplicate. Should you require additional information or have any questions regarding this correspondence, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Farr for

Frank R. Sisto
Executive Vice President
Regulatory Affairs and Generic Drug Development

FRS/dn

Enclosure

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JUN 1 9 2002
OGD / CDER

G:\PROJECT\ANDA\TRAMADOL-HCL-TABS\GeneralCorrespondence61802.doc

Department—Fax Numbers

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Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Maintenance & Engineering	(304) 598-5411	Research & Development	(304) 285-6409
		Medical Unit	(304) 598-5445	Sales & Marketing	(304) 598-3232