CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-977

Name: Tramadol Hydrochloride Tablets, 50 mg

Sponsor: TEVA Pharmaceuticals USA

Approval Date: June 19, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-977

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-977

APPROVAL LETTER

ANDA 75-977

JUN 19 2002

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

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 15, 2002, and to your amendments dated February 5, February 26, May 24, and June 11, 2002.

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

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

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

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

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

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

Sincerely yours,

Gary Buehler 6/19/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-977
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-640/Mpineiro-Sanchez/6/18/02;6/19/02
HFD-647/GJSmith/6/18/02;6/19/02
HFD-617/J.Min/6/19/02
HFD-613/C.Park/6/18/02
HFD-613/L.Golson/6/18/02

Robert West
6/19/2002

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F/T by: rlw/6/19/02

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-977

APPROVABLE LETTER

ANDA 75-977

JAN 15 2002

Teva Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O Box 1090
North Wales, PA 19454

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 February 22, April 4, June 14, and October 4, 2001.

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

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

This is not an approval letter. This drug product may not be marketed without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 301(d) of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under Section 505 of the Act and will not be listed in "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), published by the agency.

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

Sincerely yours,

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

cc: ANDA 75-977
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-640/M.Pineiro-Sanchez/ For Mahmoud Farahani 12,28,01
HFD-647/G.Smith/ D. Roselle 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 / (OK per Bob West)

F/t by rad12/27/01
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Robert L West 1/8/2002

APPROVABLE

cmc satisfactory, Lilavati Bayne 12/31/01.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-977

LABELING

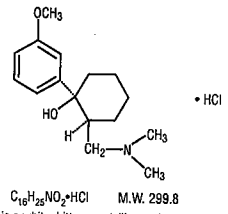
APPROVED
JUN 19 2002

TRAMADOL HYDROCHLORIDE TABLETS, 50 mg

0058 Rev. L 6/2002

DESCRIPTION

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



$C_{16}H_{25}NO_2 \cdot HCl$ M.W. 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. Tramadol hydrochloride tablets contain 50 mg of tramadol hydrochloride and are white in color. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, sodium starch glycolate 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 complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

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

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

Apart from analgesia, tramadol 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.

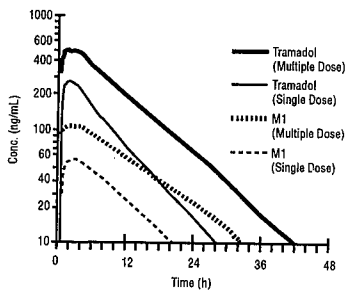


Table 1
Mean (%CV) Pharmacokinetic Parameters for Racemic Tramadol and M1 Metabolite

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 with food does not significantly affect its rate or extent of absorption, therefore, tramadol 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 Interaction**).

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, paroxetin 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 tablets have 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 tablets 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.

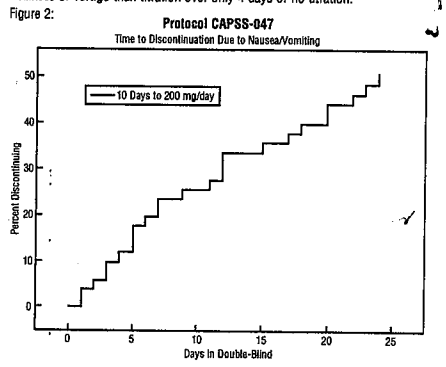
Tramadol has been studied in three long-term controlled trials involving a total of 820 patients, with 530 patients receiving tramadol. Patients with a variety of chronic painful conditions were studied in double-blind trials of one to three months duration. Average daily doses of approximately 250 mg of tramadol hydrochloride tablets 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 dose of 200 mg (50 mg q.i.d.), attained in 50 mg increments every 3 days, was found to result in fewer discontinuations due to dizziness or vertigo than titration over only 4 days or no titration.

Figure 2:

Protocol CAPSS-047
Time to Discontinuation Due to Nausea/Vomiting



INDICATIONS AND USAGE

Tramadol is indicated for the management of moderate to moderately severe pain in adults.

CONTRAINDICATIONS

Tramadol 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 within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol 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 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 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. 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 (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 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 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 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 is discontinued abruptly. (See **DRUG ABUSE AND DEPENDENCE.**) These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication.

Physical Dependence and Abuse

Tramadol 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 may complicate the clinical assessment of patients with acute abdominal conditions.

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

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

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

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

Use With Carbamazepine
Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. 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 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 with **cimetidine** does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the tramadol 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 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 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 is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours postdose was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg of M1.

Pediatric Use
The safety and efficacy of tramadol 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 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 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 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 Tablets 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 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 during clinical trials and/or reported in post-marketing experience. A causal relationship between tramadol 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 be increased to 12 hours, with a maximum daily dose of 200 mg. Since only 7% of an administered dose is removed by hemodialysis, **dialysis patients** can receive their regular dose on the day of dialysis.
- The recommended dose for adult patients with **cirrhosis** is 50 mg every 12 hours.
- In general, dose selection for an elderly patient over 65 years old should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. For elderly patients **over 75 years** old, total dose should not exceed 300 mg/day.

HOW SUPPLIED
Tramadol Hydrochloride Tablets, 50 mg, are available as white, film-coated, unscored, oval-shaped tablets, debossed "93" on one side and debossed "58" on the other side. They are available in bottles of 100 and 1000.

Store at controlled room temperature between 15° and 30°C (59° and 86°F) [see USP].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. L 6/2002

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature between 15° and 30°C (59° and 86°F) [see USP].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Rev. A 6/2001

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

APPROVED

NDC 0093-0058-10

TRAMADOL HYDROCHLORIDE Tablets **50 mg**

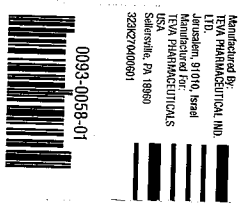
Each tablet contains:
Tramadol Hydrochloride 50 mg

JUN 19 2002

℞ only

1000 TABLETS

TEVA



Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature between 15° and 30°C (59° and 86°F) [see USP].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Rev. A 6/2001

Manufactured By:
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Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
3298270400601

JUN 19 2002

APPROVED

NDC 0093-0058-01
TRAMADOL HYDROCHLORIDE
Tablets
50 mg

Each tablet contains:
Tramadol Hydrochloride 50 mg

℞ only

100 Tablets

TEVA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-977

LABELING REVIEWS

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

ANDA Number: 75-977 Date of Submission: September 3, 2000

Applicant's Name: TEVA Pharmaceuticals USA

Established Name: Tramadol Hydrochloride Tablets, 50 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

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

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

   b. Add the term "[see USP]" to the storage temperature statement .

2. CONTAINER – 100s & 1000s

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

   b. Please assure that the established name and expression of strength appear most prominent on the final printed labels.

3. INSERT

   a. GENERAL

      i. Refer to the general comment (a) above (CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections).

      ii. Please note that USAN names are common nouns and should be treated as such in the text of labeling (*i.e.*, lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

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

   b. DESCRIPTION

      i. First paragraph:

         ...tablet is a centrally... [rather than "tablets"]

      ii. Include the molecular formula.
      iii. Second paragraph – Penultimate and last sentences:

...tablets. [redacted] contain 50 mg of tramadol hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide...

c. PRECAUTIONS – Use in the Elderly:

Revise this subsection heading to read "Geriatric Use".

d. ADVERSE REACTIONS

i. Incidence 1% to less than 5%, possibly... (Urogenital):

Delete one of the two periods after the word "retention".

ii. Incidence less than 1%, possibly... (Central Nervous System):

Delete the period after the word "concentration,".

e. HOW SUPPLIED

i. 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.

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

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

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

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

[redacted]

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 pages 3643 & 3646, B.1.2.

4. Exclusivity Data

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

D-44 (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. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   Both 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 (b).

6. DISPENSING STATEMENT

   RLD – Dispense in a tight container.

   ANDA - Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

7. PACKAGING CONFIGURATIONS

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

8. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.3, P.3985

9. SCORING

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

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

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

11. CLOSURE

Container – HDPE
Closure – 100s & 1000s (Non-CRC Metal Screw Cap) [see p.3923, B1.3]

12. Teva pharmaceutical is the manufacturer for this drug product. (p.3783, B.1.2)

13. ADVERSE REACTIONS

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

Hi Yoon,

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

---

Date of Review: 10/20/00 **Date of Submission: September 3, 2000**

Primary Reviewer: Chan Park **Date:** 12/6/00

Team Leader: **Date:**

12/6/00

cc:

ANDA: 75-977
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Review

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(This review supersedes the review done on 10/20/00)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-977 Date of Submission: September 3, 2000

Applicant's Name: TEVA Pharmaceuticals USA

Established Name: Tramadol Hydrochloride Tablets, 50 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

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

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

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

   c. Add the term "[see USP]" to the storage temperature statement .

2. CONTAINER – 100s & 1000s

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

   b. Please assure that the established name and expression of strength appear most prominent on the final printed labels.

3. INSERT

   a. GENERAL

      i. Refer to the general comment (a) above (CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections).

      ii. Please note that USAN names are common nouns and should be treated as such in the text of labeling (*i.e.*, lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

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

b. DESCRIPTION

i. First paragraph:

...tablet is a centrally... [rather than "tablets"]

ii. Include the molecular formula.

iii. Second paragraph – Penultimate and last sentences:

...tablets, ——————— contain 50 mg of tramadol hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide...

c. PRECAUTIONS – Use in the Elderly:

Revise this subsection heading to read "Geriatric Use".

d. ADVERSE REACTIONS

i. Incidence 1% to less than 5%, possibly... (Urogenital):

Delete one of the two periods after the word "retention".

ii. Incidence less than 1%, possibly... (Central Nervous System):

Delete the period after the word "concentration,".

e. HOW SUPPLIED

i. 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.

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

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

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

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

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

NOTES/QUESTIONS TO THE CHEMIST:

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 pages 3643 & 3646, 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. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   Both 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 (b).

6. DISPENSING STATEMENT

   RLD – Dispense in a tight container.

   ANDA - Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

7. PACKAGING CONFIGURATIONS

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

8. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.3, P.3985

9. SCORING

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

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

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

11. CLOSURE

Container – HDPE
Closure – 100s & 1000s (Non-CRC Metal Screw Cap) [see p.3923, B1.3]

12. Teva pharmaceutical is the manufacturer for this drug product. (p.3783, B.1.2)

13. ADVERSE REACTIONS

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

Hi Yoon,

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

---

Date of Review: 10/20/00 **Date of Submission: September 3, 2000**

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

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

cc:

ANDA: 75-977
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: 75-977 Date of Submission: April 4, 2001

Applicant's Name: TEVA Pharmaceuticals USA

Established Name: Tramadol Hydrochloride Tablets, 50 mg

Labeling Deficiencies:

INSERT

1. 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.

2. 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 the differences of dosing information between your proposed labeling and that of the reference listed drug.

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

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

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

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

FOR THE RECORD:

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

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

3. The container labels are satisfactory in DRAFT as of 4/4/01 submission.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 3643 & 3646, B.1.2.

5. Patent Data

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

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

Exclusivity Data

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

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

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

Both 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, with a child-resistant closure (as required).

8. PACKAGING CONFIGURATIONS

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

9. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.3, P.3985

10. 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 firm has changed the tablet from "unscored" to "scored" to be the same as the revised RLD tablet.

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 & 1000s (Non-CRC Metal Screw Cap) [see p.3923, B1.3]

13. Teva pharmaceutical is the manufacturer for this drug product. (p.3783, B.1.2)

14. 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: 8/27/01 **Date of Submission: 4/4/01**

Primary Reviewer: Chan Park **Date:** 8/28/01

Team Leader: **Date:** 8/28/01

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cc:

ANDA: 75-977
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\75977na2.LABELING.doc
Review

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

ANDA Number: 75-977 Date of Submission: June 11, 2002 X Feb 5, 02, May 24, 02

Applicant's Name: TEVA Pharmaceuticals USA

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 & 1000s

Satisfactory in FPL as of ~~4/4/01~~ 10 cHP submission (TP.Rev. A 6/2001, vol.3.1)

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of 6/11/02 submission (Rev. L 6/2002, vol.4.1)

REVISIONS NEEDED POST-APPROVAL - INSERT

1. GENERAL

   Replace "tramadol" with "tramadol hydrochloride" when referring to a specific dose of tramadol HCL throughout the text.

2. INDICATIONS AND USAGE

   Tramadol hydrochloride tablet is... [rather than "Tramadol is..."]

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 pages 3643 & 3646, 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

The sponsor has submitted a revised patent certification regarding "6,339,105" on 2/26/02.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

Both 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, with a child-resistant

closure (as required).

7. PACKAGING CONFIGURATIONS

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

8. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.3, P.3985

9. SCORING

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

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

10. CLOSURE

Container – HDPE
Closure – 100s & 1000s (Non-CRC Metal Screw Cap) [see p.3923, B1.3]

11. Teva pharmaceutical is the manufacturer for this drug product. (p.3783, B.1.2)

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

Date of Review: 6/18/02 **Date of Submission: 6/11/02** 215/00 / 6/24/02

Primary Reviewer: Chan Park **Date:** 6/18/02

Acting Team Leader: Lillie Golson **Date:** 6/18/02

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cc:

ANDA: 75-977
DUP/DIVISION FILE
HFD-613/CPark/ (no cc)
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-977

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 75-977

CHEMISTRY REVIEWS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

---

1. CHEMISTRY REVIEW NO. 1

2. ANDA #75-977

3. NAME AND ADDRESS OF APPLICANT
TEVA Pharmaceuticals USA
Attn: Deborah A. Jaskot
Executive Director Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

4. LEGAL BASIS FOR SUBMISSION
RLD: Ultram
R.W. Johnson
No listed patents (p. 11)
Exclusivity for new dosing regimen: Original expiration date: 8/21/01. However, pediatric exclusivity issued to R.W. Johnson extends the expiration date to 2/21/02.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Tramadol Hydrochloride Tablets

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

9. AMENDMENTS AND OTHER DATES:
Firm:
September 3, 2000 Original Submission.

FDA:
October 17, 2000 Receipt acknowledged.

10. PHARMACOLOGICAL CATEGORY
Centrally acting analgesic

11. Rx or OTC
Rx

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

DMF #
DMF #
DMF #
DMF #
DMF #

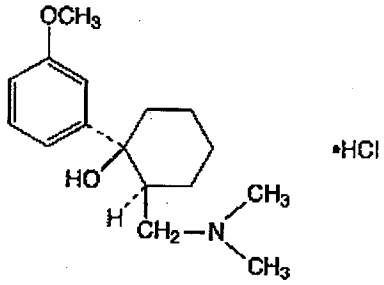
[redacted]

13. DOSAGE FORM
Tablets

14. POTENCIES
50 mg

15. CHEMICAL NAMES AND STRUCTURES

Tramadol Hydrochloride
$C_{16}H_{25}NO_2 \cdot HCl$; M.W. 299.84



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

16. RECORDS AND REPORTS
12/6/00 Labeling review #1 (C. Park)

17. COMMENTS
Chemistry: Very complete application. Minor deficiencies regarding the raw materials and the container closure will be forwarded to the applicant.

DMF # [redacted] is deficient. The holder has already been notified.

Labeling: Deficient

Bioequivalence: Pending

EER: Acceptable on 10/23/00

18. CONCLUSIONS AND RECOMMENDATIONS
The application is not recommended for approval. MINOR

19. REVIEWER: DATE COMPLETED:
Mayra L. Piñeiro-Sánchez, Ph.D. January 31, 2001

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

1. We acknowledge that data regarding manufacturing, QC release, and dissolution of the scored Tramadol HCl Tablets, 50 mg will be submitted towards the review and approval of the application. Alternatively, this information may be submitted post-approval as an **EXPEDITE "Prior Approval Supplement"** to the application. However all information should be reviewed and found acceptable before release of the drug product to the market.

2. The method validation package has been forwarded to a FDA field laboratory.

Sincerely yours,

Vilayat Sayed 3/5/01

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #75-977
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/MPiñeiro-Sánchez/2/28/01 For Mahnaz Fazeli 3/2/01
HFD-647/GJSmith/2/28/01
HFD-617/Jmin/2/28/01 3/2/01

F/T by: jsm/3/2/01
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CHEMISTRY REVIEW - **NOT APPROVABLE - MINOR**

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO. 2

2. ANDA #75-977

3. NAME AND ADDRESS OF APPLICANT
TEVA Pharmaceuticals USA
Attn: Deborah A. Jaskot
Executive Director Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

4. LEGAL BASIS FOR SUBMISSION
RLD: Ultram
Ortho-McNeil Pharmaceutical.
No listed patents (p. 11)
Exclusivity for new dosing regimen: Original expiration date: 8/21/01. However, pediatric exclusivity issued to R.W. Johnson extends the expiration date to 2/21/02.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Tramadol Hydrochloride Tablets

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

9. AMENDMENTS AND OTHER DATES:
Firm:

September 3, 2000	Original Submission.
April 4, 2001	Minor amendment.

FDA:

October 17, 2000	Receipt acknowledged.
February 5, 2001	Deficiency letter Bio.
March 5, 2001	Deficiency letter Chemistry and labeling.

10. PHARMACOLOGICAL CATEGORY
Centrally acting analgesic

11. Λ or OTC
Λ

THIS IS CHEMISTRY REVIEW #2. HEADERS ARE IN ERROR CITING #1

12. RELATED IND/NDA/DMF(s)

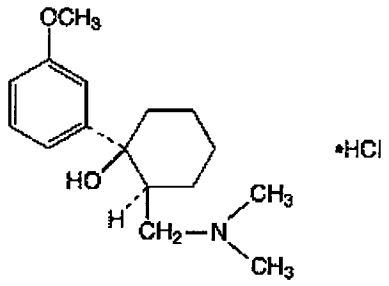
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #

13. DOSAGE FORM
Tablets

14. POTENCIES
50 mg

15. CHEMICAL NAMES AND STRUCTURES

Tramadol Hydrochloride
$C_{16}H_{25}NO_2 \cdot HCl$; M.W. 299.84



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

16. RECORDS AND REPORTS

12/6/00	Labeling review #1 (C. Park)
1/24/01	Bioequivalence review #1 (Z. Wahba)
3/2/01	Chemistry review #1 (M. Pineiro-Sanchez)
5/14/01	Chemistry review #2 (M. Pineiro-Sanchez)

17. COMMENTS

Chemistry: Deficient

DMF # is still deficient. The holder has already been notified.

Labeling: Review of amendment pending.

Bioequivalence: Review of amendment pending.

EER: Acceptable on 10/23/00

18. CONCLUSIONS AND RECOMMENDATIONS
Not recommended for approval. MINOR

19. REVIEWER: Mayra L. Piñeiro-Sánchez, Ph.D.

DATE COMPLETED: May 14, 2001

APPEARS THIS WAY
ON ORIGINAL

Redacted 16 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

cc: ANDA #75-977
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/MPiñeiro-Sánchez/
HFD-647/GJSmith/
HFD-617/Jmin/

F/T by:
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CHEMISTRY REVIEW - **NOT APPROVABLE - MINOR**

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO. 3

2. ANDA #75-977

3. NAME AND ADDRESS OF APPLICANT
TEVA Pharmaceuticals USA
Attn: Philip Erickson, R.Ph.
Director, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

4. LEGAL BASIS FOR SUBMISSION
RLD: Ultram
Ortho-McNeil Pharmaceutical.
No listed patents (p. 11)
Exclusivity for new dosing regimen: Original expiration date: 8/21/01. However, pediatric exclusivity issued to R.W. Johnson extends the expiration date to 2/21/02.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Tramadol Hydrochloride Tablets

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

9. AMENDMENTS AND OTHER DATES:
Firm:

September 3, 2000	Original Submission.
April 4, 2001	Minor amendment.
June 14, 2001	Telephone amendment

FDA:

October 17, 2000	Receipt acknowledged.
February 5, 2001	Deficiency letter Bio.
March 5, 2001	Deficiency letter Chemistry and labeling.
June 5, 2001	Telephone conference.

10. PHARMACOLOGICAL CATEGORY
Centrally acting analgesic

11. Rx or OTC
Rx

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

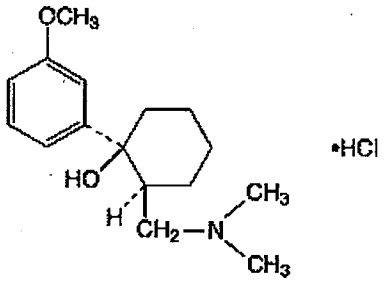
13. DOSAGE FORM
Tablets

14. POTENCIES
50 mg

15. CHEMICAL NAMES AND STRUCTURES

Tramadol Hydrochloride

$C_{16}H_{25}NO_2 \cdot HCl$; M.W. 299.84



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

16. RECORDS AND REPORTS

12/6/00	Labeling review #1 (C. Park)
1/24/01	Bioequivalence review #1 (Z. Wahba)
3/2/01	Chemistry review #1 (M. Pineiro-Sanchez)
5/14/01	Chemistry review #2 (M. Pineiro-Sanchez)

17. COMMENTS

Chemistry: Satisfactory.

DMF # —— is adequate.

Labeling: Pending.

Bioequivalence: Acceptable.

EER: Acceptable on 10/23/00

18. CONCLUSIONS AND RECOMMENDATIONS
TA pending labeling.

19. REVIEWER:
Mayra L. Piñeiro-Sánchez, Ph.D.

DATE COMPLETED:
June 27, 2001

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CHEMISTRY REVIEW #3

cc: ANDA #75-977
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/MPiñeiro-Sánchez12/17/01/ For Mahnaz Farahani. 12,28,01
HFD-647/GJSmith/ D. Noelle 12/27/01
HFD-617/JMin/12/26/01 Jeen Min 12/27/01

F/T by: rad12/27/01
V:\FIRMSnz\Teva\LTRS&REV\75977n03.NAF

CHEMISTRY REVIEW - **APPROVABLE PENDING LABELING.**

ANDA APPROVAL SUMMARY

ANDA: #75-977 DRUG PRODUCT: Tramadol HCL

FIRM: TEVA Pharmaceuticals USA
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

DOSAGE FORM: Tablet; Oral
STRENGTH: 50 mg

CGMP STATEMENT/EIR UPDATE STATUS:

Certifications of CGMP (p. 3789-3791) and of section 306(k) (p. 4271) compliance statement are included.

An acceptable EER was issued on 10/23/00.

Facilities included:

Manufacturing, processing, packaging, labeling and handling of Tramadol HCl Tabelts:

TEVA Pharmaceutical Industries, Ltd.
One Hashikma Street
Industrial Area
P.O. Box 353
Kfar-Saba 44102
ISRAEL

Release and stability studies:

Kfar-Saba site
Hashikma Street
Industrial Area
P.O. Box 353
Kfar-Saba 44102
ISRAEL

Jerusalem Site
2 Hamarpe Street
Industrial Zone
Har-Hotzvim
P.O. Box 1142
Jerusalem 91010
ISRAEL

The packaged and labeled product will be distributed by:

TEVA Pharmaceuticals USA
650 Cathill Road
Sellesville, PA 18960
USA

Warehouses:

151 Domorah Drive
Montgomeryville, PA 18963

1090 Horsham Road
North Wales, PA 19454

BIO STUDY

Acceptable.

Comparative dissolution data using the method provided in the original ANDA and that proposed by the DBE is provided (amendment 4/4/01, p. 122-127).

Apparatus USP Type 1 (basket)
100 rpm, 900 mL 0.1 N HCl

NLT —% of the labeled amount of the drug is dissolved in 30 minutes.

VALIDATION

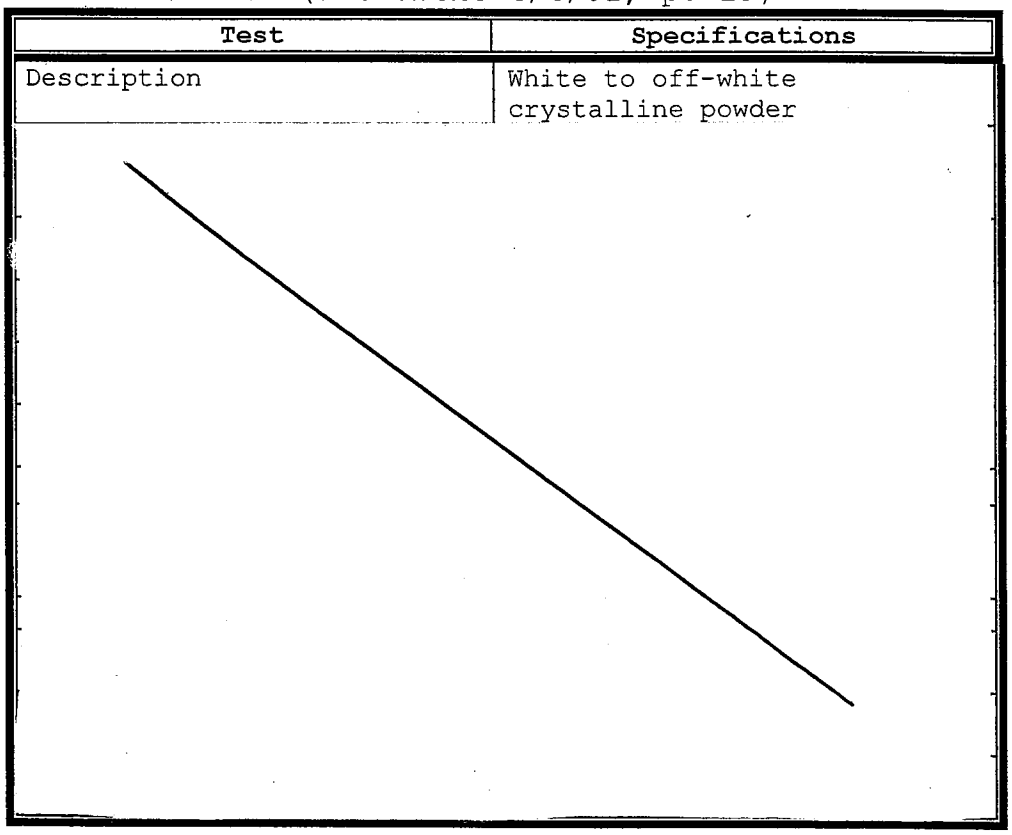
The drug substance and drug product are not compendial. A method validation package was sent to the Philadelphia District Laboratory on 2/28/01 and the method was found acceptable on 7/16/01.

DRUG SUBSTANCE

Tramadol HCl (DMF # —— is adequate per R. Rajagapalan, 5/3/01).

Tramadol HCl (amendment 4/4/01, p. 29)

Test	Specifications
Description	White to off-white crystalline powder



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APPROVAL SUMMARY dated 12/27/2001

STABILITY

A stability protocol and post-approval commitment that conform to FDA Stability Guidelines are included (p. 4240-4242, Amendment 46/14/01, p. 71-72). The firm submitted three months accelerated and 12 month room temperature stability data for lot #K-24052 (p. 4243-4262). Room temperature and accelerated stability data for the tablet with the score configuration is included in the 6/14/01 amendment (p. 17-24). Stability tests and specifications are as follow (p. 4242, amendment 4/4/01, p. 74):

Tests	Specifications
Appearance	White, film coated oval shaped tablet; Debossed "93" on one side and scored between the two numbers; Debossed "58" on the other side of the tablet.

Expiration date: 24 months based on accelerated stability data.

LABELING

Pending.

STERILIZATION VALIDATION (IF APPLICABLE)

N/A

SIZE OF BIO/STABILITY BATCHES

Exhibit batch: Lot #K-27098, ——— tablets.

PROPOSED PRODUCTION BATCH

The commercial batch size of ——— tablets is within the 10X scale-up rule.

For Mahnaz Fatahan, 12,28,01

CHEMIST: Mayra L. Piñeiro-Sánchez, Ph.D. DATE: 12/17/01

SUPERVISOR: Glen Smith D. Roselle for DATE: 12/27/01

F/t by rad12/27/01

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO. 4

2. ANDA #75-977

3. NAME AND ADDRESS OF APPLICANT
TEVA Pharmaceuticals USA
Attn: Philip Erickson, R.Ph.
Director, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

4. LEGAL BASIS FOR SUBMISSION
RLD: Ultram
Ortho-McNeil Pharmaceutical.
No listed patents (p. 11)
Exclusivity for new dosing regimen: Original expiration date: 8/21/01. However, pediatric exclusivity issued to R.W. Johnson extends the expiration date to 2/21/02.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Tramadol Hydrochloride Tablets

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

9. AMENDMENTS AND OTHER DATES:
Firm:

September 3, 2000	Original Submission.
April 4, 2001	Minor amendment.
June 14, 2001	Telephone amendment
June 11, 2002	Minor amendment

FDA:

October 17, 2000	Receipt acknowledged.
February 5, 2001	Deficiency letter Bio.
March 5, 2001	Deficiency letter Chemistry and labeling.
June 5, 2001	Telephone conference.

January 15, 2002 Approvable letter

10. PHARMACOLOGICAL CATEGORY
Centrally acting analgesic

11. Rx or OTC
Rx

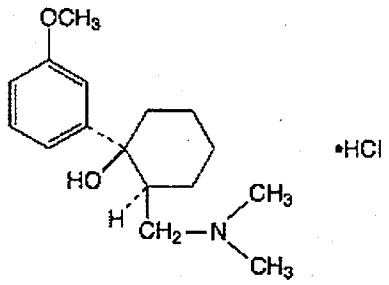
12. RELATED IND/NDA/DMF(s)
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #

13. DOSAGE FORM
Tablets

14. POTENCIES
50 mg

15. CHEMICAL NAMES AND STRUCTURES

Tramadol Hydrochloride
$C_{16}H_{25}NO_2 \cdot HCl$; M.W. 299.84



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

16. RECORDS AND REPORTS

12/6/00	Labeling review #1 (C. Park)
1/24/01	Bioequivalence review #1 (Z. Wahba)
3/2/01	Chemistry review #1 (M. Pineiro-Sanchez)
5/14/01	Chemistry review #2 (M. Pineiro-Sanchez)
12/17/01	Chemistry review #3 (M. Pineiro-Sanchez)

17. COMMENTS

Chemistry: Satisfactory. The tablet description has been modified to refer to the tablet with the unscored

configuration. The applicant confirms that there have been no other CMC changes since the receipt of the approvable letter.

DMF #[redacted] is adequate.

Labeling: Acceptable.

Bioequivalence: Acceptable.

EER: Acceptable on 10/23/00

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval

19. REVIEWER: Mayra L. Piñeiro-Sánchez, Ph.D.

DATE COMPLETED: June 18, 2002

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ON ORIGINAL

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CHEMISTRY REVIEW #4

cc: ANDA #75-977
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/MPiñeiro-Sánchez/6.18.02 6/19/02
HFD-647/GJSmith/6.18.02 6/19/02
HFD-617/Jmin/6.18.02 6/19/02

F/T by: GJS/6.19.02
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CHEMISTRY REVIEW - **APPROVAL**

ANDA APPROVAL SUMMARY

ANDA: #75-977 DRUG PRODUCT: Tramadol HCL

FIRM: TEVA Pharmaceuticals USA
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

DOSAGE FORM: Tablet; Oral
STRENGTH: 50 mg

CGMP STATEMENT/EIR UPDATE STATUS:

Certifications of CGMP (p. 3789-3791) and of section 306(k) (p. 4271) compliance statement are included.

An acceptable EER was issued on 10/23/00.

Facilities included:

Manufacturing, processing, packaging, labeling and handling of Tramadol HCl Tabelts:

TEVA Pharmaceutical Industries, Ltd.
One Hashikma Street
Industrial Area
P.O. Box 353
Kfar-Saba 44102
ISRAEL

Release and stability studies:

Kfar-Saba site
Hashikma Street
Industrial Area
P.O. Box 353
Kfar-Saba 44102
ISRAEL

Jerusalem Site
2 Hamarpe Street
Industrial Zone
Har-Hotzvim
P.O. Box 1142
Jerusalem 91010
ISRAEL

The packaged and labeled product will be distributed by:

TEVA Pharmaceuticals USA
650 Cathill Road
Sellesville, PA 18960
USA

Warehouses:

151 Domorah Drive
Montgomeryville, PA 18963

1090 Horsham Road
North Wales, PA 19454

BIO STUDY

Acceptable.

Comparative dissolution data using the method provided in the original ANDA and that proposed by the DBE is provided (amendment 4/4/01, p. 122-127).

Apparatus USP Type 1 (basket)
100 rpm, 900 mL 0.1 N HCl

NLT — % of the labeled amount of the drug is dissolved in 30 minutes.

VALIDATION

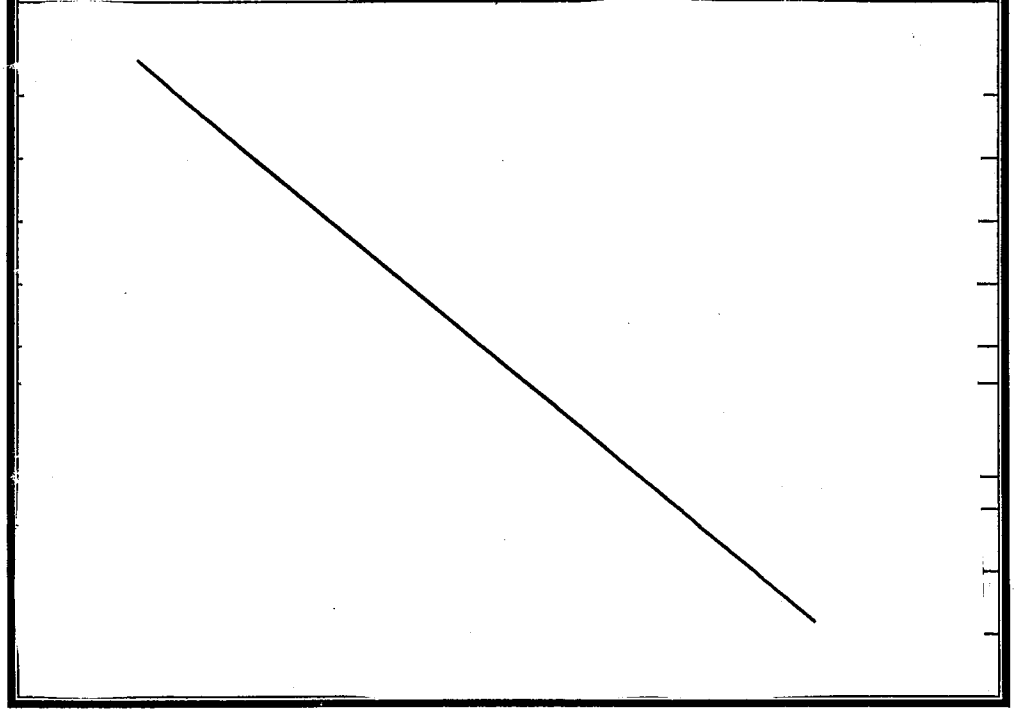
The drug substance and drug product are not compendial. A method validation package was sent to the Philadelphia District Laboratory on 2/28/01 and the method was found acceptable on 7/16/01.

DRUG SUBSTANCE

Tramadol HCl (DMF #——— is adequate per R. Rajagapalan, 5/3/01).

Tramadol HCl (amendment 4/4/01, p. 29)

Test	Specifications
Description	White to off-white crystalline powder



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APPROVAL SUMMARY DATED 6/18/02

to FDA Stability Guidelines are included (p. 4240-4242, [redacted] p. 71-72). The firm submitted three months accelerated and 12 month room temperature stability data for lot #K-24052 (p. 4243-4262). Room temperature and accelerated stability data for the tablet with the score configuration is included in the 6/14/01 amendment (p. 17-24). Stability tests and specifications are as follow (p. 4242, Am: 4/4/01, p. 74, Am: 6/11/02, p. 24):

Tests	Specifications
Appearance	White, film coated oval shaped tablet debossed "93" on one side and "58" on the other.
[redacted]	[redacted]

Expiration date: 24 months based on accelerated stability data.

LABELING

Acceptable.

STERILIZATION VALIDATION (IF APPLICABLE)

N/A

SIZE OF BIO/STABILITY BATCHES

Exhibit batch: Lot #K-27098, [redacted] tablets.

PROPOSED PRODUCTION BATCH

The commercial batch size of [redacted] tablets is within the 10X scale-up rule.

CHEMIST: Mayra L. Piñeiro-Sánchez, Ph.D DATE: June 18, 2002
SUPERVISOR: Glen Smith DATE: June 18, 2002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-977

BIOEQUIVALENCE REVIEWS

Tramadol Hydrochloride Tablets
50 mg
ANDA #75-977
Reviewer: Z.Z. Wahba
v:\firmsanz\TEVA\ltrs&rev\75977sd.900

TEVA Pharmaceuticals
Sellersville, PA
Submission date:
September 3, 2000

Review of Two Bioequivalence Studies, And Dissolution Data

OBJECTIVE:
To review:

- Teva's single dose *in vivo* bioequivalence studies under fasting and non-fasting conditions comparing its 50 mg strength Tramadol Tablet to the reference listed drug, Ortho-McNeil's Ultram® Tablet, 50 mg.

- Comparative dissolution data for both the test and reference drug products.

BACKGROUND:

Tramadol Hydrochloride is a centrally acting synthetic analgesic.

Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and its M1 metabolite are detected in the circulation. Tramadol is well absorbed orally with an absolute bioavailability of 75%. 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 2 and 3 hours, respectively, after administration of 100 mg, in healthy adults. 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.

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 (PDR, 2000).

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

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

Recommended Dose: The usual dose is 25 mg daily. The total daily dose can be increased to 50 mg, four times per day after titration (PDR, 2000).

BIOEQUIVALENCE STUDY UNDER FASTING CONDITIONS

Study Information:

Study Number: 2050
Sponsor: Teva Pharmaceuticals USA
Clinical Facility:

[ ]

Analytical Facility:

[ ]

Principle Investigator: _____ M.D.
Study Director: _____ , Ph.D.

Treatment Plan:

Test product: 2 X 50 mg Tramadol HCl Tablet (Teva), Lot #K-24052, manufacture date: 08/31/98, Batch size: not given, assay potency: 98.1%, content uniformity: 98.9%.

Reference product: 2 X 50 mg Ultram® Tablet (Ortho-McNeil), Lot #BHA1621, expiration date: 07/00, assay potency: 100.0%, content uniformity: 100.1%.

Study Plan:

Study design	Single dose, randomized, two-way crossover study under fasting conditions.
No. of subjects	30 subjects enrolled. 28 subjects completed.
Drop-outs	Subject #2 was dismissed prior to Period-2 drug administration due to non-compliance. Subject #20 was dismissed prior to Period-1 due to adverse events, namely nausea, vomiting and dizziness.
Food & Fluid Intake	Subjects fasted overnight for at least 10 hours before dosing and 4.5 hours after dosing. The drug products were administered with 240 mL of water at room temperature. Standard meals were provided at appropriate times thereafter.
Clinical study dates	Period-1: 1/30/99 Period-2: 2/06/99
Analytical study dates (start-end dates)	02/08/99 - 03/08/99
Wash out period	7 days

Blood sampling	Pre-dose (0 hour) and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24 and 36 hours post-dosing. The collected plasma samples were stored frozen at - 25°C until assayed.

Adverse Events:

Twelve subjects experienced a total of thirty adverse events during this study. All medical events were mild to moderate (pages 127-128, Clinical Report Section, volume C1.1).

Assay Methodology: (NOT TO BE RELEASED UNDER FOI)

Analytical method	HPLC with fluorescence detection
Analyte	Tramadol
Pre-Study Validation	
Sensitivity (LOQ)	10.01 ng/mL
Quality control (QC) samples	10.01, 15.0, 29.99, 479.88 and 959.76 ng/mL
QC samples validation (Overall)	Precision = 1.7 to 7.0% Accuracy (%) = -3.6 to 0.9%
Linearty	10.01 to 1281.45 ng/mL
Calibration curve validation	Precision = 1.1 to 4.2% Accuracy (% change) = -2.4 to 1.7%
Recovery	Overall % recovery = 89.5% (CV%= 2.3%)
Stability	Long term: not given Room Temp. : up to 4 hours prior to extraction Freeze/thaw Stability: for 3 cycles
During Study Validation	
Sensitivity (LOQ)	10.01 ng/mL
Quality control (QC) samples	15.0, 29.99, 479.88 and 959.76 ng/mL
QC samples validation	Precision = 3.2 to 7.3% Accuracy (%) = 95.6 to 102.5%
Linearty	10.01 to 1281.45 ng/mL
Calibration curve validation	Precision = 1.8 to 5.1% Accuracy (%change) = -2.5 to 1.7%

Statistical Analyses:

The plasma concentrations and pharmacokinetic parameters of tramadol under fasting conditions were analyzed using SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters for tramadol are summarized in the tables below:

Table #1
Mean Plasma Concentrations (ng/mL) of Tramadol in 28 Subjects Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	2.72	8.56	0.96	3.55	2.85
0.67	103.45	58.78	92.38	54.95	1.12
1	182.07	49.89	166.71	54.63	1.09
1.33	212.10	35.41	203.19	50.77	1.04
1.67	220.24	34.82	211.78	37.78	1.04
2	222.02	38.90	220.97	37.11	1.00
2.5	215.56	39.69	213.07	33.67	1.01
3	201.58	44.00	202.01	32.07	1.00
4	177.31	40.37	179.12	34.39	0.99
5	154.11	38.33	154.34	32.68	1.00
6	131.25	34.26	131.41	32.80	1.00
8	103.05	30.59	105.67	30.70	0.98
10	73.71	24.15	74.41	24.99	0.99
12	55.57	21.11	56.55	21.59	0.98
16	33.37	15.42	33.19	15.68	1.01
24	8.31	9.82	8.21	9.07	1.01
36	0.00	0.00	0.00	0.00	.

MEAN1=Test MEAN2=Reference MEAN12=Mean T/R

Table #2
Summary of Pharmacokinetics Parameters (Tramadol) in 28 Subjects Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1965.35	561.66	1953.48	535.49	1.01
AUCT	1825.83	517.32	1824.59	508.50	1.00
CMAX	239.78	43.42	231.85	36.54	1.03
KE	0.15	0.03	0.15	0.03	0.97
*LAUCI	1891.81	0.28	1884.41	0.27	1.00
*LAUCT	1758.14	0.28	1757.98	0.28	1.00
*LCMAX	236.03	0.18	229.07	0.16	1.03
THALF	4.96	1.08	4.77	0.95	1.04
TMAX	1.90	0.54	1.87	0.52	1.01

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Table #3
LSMeans and 90% Confidence Intervals
(Tramadol)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	1904.22	1884.41	1.01	97.66	104.56
LAUCT	1758.14	1757.98	1.00	96.18	103.99
LCMAX	236.03	229.07	1.03	98.93	107.32

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML

Comment on the fasting study (Tramadol):
Under fasting conditions, the mean plasma tramadol levels for the test and reference products were comparable to each other as shown in Table #1 and Figure #1. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #3).

BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS

Study Information:

Study Number: 2051
Sponsor: Teva Pharmaceuticals USA
Clinical Facility:
[ ]

Analytical Facility:
[ ]

Principle Investigator: _____ M.D.
Study Director: _____, Ph.D.

Treatment Plan:

Treatment A:
Test product, under non-fasting conditions: 2 X 50 mg Tramadol HCl Tablet (Teva), Lot #K-24052, manufacture date: 08/31/98,

Batch size: not given, assay potency: 98.1%, content uniformity: 98.9%.

Treatment B:
Reference product, under non-fasting conditions: 2 X 50 mg Ultram® Tablet (Ortho-McNeil), Lot #BHA1621, expiration date: 07/00, assay potency: 100.0%, content uniformity: 100.1%.

Treatment C:
Test product, under fasting conditions: 2 X 50 mg Tramadol HCl Tablet (Teva), Lot #K-24052, manufacture date: 08/31/98, Batch size: not given, assay potency: 98.1%, content uniformity: 98.9%.

Study Plan:

Study design	Randomized, three-way crossover, single dose study, under fasting and non-fasting conditions.
No. of subjects	18 subjects enrolled. 17 subjects completed.
Drop-outs	Subject #17 (during Period-3) did not consume his high-fat content breakfast and therefore, his samples were not analyzed.
Food & Fluid Intake	Subjects receiving treatments A and B fasted overnight (for 10 hours). Subjects who received treatment C, fasted overnight for 10 hours before dosing and for 4.5 hours after drug administration. Treatments A and B, subjects were fed a standard high fat breakfast, which was consumed in its entirety 30 minutes before drug administration. Each dose was followed by 240 mL of room temperature tap water. Standard meals were provided at appropriate times thereafter.
Clinical study dates	Period-1: 01/21/99 Period-2: 01/28/99 Period-3: 02/04/99
Analytical study dates (start-end dates)	02/09/99 - 03/04/99
Wash out period	7 days
Blood sampling	Pre-dose (0 hour) and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24 and 36 hours post-dosing. The collected plasma samples were stored frozen at - 25°C until assayed.

Adverse Events:

Ten subjects experienced a total of eighteen adverse events during this study. All medical events were mild (pages 2018-2019, and 2025, Clinical Report Section, volume C1.7).

Assay Methodology: **(NOT TO BE RELEASED UNDER FOI)**

Same as in study protocol #2050 (under fasting conditions).

IN VIVO BE STUDY & STATISTICAL ANALYSIS:

The plasma concentrations and pharmacokinetic parameters of tramadol under fasting and non-fasting conditions were analyzed using SAS-GLM procedure for analysis of variance.

Table #4
Mean Plasma Concentrations (ng/mL)
of Tramadol in 17 Subjects
Under non-fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.33	4.69	8.20	3.56	8.02	3.24	9.26	1.32
0.67	70.19	64.42	63.03	64.30	107.27	59.31	1.11
1	134.10	86.66	152.78	82.92	197.39	63.01	0.88
1.33	179.72	79.90	217.38	66.84	225.90	61.23	0.83
1.67	228.94	73.67	254.49	59.72	231.03	61.42	0.90
2	247.55	58.43	264.14	54.16	230.47	59.78	0.94
2.5	261.99	55.24	265.12	56.50	227.85	58.82	0.99
3	254.96	60.03	258.67	64.82	215.37	56.95	0.99
4	222.56	61.75	223.36	67.23	186.22	55.78	1.00
5	192.93	61.13	199.60	63.95	161.56	56.26	0.97
6	160.10	53.83	166.56	52.89	139.52	47.71	0.96
8	122.85	48.97	124.80	43.69	111.09	45.09	0.98
10	92.46	41.52	97.32	39.58	84.43	41.04	0.95
12	68.60	35.82	73.32	33.60	63.63	33.80	0.94
16	43.37	25.72	46.43	25.38	39.42	25.27	0.93
24	14.35	17.42	16.02	16.03	12.84	15.64	0.90
36	1.37	5.65	2.45	5.85	2.36	5.45	0.56

(CONTINUED)

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.33	1.45	1.10
0.67	0.65	0.59
1	0.68	0.77
1.33	0.80	0.96

1.67	0.99	1.10
2	1.07	1.15
2.5	1.15	1.16
3	1.18	1.20
4	1.20	1.20
5	1.19	1.24
6	1.15	1.19
8	1.11	1.12
10	1.10	1.15
12	1.08	1.15
16	1.10	1.18
24	1.12	1.25
36	0.58	1.04

1=Test-NonFast 2=Ref.-NonFast 3=Test-Fast
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table #5

Summary of Pharmacokinetics Parameters (Tramadol) in 17 Subjects Under Fasting and Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	2401.67	962.64	2518.72	910.90	2208.28	967.99	0.95
AUCT	2234.25	903.93	2378.75	882.45	2068.40	937.51	0.94
CMAX	280.97	55.47	293.22	50.27	243.18	59.19	0.96
KE	0.14	0.03	0.13	0.03	0.14	0.03	1.03
*LAUCI	2251.91	0.36	2376.20	0.35	2037.11	0.40	0.95
*LAUCT	2092.53	0.36	2236.94	0.36	1897.19	0.42	0.94
*LCMAX	276.05	0.19	289.05	0.18	236.61	0.24	0.96
THALF	5.34	1.31	5.46	1.20	5.37	1.35	0.98
TMAX	2.36	0.89	2.04	0.68	2.00	0.56	1.16

(CONTINUED)

	RMEAN13	RMEAN23
PARAMETER		
AUCI	1.09	1.14
AUCT	1.08	1.15
CMAX	1.16	1.21
KE	1.00	0.97
*LAUCI	1.11	1.17
*LAUCT	1.10	1.18
*LCMAX	1.17	1.22
THALF	0.99	1.02
TMAX	1.18	1.02

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Comment on the non-fasting study (Tramadol):
Under non-fasting conditions, the mean plasma tramadol levels for the test and reference products were comparable to each other as shown in Table #4 and Figure #2. The T/R geometric mean ratios (RLSM23) for AUCt, AUCi, and Cmax, were all within the acceptable range of 0.8 to 1.25 (Table #5).

FORMULATION (Not to be released under FOI)

Ingredients	**Amount mg/tablet**
Tramadol Hydrochloride	50.0
Microcrystalline cellulose [ ]	
Colloidal Silicon Dioxide NF [ ]	
Sodium Starch Glycolate NF	
Pregelatinized Starch NF [ ]	
Lactose Monohydrate NF [ ]	
Magnesium Stearate NF	
[ ]	
[ ]	
Total weight	
The film coating of [ ] mg/tablet [ ] (white) is composed of :	
Hydroxypropyl Methylcellulose USP [ ]	
Titanium Dioxide USP	
[ ]	
Polyethylene Glycol NF [ ]	
Total	

[ ]

DISSOLUTION:

At present an official compendial test for the tramadol Hydrochloride tablets does not exist. Currently, the Division of Bioequivalence recommends the following method (Per ANDA #75-968, review date 11/30/00; ANDA #75-963, review date 11/29/00; and ANDA #75-980, review date 11/29/00):

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
Specifications: NLT — % (Q) in 30 minutes

In this application the firm submitted dissolution testing results using Apparatus: 2 (paddle), 50 rpm in 900 mL of 0.1N HCl, sampling times: 10, 20, and 30 minutes. A copy of the dissolution testing data is attached to this report.

Comments on Dissolution Testing:

Firm's dissolution is not acceptable.

GENERAL COMMENTS (It should not be released under FOI)

1. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Teva's tramadol HCl tablet, 50 mg, is bioequivalent to the reference listed drug Orth-McNeil's Ultram® Tablet, 50 mg. The 90% confidence intervals for the geometric mean ratios of AUCT, AUCI and CMAX were all within the acceptable range of 80-125%.

2. Under non-fasting conditions: The firm's in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, Teva's tramadol HCl tablet, 50 mg, is bioequivalent to Orth-McNeil's Ultram® Tablet, 50 mg. The T/R geometric mean ratios for the geometric mean ratios of AUCT, AUCI, CMAX were within the acceptable range of 0.8-1.25.

3. The firm has submitted the plasma concentrations and pharmacokinetic parameters for tramadol's metabolite M1 (o-desmethyltramadol). Since this metabolite is not required for approval of this submission, this data has not been reviewed.

4. The firm's dissolution testing is not acceptable.

5. At the time of the bioequivalence study and preparation of this ANDA, the marketed reference listed drug was available only as an unscored tablet. Since this time, R.W. Johnson has received FDA approval for a new dosing schedule which includes the use of a scored 50 mg tablet. Teva Pharmaceuticals USA hereby commits to manufacture a test batch of tramadol HCl tablets 50 mg with a scoring configuration comparable to that of the innovator. Information regarding the manufacturing and QC "release" testing of this batch including dissolution profile comparisons will be submitted upon their completion towards the review and approval of this ANDA. The Office of

Generic Drugs will correspond with the firm regarding manufacture and dissolution testing of scored tramadol HCl tablets.

DEFICIENCIES

1. The firm's submitted dissolution method is not acceptable. The Division of Bioequivalence recommends the following dissolution 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

   The comparative dissolution profiles (test and reference products) should include the dissolution mean for each time point, the range (maximum and minimum), and the percentage of coefficient of variation (in a side-by-side tabular format, if possible). The dissolution testing should be done on tablets from the same lot number that was used in the in vivo bioequivalence study.

2. The data on the long-term freezing (-25 °C) stability were not provided. The stability data should cover a period equal to the time from the day each study started (collected blood samples) to the day the last sample was analyzed.

3. The firm should submit information on the batch/lot size of the test product.

RECOMMENDATIONS

1. The single-dose fasting and non-fasting bioequivalence studies conducted by Teva Pharmaceuticals on its Tramadol Hydrochloride Tablet, 50 mg, Lot # K-24052, comparing it to Ortho-McNeil's Ultram® Tablet, 50 mg, Lot #BHA1621, have been found incomplete due to the deficiencies cited above.

2. The firm's dissolution testing is not acceptable.

   The dissolution testing should be conducted using the following 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

The firm should be informed of the above deficiencies.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED BDAVIT BZW 1/24/01 1/25/01
FT INITIALED BDAVIT Barbara Davit Date: 1/26/01

Concur: for Dale P. Conner Date: 1/30/2001
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:75-977 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Tramadol Hydrochloride Tablets, 50 mg

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

1. Your submitted dissolution testing is not acceptable. The Division of Bioequivalence recommends the following dissolution 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

   The comparative dissolution profiles (test and reference products) should include all individual time points data, the dissolution mean for each time point, the range (maximum and minimum), and the percentage of coefficient of variation (in a side-by-side tabular format, if possible). The dissolution testing should be done on tablets from the same lot number that was used in the in vivo bioequivalence study.

2. Please provide the raw data of the long-term freezing (-25 °C) stability. The stability data should cover a period equal to the time from the day each study started (collected blood samples) to the day the last sample was analyzed.

3. Please submit information on the batch/lot size of the test product.

Sincerely yours,

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

CC: ANDA #75-977
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer (Z. Wahba)
HFD-658/ Team Leader (B. Davit)

Endorsements:
HFD-658/ Z. Wahba ZW 1/25/01
HFD-658/ B. Davit BMD 1/25/01
HFD-650/ D. Conner for DWP 1/30/2001

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BIOEQUIVALENCY - **INCOMPLETE** submission date: 9/03/00

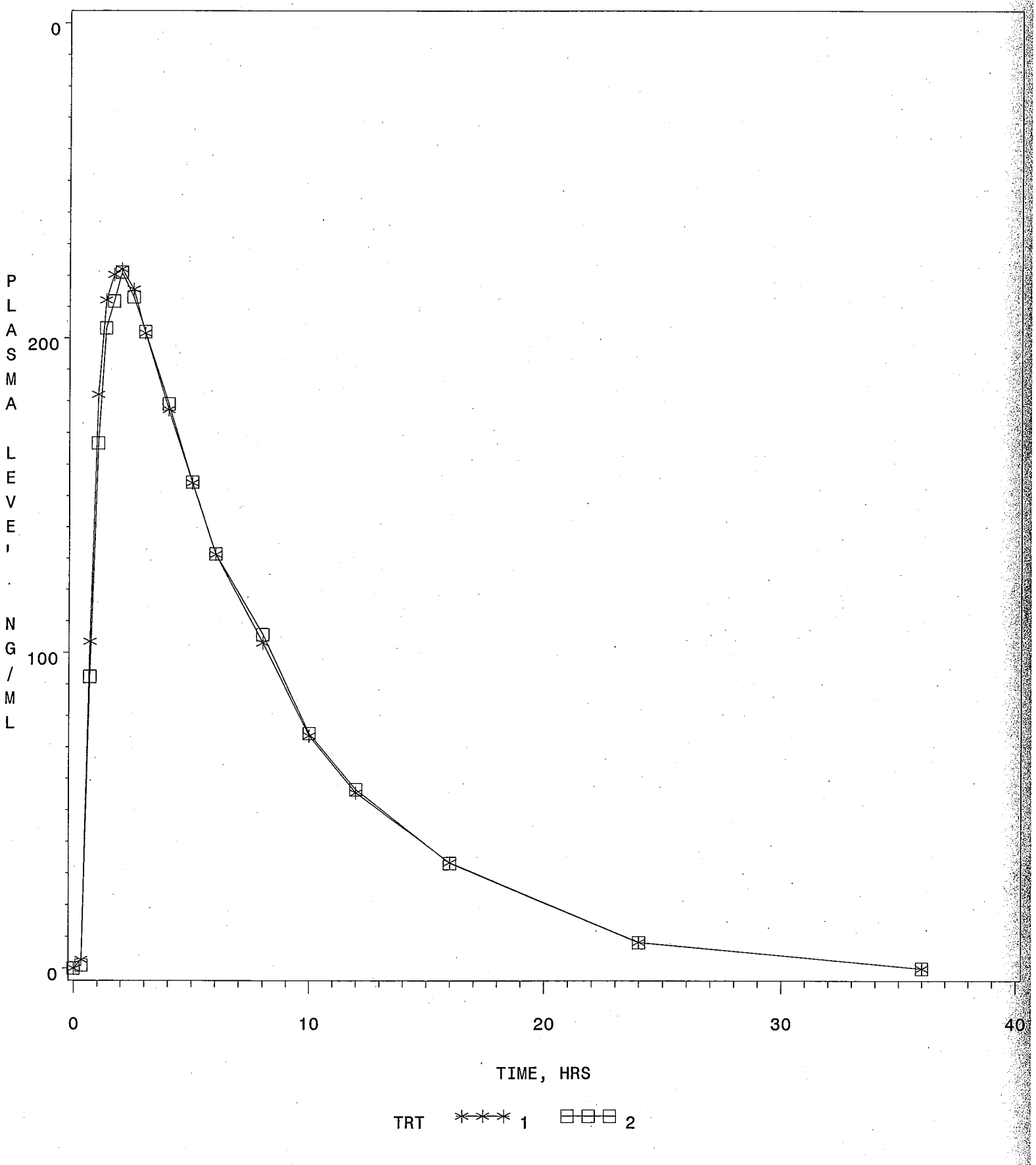
1. **FASTING STUDY (STF)**
   Clinical: [redacted]
   Strength: 50 mg
   Outcome: IC
   Analytical: [redacted]

2. **NON-FASTING STUDY (STF)**
   Clinical: [redacted]
   Strength: 50 mg
   Outcome: IC
   Analytical: [redacted]

OUTCOME DECISIONS: **INCOMPLETE**

FIG P-1 . PLASMA TRAMADOL LEVELS

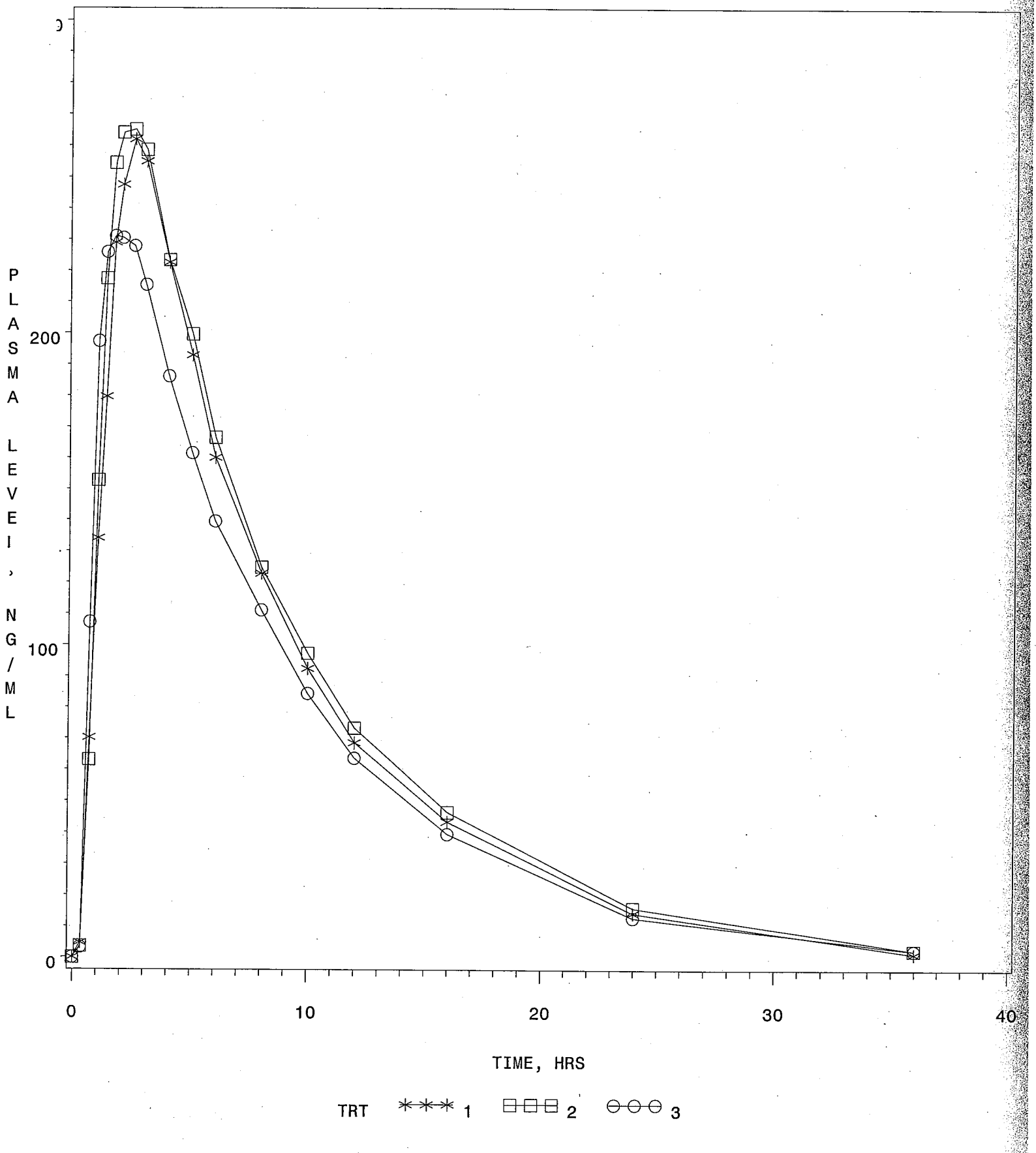
TRAMADOL TABLETS, 50 MG, ANDA #75-977
UNDER FASTING CONDITIONS
DOSE=2 X 50 MG



1=TEST(Teva) 2=REF(Ortho-McNeil)

FIG P-2 . PLASMA TRAMADOL LEVELS

TRAMADOL TABLETS, 50 MG, ANDA #75-977
UNDER FASTING/NONFASTING CONDITIONS
DOSE=2 X 50 MG



Tramadol Hydrochloride Tablets
50 mg
ANDA #75-977
Reviewer: Z.Z. Wahba
v:\firmsanz\TEVA\ltrs&rev\75977a1.201

TEVA Pharmaceuticals
North Wales, PA
Submission date:
February 22, 2001

REVIEW OF AN AMENDMENT

BACKGROUND

1. The firm previously submitted two in vivo bioequivalence studies (single-dose under fasting and fed conditions) comparing its test product Tramadol Tablet, 50 mg, to the reference listed drug, Ortho-McNeil's Ultram® Tablet, 50 mg. The submission was reviewed and was found incomplete by the Division of Bioequivalence (the review date 1/30/2001) due to deficiency comments.

2. In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

DEFICIENCY COMMENT #1

The Division of Bioequivalence asked the firm to submit new dissolution data following the Agency's dissolution 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

RESPONSE TO THE DEFICIENCY COMMENT #1

- The firm submitted dissolution data following the Agency's dissolution method. The dissolution data meet the dissolution specifications [Not less than —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes].

- The dissolution comparison profile for the test and reference products is included in this report (Attachment #1).

- The dissolution data for the test product are acceptable.

The firm's response to comment #1 is acceptable.

DEFICIENCY COMMENT #2

The firm was asked to provide the raw data of the long-term frozen storage (-25 °C) stability. The stability data should cover a

period equal to the time from the day each study started (collected blood samples) to the day the last sample was analyzed.

RESPONSE TO THE DEFICIENCY COMMENT #2

The firm provided long term stability data for tramadol in plasma at -25°C and -70°C. These plasma samples were stored for 112 days, which covers the length of the bioequivalence study.

Long term stability (The concentrations of the QC samples were ——— ng/mL)	At -25°C	At -70°C
Accuracy (% change)		
Precision (CV%)		

The firm's response to comment #2 is acceptable.

DEFICIENCY COMMENT #3

Please submit information on the batch/lot size of the test product.

RESPONSE TO THE DEFICIENCY COMMENT #3

The batch/lot size for the test product was ——— tablets.

The firm's response to comment #3 is acceptable.

RECOMMENDATIONS

1. The single-dose fasting and non-fasting bioequivalence studies conducted by Teva Pharmaceuticals on its Tramadol Hydrochloride Tablet, 50 mg, Lot # K-24052, comparing it to Ortho-McNeil's Ultram® Tablet, 50 mg, Lot #BHA1621, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Teva's Tramadol Hydrochloride Tablet 50mg, is bioequivalent to the reference listed product, Ortho-McNeil's Ultram® Tablet 50 mg.

2. The dissolution testing conducted by the firm on its Tramadol Hydrochloride Tablet, 50 mg, Lot # K-24052 is acceptable.

3. The dissolution testing should be incorporated into firm's 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.

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

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Review Branch III
Division of Bioequivalence 4/25/01

RD INITIALED BDAVIT
FT INITIALED BDAVIT Barbara M Davit Date: 4/25/01

Concur: Dale P. Conner Date: 4/27/01
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-977 APPLICANT: Teva Pharmaceuticals USA

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 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 toxicology data, 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,

Dale P. Conner

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

CC: ANDA #75-977
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer (Z. Wahba)
HFD-658/ Team Leader (B. Davit)

Endorsements:
HFD-658/ Z. Wahba ZW 4/25/01
HFD-658/ B. Davit BWD 4/25/01
HFD-650/ D. Conner 4/27/01

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BIOEQUIVALENCY - **Acceptable** submission date: 2/22/01

1. STUDY AMENDMENT -dated 2/22/01 Strengths: 50 mg

OUTCOME DECISIONS: **AC** - Acceptable

WINBIO COMMENTS: Acceptable

APPEARS THIS WAY
ON ORIGINAL

Attachment #1

TEVA PHARMACEUTICAL INDUSTRIES LTD.

PHARMACEUTICAL OPERATIONS DIVISION - RESEARCH & DEVELOPMENT
P.O.BOX 353 KFAR SABA 44102 ISRAEL TEL. +972-9-7648206 FAX. +972-9-7648636 or 9-7649525

COMPARATIVE DISSOLUTION PROFILE

Product Name: TRAMADOL HCl TABLETS 50mg

Analysis No: CDP-424/01

TAB. #	% OF LABELED AMOUNT DISSOLVED							
	10 MINUTES		20 MINUTES		30 MINUTES		45 MINUTES	
	TEVA K-24052	Ultram® BHA1621	TEVA K-24052	Ultram® BHA1621	TEVA K-24052	Ultram® BHA1621	TEVA K-24052	Ultram® BHA1621
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Min								
Max								
Mean	98	55	99	99	99	101	99	101
RSD (%)	1.0	10.1	0.6	2.8	0.6	1.2	1.0	1.4

CORPORATE HEADQUARTERS
5 BASEL ST., P.O.BOX 3190 PETAH TIQVA 49131 ISRAEL TEL. +972-3-9267267 FAX. +972-3-9234050

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-977 SPONSOR : TEVA Pharmaceuticals

DRUG AND DOSAGE FORM : Tramadol HCl Tablets STRENGTH(S) : 50 mg

TYPES OF STUDIES : In vivo bioequivalence studies under fasting and non-fasting conditions.

CLINICAL STUDY SITE(S) : ———————

ANALYTICAL SITE(S) : ———————

STUDY SUMMARY : The two studies demonstrated that under fasting and non-fasting conditions, Teva's Tramadol Tablet, 50 is bioequivalent to Ortho-McNeil's Ultram® Tablet, 50 mg.

DISSOLUTION : The dissolution data are acceptable.

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic _No X New facility _Yes (new analytical facility) _ For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III

INITIAL : ZZW DATE : 4/25/01

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : BMD DATE : 4/25/01

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

INITIAL : DPC DATE : 10/23/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-977

ADMINISTRATIVE DOCUMENTS

75977

Subject: Tramadol Dosage Titration

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

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

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

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

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

CC:

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

Endorsements:

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

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

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

3.1
Park, Chan

Record of Telephone Conversation

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

1) Incorporate a change in the in-process limits for the [redacted] after [redacted] of the batch record.

2) Submit stability data for the tablet with the scored configuration in the proposed marketing container.

3) Update the stirring rate in the dissolution method to 100 rpm as described on p.78 of the 4/4/01 chemistry amendment.

Date:
June 5, 2001

ANDA Number:
75-977

Product Name:
Tramadol Tablets, 50 mg

Firm Name:
Teva

Firm Representative:
Philip Erickson

Phone Number:
215-591-3000

FDA Representative:
Jeen Min
Mayra Pineiro-Sanchez

Signatures:
Jeen Min 4/12/01

CC: ANDA 75-977

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Record of Telephone Conversations For Tramadol

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

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

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

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

Date:
January 9, 2002

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

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

FDA Representative:
Jeen Min

Signatures:
Jeen Min 1/9/02

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OGD APPROVAL ROUTING SUMMARY

ANDA # 75-977 Applicant Teva

Drug Tramadol Hydrochloride Tablets Strength 50 mg

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

REVIEWER:	DRAFT RECEIPT	FINAL ACTION
1. Project Manager Jeen Min	Date 12/26/01	Date
Review Support Branch 9	Initials JM	Initials

Application Summary:

Original Rec'd date 9/3/00
Date Acceptable for Filing 9/5/00 ✓
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 10/23/00
Date of Office Bio Review 10/23/01
Date of Labeling Approv. Sum
Date of Sterility Assur. App. N/A
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.	Date	Date
Chemistry Div. I or II	Initials	Initials
Comments:		

3. Frank Holcombe	Date	Date
Assoc. Dir. For Chemistry	Initials	Initials

Comments: (First generic drug review)
NA-Refer to ——— ANDA for this drug product.

4. Pat Beers Block	Date	Date
Supv., Review Support Branch	Initials	Initials

EER Status: Refer to DLRS review below Jeen 1/8/2002

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 1/8/02 Initials RW | Date 1/8/02 Initials RW/for

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: 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. Teva has addressed the D-44 exclusivity and the D-63 exclusivity.

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
Date Checked Reviews granted.
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐
PI
N/A
RLD- Ultram Tablets 50mg
RW- Ortho-McNeil Pharmaceutical Research Institute
NDA 20-281

6. Peter Rickman
Acting Director, DLPS
Date 1/8/02 Initials RW | Date 1/8/02 Initials /for

Comments: Acceptable EES dated 10/23/00 (Verified 1/7/02). No OAI alerts noted. Bioequivalency studies (single-dose fasting and non-fasting) on unscored tablets found satisfactory 12/12/01. Dissolution studies also found acceptable. DSI inspection requested for clinical site ( ) and analytical site ( ). Inspection request cancelled- both sites have an acceptable DSI inspectional history. Office-level bio release 10/23/01. ORC acceptable 12/27/01. Methods validation completed and acceptable. Labeling remains under review.

7. Robert L. West
Acting Deputy Director, OGD
Date 1/8/02 Initials RW | Date 1/8/2002 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-41 exclusivity should be included in the generic labeling, but that the D-63 exclusivity may carved out. We are currently awaiting publication of the discontinued labeling guidance in final format. Once that occurs, we will request FPI (package insert) for unscored tablets. Plan: Issue approvable letter.

8. Gary Buehler
Acting Director, OGD
Comments:
Date 1/15/02 Initials GB | Date 1/15/02 Initials GB

~~Janet Woodcock, M.D.~~
Director
Center for Drug Evaluation
And Research
Date ____ Initials ____ | Date ____ Initials ____

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

9. Project Manager Teen Min
Review Support Branch
Date 1/15/02 Initials [illegible] | Date 1/15/02 Initials [illegible]

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

Applicant notification:
3:50 pm Time notified of approval by phone 3:50 pm Time approval letter faxed

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

v:\reports\approval\approvrou

MEMORANDUM

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

Date: June 10, 2002

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

Subject: Approval of Tramadol Abbreviated New Drug Applications

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

Background

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

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

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

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

Previous Proposals

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

FDA is authorized to approve an ANDA that omits an indication or other aspect of labeling of the listed drug that is protected by patent or exclusivity. 21 CFR 314.94(a)(8)(iv). The Best Pharmaceuticals for Children Act (BPCA) was signed into law in January of 2002. Section 11 of the BPCA allows incorporation of language in the labeling of generic products that informs health care practitioners that the reference listed drug has been approved for pediatric use. Teva utilized this concept to make two proposals for labeling to allow FDA to approve generic tramadol products omitting the protected 25 mg titration dosing schedule. The firm suggested that the Dosage and Administration section recommend use only in patients for whom rapid onset of pain relief is required, retaining the same language in the approved Ultram labeling, and, 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.

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

MEMORANDUM

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

Date: June 10, 2002

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

Subject: Approval of Tramadol Abbreviated New Drug Applications

To: Abbreviated New Drug Applications (Listed Below)

Background

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

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

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

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

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

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

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

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

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

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

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

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

Resolution of Tramadol ANDA Labeling Issues

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

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

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

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

Scope of Exclusivity

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

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

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

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

M E M O R A N D U M

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

Date: June 13, 2002

To: The Record

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

Subject: Approval Process for Generic Tramadol Hydrochloride Tablets

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

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

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

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

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

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

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

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

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

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

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

OFFICE OF GENERIC DRUGS APPROVAL ROUTING SUMMARY

TRAMADOL HYDROCHLORIDE TABLETS, 50 MG

ANDA NUMBER: 75-977

APPLICANT: Teva Pharmaceuticals USA

Date of Issuance of Approvable Letter: January 15, 2002

Date of Submission of Final-printed Package Insert Labeling: JUNE 11, 2002

Final-printed Labeling (FPL) Reviewed and Found Acceptable On: JUNE 18, 2002

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

Methods Validation Status: Acceptable (See Approval Summary)

Has Applicant Initiated Changes to the CMC Section of the Application Since Issuance of the Approvable Letter? Yes, These changes have been reviewed and found to be acceptable See chemistry review #4.

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 6/19/2002

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

or

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-977

CORRESPONDENCE

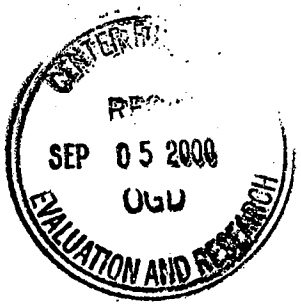
75-977

Deborah A. Jaskot
Executive Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

1090 Horsham Road, PO Box 1090, North Wales, PA 19454
Phone: (215) 591-3000
FAX: (215) 591-8812

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX : (215) 721 9669



September 3, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
TRAMADOL HYDROCHLORIDE TABLETS, 50 mg

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product Tramadol Hydrochloride Tablets, 50 mg.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of 23 volumes; 11 for the archival copy and 12 for the review copy.

The application contains a full report of two *in vivo* bioequivalence studies. These studies compared Tramadol Hydrochloride Tablets, 50 mg manufactured by TEVA Pharmaceutical Industries, Ltd. to the reference listed drug, Ultram® under both fasting and post-prandial conditions.

At the time of the dosing of the bioequivalence study and preparation of this Abbreviated New Drug Application, the marketed reference listed drug was available only as an unscored tablet. Since this time, R.W. Johnson has received FDA approval for a new dosing schedule which includes the use of a scored 50 mg tablet. The configuration of the tablet presented in this original abbreviated new drug application is consistent with the dosage and administration instructions included in our proposed product labeling which does not, in Teva's opinion, violate R.W. Johnson's exclusivity.

Teva Pharmaceuticals USA hereby commits to manufacture a test batch of Tramadol HCl Tablets 50 mg with a scoring configuration comparable to that of the innovator. Information regarding the manufacturing and QC "release" testing of this batch including dissolution profile comparisons will be submitted upon their completion towards the review and approval of this ANDA.

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3000, ext. 3142, or by facsimile at (215) 591-8812.

Sincerely,

Deborah A. Jaskot
Executive Director, Regulatory Affairs

DAJ/tdt
Enclosures

ANDA 75-977

OCT 17 2000

Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Madam:

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 5, 2000

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

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

Should you have questions concerning this application, contact:

Jeen Min
Project Manager
(301) 827-5849

Sincerely yours,

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

ANDA 75-977
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 10/16/00
HFD-615/PPatel, CSO _____ date 10/16/00
Word File V:\Firmsnz\Teva\ltrs&rev\75977.ACK
F/T PMP 10/16/00
ANDA Acknowledgment Letter!

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NEW CORRESPONDENCE

NEW CORRESP 1
NC/Brb

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-977
TRAMADOL HYDROCHLORIDE TABLETS, 50 mg
NEW CORRESPONDENCE - RESPONSE TO DECEMBER 7, 2000 TELEPHONE REQUEST

Dear Mr. Buehler:

We submit herewith two sets of duplicate $3^1/_2$" diskettes containing the parent data for the Food Effect, 3-Way Single Dose and Fasting, 2-Way Single Dose bioequivalence studies in response to a December 7, 2000 telephone request from Lizzie Sanchez of the Division of Bioequivalence, Office of Generic Drugs. Ms. Sanchez acknowledged the receipt of the diskettes containing the metabolite data and indicated that the diskettes containing the parent data were not provided. As such the diskettes containing the parent data are provided for your review and retention. We apologize for any inconvenience this inadvertent exclusion may have caused the reviewer.

It is Teva Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the request set forth in the December 7, 2000 telephone request. This information is submitted towards your continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/RY

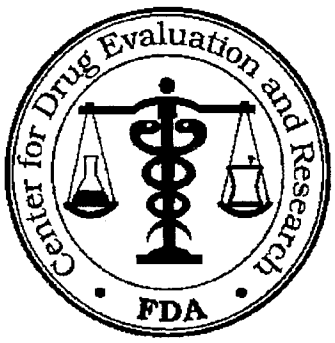
PE/brb
Enclosures

BIOEQUIVALENCY AMENDMENT

ANDA 75-977

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

FEB 25 2001



TO: APPLICANT: TEVA Pharmaceuticals USA TEL: 215-591-3000

ATTN: Deborah J. Jaskot FAX: 215-591-8812

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on September 3, 2000, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tramadol Hydrochloride Tablets, 50 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

PMP

FEB 5 2001

1.1

GAS

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:75-977 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Tramadol Hydrochloride Tablets, 50 mg

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

1. Your submitted dissolution testing is not acceptable. The Division of Bioequivalence recommends the following dissolution 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

   The comparative dissolution profiles (test and reference products) should include all individual time points data, the dissolution mean for each time point, the range (maximum and minimum), and the percentage of coefficient of variation (in a side-by-side tabular format, if possible). The dissolution testing should be done on tablets from the same lot number that was used in the in vivo bioequivalence study.

2. Please provide the raw data of the long-term freezing (-25 °C) stability. The stability data should cover a period equal to the time from the day each study started (collected blood samples) to the day the last sample was analyzed.

3. Please submit information on the batch/lot size of the test product.

Sincerely yours,

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

rate Headquarters:
PHARMACEUTICALS USA
Horsham Road, PO Box 1090
Wales, PA 19454-1090

(215) 591 3000
215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

N/AB

ruary 22, 2001

ORIG AMENDMENT

BIOEQUIVALENCE AMENDMENT

y Buehler, Director
ice of Generic Drugs
d and Drug Administration
cument Control Room
tro Park North II
00 Standish Place, Room 150
ckville, MD 20855-2773

DA #75-977
AMADOL HYDROCHLORIDE TABLETS, 50 mg
OEQUIVALENCE AMENDMENT - RESPONSE TO FEBRUARY 5, 2001 REVIEW LETTER

ar Mr. Buehler:

esponse to a bioequivalence review letter received from the Office of Generic Drugs, Division Bioequivalence, dated February 5, 2001, we submit herein a bioequivalence amendment for the ove-referenced pending ANDA. The comments are addressed in the order they were presented the February 5, 2001 review letter, a copy of which is provided in **Attachment 1**.

As requested, the dissolution method used for Tramadol Tablets, 50 mg has been revised to the following:

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

Please find in **Attachment 2** dissolution testing results using this method for Tramadol Tablets, 50 mg (Lot K-24052) and Ultram® Tablets, 50 mg (Lot BHA 1621), which are the lots used in the bioequivalence studies for this ANDA. Please note that the dissolution method, SI-11186 will be updated to note these revisions and will be provided to the Agency as soon as the revisions are complete.

ATTACHMENT 1
ATTACHMENT 2
ATTACHMENT 3
ATTACHMENT 4

NC/BIO 12.18.00 12.18.00 21

Long-term frozen stability data provided by the contract research organization that conducted the bioequivalence studies contained in the above-referenced ANDA are provided in **Attachment 3**. Please note that these data are from plasma samples which were stored frozen (data at both -25° C and -70° C are provided) for 112 days, which covers the length of time plasma samples were stored frozen in our bioequivalence studies.

Please note that the batch size for Lot K-24052 was ——— tablets, which is also the intended commercial batch size. Enclosed in **Attachment 4**, please find pages from the original ANDA for reference which indicate batch sizes for both the ANDA batch (K-24052) as well as future commercial batches (Section VI, page 72; Section XI.3, pages 3840 and 3841; and pages from the executed manufacturing batch card found in Section XII.2, pages 3853, 3875 and 3876).

s Teva Pharmaceuticals USA's opinion that the information presented herein represents a nplete response to the deficiency's set forth in the February 5, 2001 review letter. This rmation is submitted towards your continued review and approval of this ANDA. If there are further questions, please do not hesitate to contact me at (215) 591-3141 or facsimile at (215) -8812.

icerely,

/jbp
closures

CENTER FOR DRUG
FEB 23 2001
OGD
EVALUATION AND RESEARCH

ATTACHMENT 1
ATTACHMENT 2
ATTACHMENT 3
ATTACHMENT 4

NC/810 12.18.00 12.19.00

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

April 4, 2001

N/AM

MINOR AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA # 75-977
TRAMADOL HCl TABLETS, 50 mg
MINOR AMENDMENT – RESPONSE TO MARCH 5, 2001 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced pending ANDA in response to your March 5, 2001 review letter. The deficiencies are addressed in the order in which they were presented. For ease of your review, a photocopy of the letter is provided in ***Attachment 1***.

I. Chemistry, Manufacturing and Controls

A. Chemistry Deficiencies

1. Per your recommendation, the drug substance monograph has been revised [ ] (***Attachment 2***)

[ ]

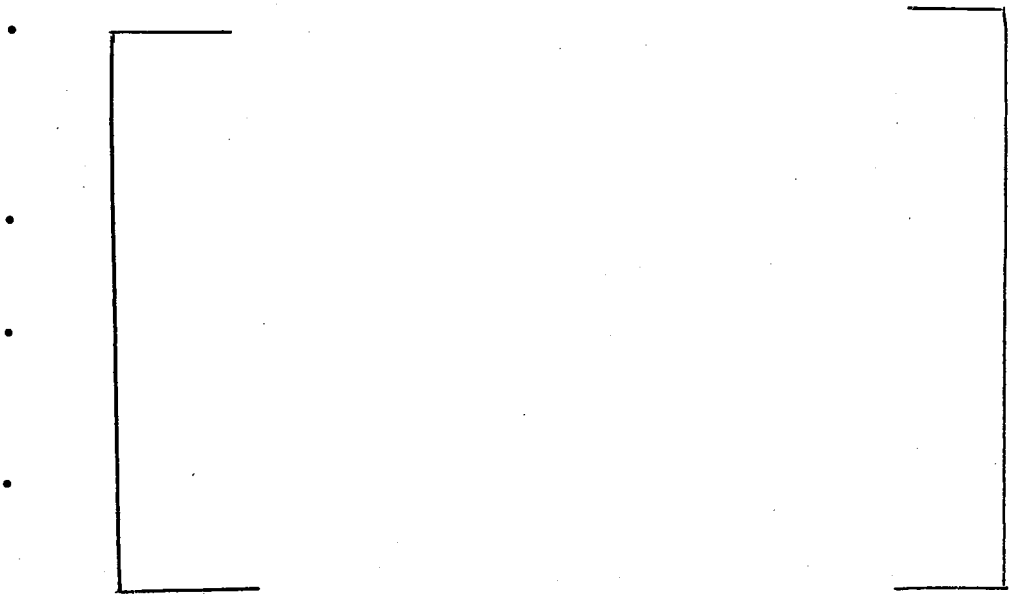
Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

4/4/2001 TEVA LETTER



2. The method validation package has been forwarded to an FDA field laboratory.

II Labeling

1. GENERAL

   a. We acknowledge the issuance of dosing exclusivity (D-63) for the new titration information approved on December 23, 1999, for the insert labeling of the reference listed drug, Ultram®. Enclosed, please find an updated Exclusivity Statement. ***(Attachment 13)***

   b. Please note that TEVA's proposed labeling will not include the dosing information covered by the D-63 or D-44 exclusivities as approved for the reference listed drug, Ultram® until their respective expiration dates.

2. CONTAINER – 100s & 1000s

   Draft printed container labels and a side-by-side comparison which incorporate revisions from deficiency comments are provided herein. ***(Attachment 14)***

3. INSERT

   Draft printed insert and a side-by-side comparison which incorporate revisions from deficiency comments are provided herein. ***(Attachment 15)***

The information provided herein represents, in our opinion, a complete response to your letter of March 5, 2001 and is submitted for your continued review and approval of this pending ANDA # 75-977. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/dl
Enclosures

APPEARS THIS WAY
ON ORIGINAL

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 8, 2001

NEW CORRESP
NEW CORRESPONDENCE
NC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA # 75-977
TRAMADOL HCl TABLETS, 50 mg
NEW CORRESPONDENCE

Dear Mr. Buehler:

We submit herewith a new correspondence to the above-referenced pending ANDA in response to a request made in a May 3, 2001 telephone conversation by Glen Smith of your office to Robert Vincent of TEVA Pharmaceuticals USA. Specifically, this communication pertained to our April 4, 2001Minor Amendment, which contained information on batch K-27098 of the scored tablets. Mr. Smith has indicated that in order to maintain a classification of "Minor Amendment" we should submit a certification that the addition of a scoring configuration was the only change as compared to the tablets used in our original bioequivalence studies. As such, please find enclosed a certification that there have been no changes to drug product composition, process or specifications from the original ANDA batch beyond the addition of scoring. ***(Attachment 1)***

This information is submitted for your continued review and approval of this pending ANDA # 75-977. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/dl
Enclosures

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

ORIG AMENDMENT

June 14, 2001

TELEPHONE AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-977
TRAMADOL HYDROCHLORIDE TABLETS, 50 mg
TELEPHONE AMENDMENT- RESPONSE TO JUNE 5, 2001 TELEPHONE CONTACT

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA in response to a telephone contact between Jeen Min of the Office of Generic Drugs and Philip Erickson, Director of Regulatory Affairs on June 5, 2001. Mr. Min phoned requesting several items needed to complete the review of our pending ANDA. These items are addressed below in the order in which they were presented in the aforementioned conversation.

1. According to our commitment, [redacted] specifications stated in the proposed batch record match those found in the provided executed batch record.

2. The Tramadol Hydrochloride 50 mg Tablets Analytical Method for Product (AM-PR0031, Edition 03), used for both release and stability testing, has been revised to reflect the updated rpm speed (100 rpm). A revised Analytical Method for Product is provided as **Attachment 2.**

3. As requested, we have provided all accumulated stability data for the scored tablet configuration (**Attachment 3**). Also included is a copy of the current Finished Product Stability Protocol (**Attachment 4**).

This information is submitted for your continued review and approval of this pending application. If you have any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jws
Enclosures

APPEARS THIS WAY ON ORIGINAL

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

NDA ORIG AMENDMENT
N/AF

October 4, 2001

LABELING AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA # 75-977
TRAMADOL HCl TABLETS, 50 mg
LABELING AMENDMENT - RESPONSE TO AUGUST 28, 2001 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a Labeling Amendment to the above-referenced pending ANDA in response to the August 28, 2001 review letter. A copy of the aforementioned letter is provided for ease of your review. ***(Attachment 1)***

Per your request, we have updated our insert labeling to be in accordance with the changes in innovator labeling, which were approved on August 15, 2001. In accordance with 21 CFR 314.94(a)(8)(iv), please find enclosed four copies of draft package insert labeling along with a side-by-side comparison of the proposed labeling with the previous revision. We acknowledge the Agency's request not to submit final printed insert labeling until adequate guidance is available regarding the differences of dosing information between our proposed labeling and that of the reference listed drug. ***(Attachment 2)***

Also, in accord with 21 CFR 314.94(a)(8)(iv), please find enclosed twelve copies of the final print container labels for the 100 and 1000 tablets package sizes. ***(Attachment 3)***

It is TEVA USA's opinion that the information presented herein represents a full and complete response to all of the comments set forth in the August 28, 2001 review letter. This information is submitted for your continued review and approval of ANDA # 75-977. If there are any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

PE/dl
Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
RECEIVED
OCT 05 2001
OGD

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

January 17, 2002

PATENT AMENDMENT

NEW CORRESP
NC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-977
TRAMADOL HYDROCHLORIDE TABLETS, 50 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,339,105

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced "approvable" ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,339,105, which on its face, has been assigned to Ortho-McNeil Pharmaceutical, Inc.. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations*, Teva wishes to provide the enclosed certification with regard to this patent.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

CENTER FOR DRUG
JAN 18 2002
OGD
EVALUATION AND RESEARCH

1/23/02
Not list in Orange Book.
E-mailed Marya Holovec to confirm.
M.M.P

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

February 5, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, Maryland, 20855-2773

UNSOLICITED AMENDMENT

N/AF

ORIG AMENDMENT

ANDA 75-977
TRAMADOL HYDROCHLORIDE TABLETS, 50 mg
UNSOLICITED AMENDMENT

Dear Mr. Buehler:

We submit herewith an unsolicited amendment to the above referenced approvable ANDA. This amendment provides two alternative plans for labeling designed to omit the exclusivity-protected 25 mg titration dosing schedule approved for the Reference Listed Drug (RLD) Ultram®, without relying upon the Discontinued Labeling Guidance as a basis of approval and without compromising the safety of Teva's tramadol product. Specifically, the Dosage and Administration section will recommend use only in patients for whom rapid onset of pain relief is required, using the same language in the approved Ultram labeling, and, like the approved Ultram labeling, will not recommend the exclusive 25 mg titration dosing schedule for such patients. The proposed labeling (as does the approved innovator's labeling) includes a description of the 50 mg titration dosing in the Titration Trials section and therefore provides information on a titration dose to improve tolerability. Since the 50 mg titration dosing schedule is protected by D-44 exclusivity, Teva does not seek approval of the ANDA until February 21, 2002, at which time it plans to include the 50 mg titration dosing information only in the Titration Trials section of the labeling. As an alternative, we propose to use the foregoing approach but with

[ ]

With these proposed changes we believe this ANDA will be eligible for final approval, and **we hereby request that such approval be made effective on February 21, 2002**, the expiration date of Ortho-McNeil's exclusivity (D-44) on a 50 mg titration dosing schedule.

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FEB 05 2002

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2/5/2001 TEVA LETTER

and does not present any issues of safety for the use of the drug as labeled. The labeling describes a non-scored tablet which was submitted in Teva's original application. This will be the marketed product description in order to ensure that the innovator's legitimate exclusivity rights are protected. In addition to the new insert labeling, a revised certification statement is also provided. (Attachment D)

We request that FDA promptly review this submission and respond with any questions or comments within 10 business days, so that any remaining issues can be discussed and resolved prior to the February 21 expiration of McNeil's first dosing exclusivity period.

Sincerely,

Deborah Jaskot

DJ/bj
Enclosures

APPEARS THIS WAY
ON ORIGINAL

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

This Patent Not listed on O.B as of 1/14/02 @ 12:45pm. Therefore patent cert is inappropriate

NAE
1/14/02

February 13, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
NC

ANDA # 75-977
TRAMADOL HYDROCHLORIDE TABLETS, 50 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,339,105

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced "approvable" ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,339,105, which on its face, has been assigned to Ortho-McNeil Pharmaceutical, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations*, Teva wishes to provide the enclosed certification with regard to this patent.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

PE/jbp
Enclosures

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FEB 13 2002
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TEVA

Administrative Offices:
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North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

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FAX: (215) 591 8600

(This patent is not listed in O.B. as of 2/14/02 @ 12:45pm - Therefore PIV cert is inappropriate)

NAI mhs 2-14-02

NAI 2/15/02 Clark
See comment above

February 14, 2002

PATENT AMENDMENT

NEW CORRESP

NC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-977
TRAMADOL HYDROCHLORIDE TABLETS, 50 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,339,105

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced "approvable" ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,339,105, which on its face, has been assigned to Ortho-McNeil Pharmaceutical, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations*, Teva wishes to provide the enclosed certification with regard to this patent. A letter from Johnson & Johnson indicating Ortho-McNeil's intent to list this patent in the Orange Book is attached for your information. Please note that U.S. Patent No. 6,339,105 issued on January 15, 2002, therefore Teva anticipates that Ortho-McNeil would have taken steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

PE/jbp
Enclosures

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Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

P.E.P 3/5/02 NAI

February 15, 2002

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NC

NEW CORRESP

NAI gm 3/12/02

ANDA # 75-977
TRAMADOL HYDROCHLORIDE TABLETS, 50 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,339,105

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced "approvable" ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,339,105, which on its face, has been assigned to Ortho-McNeil Pharmaceutical, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations*, Teva wishes to provide the enclosed certification with regard to this patent. A letter from Johnson & Johnson indicating Ortho-McNeil's intent to list this patent in the Orange Book is attached for your information. Please note that U.S. Patent No. 6,339,105 issued on January 15, 2002, therefore Teva anticipates that Ortho-McNeil would have taken steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

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Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

VRT
P.M.P
3/4/02

February 26, 2002

PATENT AMENDMENT
NEW CORRESP
NC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-977
TRAMADOL HYDROCHLORIDE TABLETS, 50 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,339,105

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced "approvable" ANDA for the purpose of providing a revised patent certification statement. Teva recently filed a patent certification containing a paragraph IV certification for U.S. Patent 6,339,105. Based on knowledge obtained since that certification was submitted and the delay in availability of the detailed use code, we provide herein a revised certification with the intent to change our paragraph IV certification to a statement under 21 CFR § 314.94(a)(12)(iii)(A). The proposed labeling submitted in our amendment of February 5, 2002 is appropriate to this use statement.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Deborah Jaskot /for

PE/jbp
Enclosure

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2/28/2002 TEVA LETTER

("ADDENDUM TO UNSOLICITED LABELING AMENDMENT DATED 2/5/2002")

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

N/AF

ORIG AMENDMENT

May 24, 2002

UNSOLICITED AMENDMENT:
FINAL PRINT LABELING

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 75-977
TRAMADOL HYDROCHLORIDE TABLETS, 50 mg
UNSOLICITED AMENDMENT- FINAL PRINT LABELING

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced "approvable" ANDA for the purpose of providing final print insert labeling for this product. Please note that the draft of this insert was provided to the Agency in a February 5, 2002 amendment to ANDA 75-977 as "proposal A". Further, please note that TEVA believes the submission of this final print labeling completes the application process for this product and we therefore anticipate final approval of this ANDA upon the Agency's satisfactory review of this insert labeling. Therefore, please find enclosed twelve copies of final print insert labeling which is identical in content to that provided as "proposal A" in our February 5, 2002 amendment.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

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MAY 2 8 2002
OGD / CDER

Park, Chan H

om: Park, Chan H
nt: Tuesday, June 11, 2002 11:13 AM
o: 'Djaskot@tevausa.com'
Subject: 75-977 (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
	'Djaskot@tevausa.com'	
	Park, Chan H	Delivered: 6/11/02 11:13 AM

APPEARS THIS WAY
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

June 11, 2002

NDA #75-977
ORIG AMENDMENT
MINOR AMENDMENT -
FINAL APPROVAL REQUESTED

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-977
TRAMADOL HYDROCHLORIDE TABLETS, 50 mg
MINOR AMENDMENT – FINAL APPROVAL REQUESTED

Dear Mr. Buehler:

We submit herewith a Minor Amendment – Final Approval Requested for the above-referenced pending ANDA in response to a June 11, 2002 electronic mail communication from the Office of Generic Drugs. This application was originally granted approvable status on January 15, 2002.

As requested, our insert labeling has been revised in accord with the agency's instructions. A comparison to our previous revision insert labeling has been updated accordingly. Please find 12 copies of final insert labeling, as well as a comparison to our previous revision in **Attachment 1**.

We confirm that there have been no chemistry, manufacturing, or controls changes since our receipt of the approvable letter. Please note that all control documents for the unscored tablet as provided in our original application will be used in the manufacture and release of the drug product except for those provided herein. A Release Specification Summary and Finished Product Stability Protocol reflecting the _____ specifications (requested in your March 5, 2001 review letter) are provided in **Attachment 2**.

We look forward to your immediate final approval of ANDA # 75-977. Should you have any questions regarding the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosures

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JUN 12 2002
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