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, [illegible] 12/31/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-977

LABELING

APPROVED

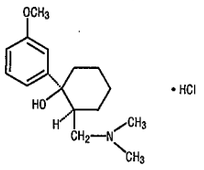
JUN 19 2002

TRAMADOL HYDROCHLORIDE TABLETS, 50 mg

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.

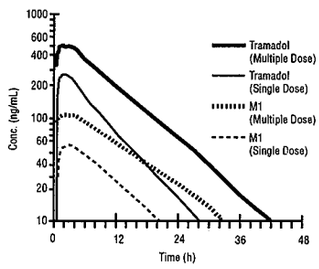


Table 1
Mean (%CV) Pharmacokinetic Parameters for Racemic Tramadol and M1 Metabolite

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.

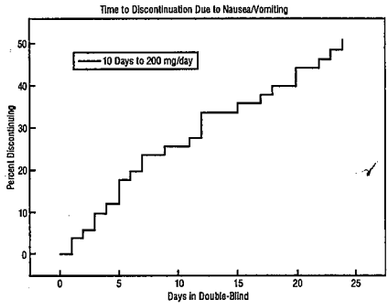
Tramadol has been studied in three long-term controlled trials involving a total of 820 patients, with 530 patients receiving tramadol. Patients with a variety of chronic painful conditions were studied in double-blind trials of one to three months duration. Average daily doses of approximately 250 mg 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 anoreactics),**
- **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.

of Overdosage
us potential consequences of overdosage with tramadol are central nervous m depression, respiratory depression and death. In treating an overdose, ry attention should be given to maintaining adequate ventilation along with al supportive treatment (see **OVERDOSAGE**).

AUTIONS
Abdominal Conditions
idministration of tramadol may complicate the clinical assessment of its with acute abdominal conditions.

n Renal and Hepatic Disease
red renal function results in a decreased rate and extent of excretion of dol and its active metabolite, M1. In patients with creatinine clearances of han 30 mL/min, dosing reduction is recommended (see **DOSAGE AND NISTRATION**). Metabolism of tramadol and M1 is reduced in patients with nced cirrhosis of the liver. In cirrhotic patients, dosing reduction is nmended (see **DOSAGE AND ADMINISTRATION**).

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

nation for Patients
madol hydrochloride tablets may impair mental or physical abilities uired for the performance of potentially hazardous tasks such as driving a or operating machinery.
madol hydrochloride tablets should not be taken with alcohol containing verages.
madol hydrochloride tablets should be used with caution when taking med- ions such as tranquilizers, hypnotics or other opiate containing analgesics.
patient should be instructed to inform the physician if they are pregnant, nk they might become pregnant, or are trying to become pregnant (see **ECAUTIONS, Labor and Delivery**).
patient should understand the single-dose and 24-hour dose limit and the e interval between doses, since exceeding these recommendations can ult in respiratory depression, seizures and death.

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

With Carbamazepine
nts taking carbamazepine may have a significantly reduced analgesic effect madol. Because carbamazepine increases tramadol metabolism and because seizure risk associated with tramadol, concomitant administration of dol and carbamazepine is not recommended.

With Quinidine
dol is metabolized to M1 by CYP2D6. **Quinidine** is a selective inhibitor of soenzyme, so that concomitant administration of quinidine and tramadol s in increased concentrations of tramadol and reduced concentrations of The clinical consequences of these findings are unknown. *In vitro* drug ction studies in human liver microsomes indicate that tramadol has no on quinidine metabolism.

With Inhibitors of CYP2D6
tro drug interaction studies in human liver microsomes indicate that omitant administration with inhibitors of CYP2D6 such as fluoxetine, oxetine, and amitriptyline could result in some inhibition of the metabolism of dol.

With Cimetidine
omitant administration of tramadol with **cimetidine** does not result in ally significant changes in tramadol pharmacokinetics. Therefore, no alteration tramadol dosage regimen is recommended.

With MAO Inhibitors
actions with **MAO Inhibitors**, due to interference with detoxification anisms, have been reported for some centrally acting drugs (see **WARNINGS, With MAO Inhibitors**).

With Digoxin and Warfarin
marketing surveillance has revealed rare reports of digoxin toxicity and tion of warfarin effect, including elevation of prothrombin times.

nogenesis, Mutagenesis, Impairment of Fertility
ght, but statistically significant, increase in two common murine tumors, onary and hepatic, was observed in a mouse carcinogenicity study, particularly ed mice. Mice were dosed orally up to 30 mg/kg (90 mg/m^2 or 0.36 times aximum daily human dosage of 246 mg/m^2) for approximately two years, ugh the study was not done with the Maximum Tolerated Dose. This ng is not believed to suggest risk in humans. No such finding occurred in carcinogenicity study (dosing orally up to 30 mg/kg, 180 mg/m^2, or 0.73 the maximum daily human dosage).

adol was not mutagenic in the following assays: Ames *Salmonella* microsomal ation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay ne absence of metabolic activation), dominant lethal mutation tests in mice, nosome aberration test in Chinese hamsters, and bone marrow micronucleus in mice and Chinese hamsters. Weakly mutagenic results occurred in the nce of metabolic activation in the mouse lymphoma assay and micronucleus n rats. Overall, the weight of evidence from these tests indicates that adol does not pose a genotoxic risk to humans.

fects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg mg/m^2) in male rats and 75 mg/kg (450 mg/m^2) in female rats. These dosages 2 and 1.8 times the maximum daily human dosage of 246 mg/m^2, respectively.

nancy, Teratogenic Effects: *Pregnancy Category C*
adol has been shown to be embryotoxic and fetotoxic in mice (120 mg/kg 60 mg/m^2), rats (≥25 mg/kg or 150 mg/m^2) and rabbits (≥75 mg/kg or mg/m^2) at maternally toxic dosages, but was not teratogenic at these dose . These dosages on a mg/m^2 basis are 1.4, ≥0.6, and ≥3.6 times the maximum human dosage (246 mg/m^2) for mouse, rat and rabbit, respectively.

rug-related teratogenic effects were observed in progeny of mice (up to mg/kg or 420 mg/m^2), rats (up to 80 mg/kg or 480 mg/m^2) or rabbits to 300 mg/kg or 3600 mg/m^2) treated with tramadol by various routes. yo and fetal toxicity consisted primarily of decreased fetal weights, skeletal ification and increased supernumerary ribs at maternally toxic dose levels. ient delays in developmental or behavioral parameters were also seen in from rat dams allowed to deliver. Embryo and fetal lethality were reported in one rabbit study at 300 mg/kg (3600 mg/m^2), a dose that would cause me maternal toxicity in the rabbit. The dosages listed for mouse, rat and t are 1.7, 1.9 and 14.6 times the maximum daily human dosage (246 mg/m^2), actively.

teratogenic Effects
adol was evaluated in peri- and post-natal studies in rats. Progeny of dams ving oral (gavage) dose levels of 50 mg/kg (300 mg/m^2 or 1.2 times the mum daily human tramadol dosage) or greater had decreased weights, and survival was decreased early in lactation at 80 mg/kg (480 mg/m^2 or 1.9 and r the maximum daily human dose).

e are no adequate and well-controlled studies in pregnant women. Tramadol ld be used during pregnancy only if the potential benefit justifies the potential to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death 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

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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**

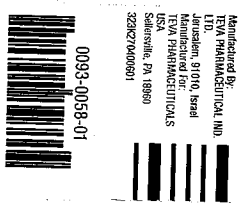
Each tablet contains:
Tramadol Hydrochloride 50 mg

JUN 19 2002

℞ only

1000 TABLETS

TEVA



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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: