20281

MOODY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 0 3 1995

NDA 20-281

The R. W. Johnson Pharmaceutical Research Institute
700 Route 202 South
P. O. Box 670
Raritan, New Jersey 08869

Attention: Ms. Jean O'Connor
Senior Director
Regulatory Affairs

Dear Ms. O'Connor:

Please refer to your August 28, 1992 new drug application and your resubmission dated September 30, 1993 submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Ultram (tramadol hydrochloride), 50 and 100 mg Tablets.

We also refer to our approvable letter dated February 17, 1995.

We acknowledge receipt of twenty-six amendments noted on the attached page.

This new drug application provides for the management of moderate to moderately severe pain.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed revised draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed revised draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-281. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

We note your correspondence dated February 20, 1995 agreeing to PHASE IV commitments which include additional studies. Please submit protocols for these studies as soon as possible. The original copy of the PHASE IV study protocols and reports should be submitted to this Division, with a copy to the Division of Drug Information Resources, HFD-80. Since that Division is responsible for tracking PHASE IV studies, a copy of all future communications regarding PHASE IV studies should also be sent to them. As stated above, we note your agreement to the following PHASE IV commitments:

1. To evaluate pediatric use data from European experience. Present to the Agency, within one year of the approval of the NDA, analysis of the available data that could support pediatric labeling.

2. To design and execute a pharmacokinetic study to investigate the effects of Ultram on quinidine concentrations in human subjects. Submit a protocol to the agency within six months of the NDA approval. Submit a completed report and any related labeling changes within one year of approval of the protocol.

3. To investigate the carcinogenic potential of Ultram through epidemiological studies, in lieu of additional animal studies. Within one year of approval of the NDA, submit a proposal for an epidemiology study of Ultram using existing foreign data bases. It should have the objective of being capable of detecting a doubling of common significant malignancies such as cancer of the gastrointestinal system or cancer of the genitourinary system. The timetable for execution of the study is to be negotiated depending on the nature of the proposal.

In addition to the PHASE IV commitments, we note that you have agreed to comply with the recommendations from the August 3, 1994 Drug Abuse Advisory Committee (DAAC) meeting to develop a plan for detection, intervention and reporting of abuse of Ultram.

As Ultram may have an abuse potential of an unknown degree, you are not permitted to advertise, promote or market the drug product by calling attention to its unscheduled status under the U.S. Controlled Substances Act.

We also note your memorandum dated April 11, 1994 signed by Andrew B. Wojatsek, Vice-President for Marketing and Sales for McNeil Pharmaceutical to Dr. Gary P. Horowitz, Senior Director of your Regulatory Affairs section, comprising "a commitment on the part of McNeil Pharmaceutical to avoid any promotional efforts for Ultram that use the tradename or any portion of it in any fashion to imply exaggerated efficacy or to exaggerate any other property of the product." Additionally, we note your letter dated April 13, 1994 addressed to Dr. John Hyde of this staff signed by Dr. Horowitz affirming your "commitment to avoid any implication of enhanced activity of tramadol hydrochloride through the use of this tradename."

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Corinne P. Moody, Project Manager, at (301) 443-3741.

Sincerely yours,

Review Team
Pilot Drug Evaluation Staff, HFD-007
Center for Drug Evaluation and Research

Robert F. Bedford, M.D.
Acting Director

John Hyde, Ph.D., M.D.
Medical Officer

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Pharmacologist

for Iftekhar Mahmood, Ph.D.
Pharmacokineticist

Pramoda Maturu, Ph.D., MBA
Chemist

Corinne P. Moody
Project Manager

Enclosures

ULTRAM® (tramadol hydrochloride) tablets

DESCRIPTION

ULTRAM® (tramadol hydrochloride) 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:

[Structural Formula]

The molecular weight of tramadol hydrochloride is 299.8. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder. It is readily soluble in water and ethanol and has a pKa of 9.41. The water/n-octanol partition coefficient is 1.35 at pH 7. ULTRAM tablets contain 50 mg of tramadol hydrochloride and are white in color. Inactive ingredients in the tablet are corn starch, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and wax.

CLINICAL PHARMACOLOGY

Pharmacodynamics

ULTRAM is a centrally acting synthetic analgesic compound that is not derived from natural sources nor is it chemically related to opiates. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding to μ-opioid receptors and inhibition of reuptake of norepinephrine and serotonin. ULTRAM's opioid activity derives from low affinity binding of the parent compound to μ-opioid receptors and higher affinity binding of the M1 metabolite. 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. The contribution to human analgesia of tramadol relative to M1 is unknown.

Tramadol-induced antinociception is only partially antagonized by the opiate antagonist naloxone in several animal tests. In addition, tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as have some other opioid analgesics. These latter mechanisms may contribute independently to the overall analgesic profile of ULTRAM. Onset of analgesia in humans is evident within one hour after administration and reaches a peak in approximately two to three hours. Peak plasma concentrations are reached about two hours after administration, which correlates closely with the time to peak pain relief.

Apart from analgesia, ULTRAM administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of an opioid. However, tramadol causes significantly less respiratory depression than morphine. In contrast to morphine, tramadol has not been shown to cause histamine release. At therapeutic doses, ULTRAM has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic changes in blood pressure have been observed.

Pharmacokinetics

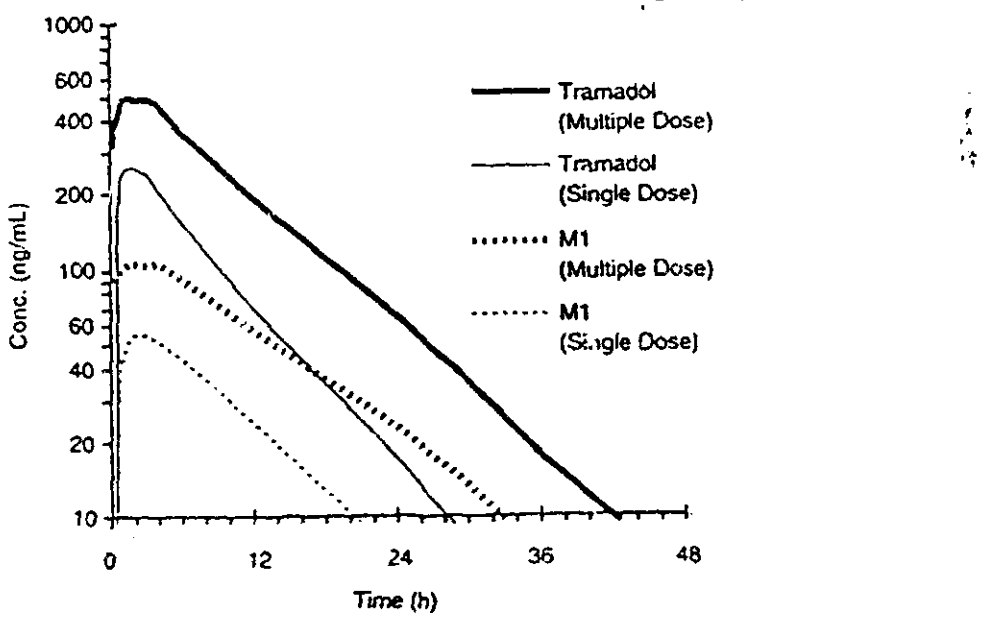
Absorption:

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a 100 mg oral dose is approximately 75%. 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. The mean peak (± SD) plasma concentration of racemic tramadol is 308 ± 78 ng/mL and occurs at approximately two hours after a single 100 mg oral dose in healthy subjects. At this dose, the mean peak plasma concentration of the active mono-*O*-desmethyl metabolite, racemic M1, is 55 ± 20 ng/mL and occurs approximately three hours post-dose. The separate [+]- and [-]-enantiomers of tramadol generally follow a parallel time course in plasma after a single 100 mg oral dose of ULTRAM. Following 100 mg oral administration of tramadol, the maximum plasma concentrations of the [-]-enantiomer of tramadol are somewhat lower than those of the [+]-enantiomer (148 ± 33 vs. 168 ± 36 ng/mL, respectively). The [-]-M1 enantiomer is present at slightly higher plasma concentrations than the [+]-M1 enantiomer (35 ± 10 vs. 26 ± 13 ng/mL, respectively). At steady state following a 100 mg q.i.d. regimen of tramadol, 3 out of 18 subjects formed relatively low amounts of [+]-M1, while their [-]-M1 formation remained similar to that of other subjects. This is believed not to be clinically significant.

Plasma concentrations of racemic tramadol are predictable over a 50 mg to 100 mg single-dose range. This is also true under multiple-dose conditions. Steady state is achieved after two days of dosing ULTRAM by a 100 mg q.i.d. regimen (maximum plasma concentration was 592 ± 177 ng/mL). The plasma half-life of tramadol, following single and multiple dosing, was 6 and 7 hours, respectively. This increase in half-life upon multiple dosing is not considered to be clinically significant or to warrant dosage adjustment for chronic use.

Mean plasma racemic tramadol and racemic M1 concentration-versus-time profiles following a single 100 mg oral dose of ULTRAM and following twenty-nine 100 mg doses four times daily are shown in Figure 1.

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.



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 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range. Although not confirmed in humans, tramadol has been shown in rats to cross the blood-brain barrier.

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. Only one metabolite (mono-*O*-desmethyltramadol, denoted M1) is pharmacologically active. Production of M1 is dependent on the CYP2D6 isoenzyme of cytochrome P450.

Elimination:
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 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 a larger area under the serum-concentration-versus-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).

Age:

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 slightly elevated (208 vs. 162 ng/mL) and the elimination half-life is slightly 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. This difference may not be of any clinical significance.

Clinical Studies

ULTRAM has been given in single oral doses of 50, 75, 100, 150 and 200 mg to patients with pain following surgical procedures (orthopedic, gynecological, cesarean section) 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 ULTRAM 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. In single-dose models of pain following surgical procedures, 150 mg provided analgesia generally comparable to the combination of acetaminophen 650 mg with propoxyphene napsylate 100 mg, with a tendency toward later peak effect.

ULTRAM has been studied in three long-term controlled trials involving a total of 820 patients, with 530 patients receiving ULTRAM. Patients with chronic conditions such as low back pain, cancer, neuropathic pain, and orthopedic and joint conditions, entered a double-blind phase of one to three months. Average daily doses of approximately 250 mg of ULTRAM in divided doses produced analgesia comparable with five doses of acetaminophen 300 mg with codeine phosphate 30 mg (TYLENOL® with Codeine #3) daily, five doses of aspirin 325 mg with codeine phosphate 30 mg daily, and with two to three doses of acetaminophen 500 mg with oxycodone hydrochloride 5 mg (TYLOX®) daily. Following the double-blind period, [illegible] patients took ULTRAM in an open

period for up to two years.

INDICATIONS AND USAGE

ULTRAM is indicated for the management of moderate to moderately severe pain.

CONTRAINDICATIONS

ULTRAM should not be administered to patients who have previously demonstrated hypersensitivity to tramadol or in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.

WARNINGS

Seizure Risk
Tramadol causes seizures in animal models, and a few seizures have been reported in humans receiving excessive single oral doses (700 mg) or large intravenous doses (300 mg). Administration of ULTRAM may enhance the seizure risk in patients taking MAO inhibitors, neuroleptics, other drugs that reduce the seizure threshold, patients with epilepsy, or patients otherwise at increased risk for seizure. In animal studies, naloxone administration increased the risk of convulsions.

Use with CNS Depressants
ULTRAM should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, phenothiazines, tranquilizers or sedative hypnotics.

Use with MAO Inhibitors
ULTRAM should be used with great caution in patients taking monoamine oxidase inhibitors, since tramadol inhibits the uptake of norepinephrine and serotonin.

PRECAUTIONS

Respiratory Depression
When large doses of ULTRAM are administered with anesthetic medications or alcohol, respiratory depression may result. Cases of intraoperative respiratory depression, usually with large intravenous doses of tramadol and with concurrent administration of respiratory depressants, have been reported in foreign experience. Such cases should be treated as overdoses (see OVERDOSAGE). ULTRAM should be administered cautiously in patients at risk for respiratory depression.

Increased Intracranial Pressure or Head Trauma
ULTRAM should be used with caution in patients with increased intracranial pressure or head injury. 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 ULTRAM.

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

Patients Physically Dependent on Opioids
ULTRAM is not recommended for patients who are dependent on opioids. Patients who have recently taken substantial amounts of opioids may experience withdrawal symptoms. Because of the difficulty in assessing dependence in patients who have previously received substantial amounts of opioid medication, caution should be used in the administration of ULTRAM to such patients.

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
Patients being treated with ULTRAM should receive the following information:

ULTRAM may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

Drug Interactions
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.

Concomitant administration of ULTRAM with **carbamazepine** causes a significant increase in tramadol metabolism, presumably through metabolic induction by carbamazepine. Patients receiving chronic carbamazepine doses of up to 800 mg daily may require up to twice the recommended dose of ULTRAM.

Tramadol is metabolized to M1 by the CYP2D6 P-450 isoenzyme. **Quinidine** is a selective inhibitor of that isoenzyme; so that concomitant administration of quinidine and ULTRAM results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of this effect have not been fully investigated, and the effect on quinidine concentrations is unknown.

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

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 (dosing orally up to 30 mg/kg 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.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg in male rats and 75 mg/kg in female rats.

Teratogenic Effects: Usage in Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. ULTRAM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Tramadol has been shown to be embryotoxic and fetotoxic in mice, rats and rabbits at maternally toxic doses 3 to 15 times the maximum human dose or higher (120 mg/kg in mice, 25 mg/kg or higher in rats and 75 mg/kg or higher in rabbits), but was not teratogenic at these dose levels. No harm to the fetus due to tramadol was seen at doses that were not maternally toxic.

No drug-related teratogenic effects were observed in progeny of mice, rats or

rabbits treated with tramadol by various routes (up to 140 mg/kg for mice, 80 mg/kg for rats or 300 mg/kg for rabbits). 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, a dose that would cause extreme maternal toxicity in the rabbit.

In peri- and post-natal studies in rats, progeny of dams receiving oral (gavage) dose levels of 50 mg/kg or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (6 to 10 times the maximum human dose). No toxicity was observed for progeny of dams receiving 8, 10, 20, 25 or 40 mg/kg. Maternal toxicity was observed at all dose levels, but effects on progeny were evident only at higher dose levels where maternal toxicity was more severe.

Labor and Delivery

ULTRAM should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks, because safe use in pregnancy has not been established. 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 ULTRAM, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

ULTRAM 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 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.

Pediatric Use

The pediatric use of ULTRAM is not recommended because safety and efficacy in patients under 16 years of age have not been established.

Use in the Elderly

In subjects over the age of 75 years, serum concentrations are slightly elevated and the elimination half-life is slightly prolonged. The aged also can be expected to vary more widely in their ability to tolerate adverse drug effects. Daily doses in excess of 300 mg are not recommended in patients over 75 (see DOSAGE AND ADMINISTRATION).

ADVERSE EXPERIENCES

ULTRAM 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 1 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 ULTRAM 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 ULTRAM and the active control groups, TYLENOL® with Codeine #3 (acetaminophen 300 mg with codeine phosphate 30 mg), and aspirin 325 mg with codeine phosphate 30 mg.

Table 1
Cumulative Incidence of Adverse Reactions for ULTRAM in Chronic Trials of Nonmalignant Pain.

	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 less than 5%, possibly causally related: Table 2 lists adverse reactions that occurred with an incidence of less than 5% in clinical trials, and for which the possibility of a causal relationship with ULTRAM exists. Reactions are separated according to whether the incidence was greater or less than 1%.

Table 2
Possibly ULTRAM-Related Adverse Reactions with an Incidence of Less Than 5%

Body System	Incidence of Adverse Reaction	
	From 1% to < 5%	Less Than 1%
Body as a Whole	Malaise	Allergic reaction; Accidental injury; Weight loss
Cardiovascular	Vasodilation	Syncope; Orthostatic hypotension; Tachycardia
Central Nervous System	Anxiety; Confusion; Coordination disturbance; Euphoria; Nervousness; Sleep disorder	Seizure (see WARNINGS); Paresthesia; Cognitive dysfunction; Hallucinations; Tremor; Amnesia; Difficulty in concentration; Abnormal gait
Gastrointestinal	Abdominal pain; Anorexia; Flatulence	
Musculoskeletal	Hypertonia	
Respiratory		Dyspnea
Skin	Rash	Urticaria; Vesicles
Special Senses	Visual disturbance	Dysgeusia
Urogenital	Urinary retention; Urinary frequency; Menopausal symptoms	Dysuria; Menstrual disorder

Other adverse experiences, causal relationship undetermined: A variety of other adverse events were reported infrequently in patients taking ULTRAM during clinical trials. A causal relationship between ULTRAM and these events has not been determined. However, the most significant events are listed below as alerting information to the physician.

Body as a whole: Suicidal tendency.

Cardiovascular: Abnormal ECG, hypertension, myocardial ischemia, palpitations.

Central Nervous System: Migraine.

Gastrointestinal: Gastrointestinal bleeding, hepatitis, stomatitis

Laboratory abnormalities: Creatinine increase, elevated liver enzymes, hemoglobin decrease, proteinuria.

Sensory: Cataracts, deafness, tinnitus.

DRUG ABUSE AND DEPENDENCE

Although tramadol can produce drug dependence of the μ-opioid type (like codeine or dextropropoxyphene) and potentially may be abused, there has been little evidence of abuse in foreign clinical experience. In clinical trials, tramadol produced [redacted] similar to an opioid, and at supratherapeutic doses was recognized as an opioid in subjective/behavioral studies. Tolerance development has been reported to be relatively mild and withdrawal, when present, is not considered to be as severe as that produced by other opioids. Part of tramadol's activity is believed derived from its active metabolite, which is responsible for some delay in onset of activity and some extension of the duration of μ-opioid activity. Delayed μ-opioid activity is believed to reduce a drug's abuse liability.

An assay for tramadol is not included in routine urine screens for drugs of abuse.

DOSAGE AND ADMINISTRATION

For the treatment of painful conditions, ULTRAM 50 mg to 100 mg can be administered as needed for relief every four to six hours, not to exceed 400 mg per day. For moderate pain, ULTRAM 50 mg may be adequate as the initial dose, and for more severe pain, ULTRAM 100 mg is usually more effective as the initial dose.

Individualization of Dose

Available data do not suggest that a dosage adjustment is necessary in elderly patients 65 to 75 years of age unless they also have renal or hepatic impairment. For elderly patients **over 75 years old**, not more than 300 mg/day in divided doses as above is recommended. In all patients with **creatinine clearance less than 30 mL/min**, it is recommended that the dosing interval of ULTRAM 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 patients with **cirrhosis** is 50 mg every 12 hours. Patients receiving chronic **carbamazepine** doses up to 800 mg daily may require up to twice the recommended dose of ULTRAM.

OVERDOSAGE

Few cases of overdose with tramadol have been reported. Estimates of ingested dose in foreign fatalities have been in the range of 3 to 5 g. A 3 g intentional overdose in a patient in the clinical studies produced emesis and no sequelae. The lowest dose reported to be associated with fatality was possibly between 500 and 1000 mg in a 40 kg woman, but details of the case are not

completely known.

Serious potential consequences of overdosage are respiratory depression and seizure. Naloxone will reverse some, but not all, symptoms caused by overdosage with ULTRAM, so that general supportive treatment is recommended. Primary attention should be given to the assurance of adequate respiratory exchange. Hemodialysis is not expected to be helpful because it removes only a small percentage of the administered dose. Convulsions occurring in mice following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines, but were increased with naloxone. Naloxone did not change the lethality of an overdose in mice.

HOW SUPPLIED

ULTRAM (tramadol hydrochloride) 50 mg tablet (white, film-coated capsule-shaped tablet) engraved "McNeil" on one side and "659" on the other side.

ULTRAM (tramadol hydrochloride) 50 mg tablet - NDC 0045-0659 bottles of 100 tablets, and packages of 100 unit doses in blister packs (10 cards of 10 tablets each).

Dispense in a tight container. Store at controlled room temperature (15° to 30°C, 59° to 86°F).

Caution: Federal law prohibits dispensing without prescription.

Ortho Pharmaceutical Corporation
Raritan, NJ USA 08869, and
McNeil Pharmaceutical
Spring House, PA USA 19477

Revised 3/3/95

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-281

FEB 17 1995

The R. W. Johnson Pharmaceutical Research Institute
700 Route 202 South
P. O. Box 670
Raritan, New Jersey 08869

Attention: Ms. Jean O'Connor
Senior Director
Regulatory Affairs

Dear Ms. O'Connor:

Please refer to your August 28, 1992, new drug application and your resubmission dated September 30, 1993, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for tramadol hydrochloride, 50 and 100 mg tablets.

We acknowledge receipt of 24 amendments noted on the attached page, including a major amendment dated November 4, 1994, which extended the user fee due date to February 18, 1995.

This new drug application provides for the management of moderate to moderately severe pain.

We have completed the review of this application as submitted with draft labeling. Before the application may be approved, however, it will be necessary for you to submit revised labeling for the drug identical in content to the enclosed revised draft.

Additionally, before the application may be approved, agreement must be reached on the proprietary name.

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In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

NDA 20-281

List of Amendments

1. 07-01-93
2. 09-30-93
3. 10-01-93
4. 11-01-93
5. 12-10-93
6. 01-20-94
7. 02-09-94
8. 03-04-94
9. 03-11-94
10. 03-30-94
11. 04-07-94
12. 06-10-94
13. 06-24-94
14. 06-27-94
15. 06-29-94
16. 07-12-94
17. 07-29-94
18. 11-04-94
19. 11-11-94
20. 11-14-94
21. 11-21-94
22. 01-23-95
23. 02-03-95
24. 02-14-95

Should you have any questions, please contact Corinne P. Moody, Project Manager at (301) 443-3741.

Sincerely yours,

Review Team
Pilot Drug Evaluation Staff, HFD-007
Center for Drug Evaluation and Research

Enclosures

Robert F. Bedford, M.D. Acting Director	John Hyde, Ph.D., M.D. Medical Officer
Rudolph Widmark, M.D. Medical Officer	Michael Klein, Ph.D. Interdisciplinary Scientist
Harry Geyer, Ph.D. Pharmacologist	Iftekhar Mahmood, Ph.D. Pharmacokineticist
Pramoda Maturu, Ph.D., MBA Chemist	Corinne P. Moody Project Manager

EXCLUSIVITY SUMMARY FOR NDA # 20-281 SUPPL # ____

Trade Name Ultram Generic Name tramadol HCl

Applicant Name RW Johnson HFD # 007

Approval Date If Known 03-03-95

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

If yes, what type? (SE1, SE2, etc.) N/A

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

Form OGD-011347 Revised 7-90

cc: Original NDA Division File HFD-85 Mary Ann Ward

HFD-007/Moody

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

N/A

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

! _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Corinne P. Moody 03-03-95
Signature Date
Title: Project Manager

RF Bedford Mar 7 1995
Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-85 Mary Ann Ward
NDA 20-251 HFD-007
HFD-007/Moody

ITEM 13

PATENT AND EXCLUSIVITY INFORMATION
ULTRAM® tramadol hydrochloride

1. ACTIVE INGREDIENT(S)

   Tramadol hydrochloride

2. STRENGTH

   100 mg tablets

3. TRADE NAME

   ULTRAM®

4. DOSAGE FORM/ROUTE OF ADMINISTRATION

   tablet/oral

5. APPLICANT FIRM NAME

   The R. W. Johnson Pharmaceutical Research Institute

6. NDA NUMBER

   20,281

7. APPROVAL DATE

   Pending

8. EXCLUSIVITY -

   Five years after approval of the NDA

9. APPLICABLE PATENT NUMBERS AND EXPIRATION DATE OF EACH

3,652,589	March 26, 1989
3,830,934	August 20, 1991

CERTIFICATION REQUIREMENT FOR APPROVAL OF A DRUG PRODUCT

The R. W. Johnson Pharmaceutical Research Institute certifies that we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this NDA.

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-281 Trade (generic) names Ultram (tramadol HCl)
Tablets, 50 & 100 mg

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
✓ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: The drug has been marketed in foreign countries for about 17 years. The sponsor has committed to evaluating the pediatric use data from European experience, and to present to the agency an analysis of available data that could support pediatric labeling.

Corinne P. Moody
Signature of Preparer

03-03-95
Date

cc: Orig NDA 20-281
HFD-007/Div File
A Action Package
FD-001/Moody

Tramadol Clinical Efficacy

The sponsor's therapeutic trials consisted of 20 single-dose analgesia studies, 2 short multiple-dose studies, and 3 long-term (1 to 3 month) studies of chronic painful conditions. In addition, there were three studies of abuse liability, a study of effect on GI motility, and several metabolic and PK studies.

The parts of the NDA covered in this section are the single-dose studies and the three long term studies. The 2 short multi-dose studies are not covered other than that their data are included in the safety summary. The abuse liability studies are key for the scheduling deliberation, and they are reviewed in a separate section of this Pack.

A list reports in this section is presented on the next page as an annotated table of contents:

Contents of Tramadol Clinical Efficacy Section

Tramadol Single-Dose Analgesia Trials Synopsis

These dental and surgical pain models established the analgesic efficacy of tramadol at a dose of 100 mg or more. Single doses below 100 mg did not consistently provide analgesia. The 100 mg dose tended to do better than 60 mg of codeine, but in several studies it did worse than 650 mg aspirin with 60 mg codeine. A 150 mg dose seemed comparable to 650 mg acetaminophen with 100 mg propoxyphene, but the 100 mg was not adequately compared to that combination. Some dental models showed a plateau, or even a second rise, late in the observations period, suggesting the effect of an active metabolite.

Tramadol Study TKB: Three Month Study of Chronic Pain

Tramadol Study TKM: One Month Study of Pain of Malignancy

Tramadol Study TL2: One Month Study of Chronic Pain in Elderly

These reports cover the three long-term trials. Each had an active analgesic/narcotic control and no placebo. Tramadol use rose by 7% to 16% over the double-blind portions of the studies. Tramadol was generally very close to the control in terms of pain scores and global scores. In all three trials, patients tended to leave the study faster in the tramadol arm. In study TKB a small subset participated in a 3-day withdrawal study which did not find much change in withdrawal scores over the period, but which did not distinguish tramadol from the control, either.

Tramadol Integrated Safety Summary

MEDICAL OFFICER REVIEW

NDA #: 20-281
NAME: ULTRAM (Tramadol Hydrochloride).
SPONSOR: R.W. Johnson
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.
REVIEW DATE: January 12, 1995.
CSO: C. Moody

INTRODUCTION:

This report provides an integrated review of safety results from the clinical trials and from the foreign cases reported by the German manufacturer, Gruenenthal. Deaths, serious adverse events, and changes in vital signs and laboratory values are reviewed more extensively as separate reports in this section of the Pack. This section also includes a review of data on the respiratory effects of tramadol. This integrated summary incorporates the conclusions from those separate reports, and includes analysis of the non-serious adverse events recorded from the U.S. therapeutic trials.

DEATHS

A detailed review of death reports from U.S. trials and foreign experience appears as a separate report under this same section. From that review, the risk of death from tramadol taken in usual oral doses (100 to 200 mg) appears to be quite low, as there is no clearly incriminating case report. Of course, rare allergic or idiopathic fatal reactions cannot be ruled out. Tramadol may be fatal if taken orally at about ten times the recommended single oral dose (possibly as little as 12 mg/kg).

Of particular note was the complete lack of any clear cases of tramadol causing death from respiratory depression. Although respiratory depression was mentioned in two of the cases, they were not very indicting of tramadol.

SERIOUS ADVERSE EVENTS

A detailed review of serious non-fatal reports from U.S. trials and foreign experience appears as a separate report under this same section.

Three patients in U.S. abuse liability studies had seizures attributable to tramadol. Two patients in chronic studies had seizures; attribution was unclear. There were also seizure reports from foreign experience. It appears that tramadol may cause seizures in single high doses (which can

be as low a 700 mg PO or 200 mg IV). The risk may be increased for patients taking neuroleptics. The seizure risk for chronic use of recommended doses is unclear.

There were foreign reports of non-fatal respiratory depression, mostly associated with IV administration. Tramadol may cause respiratory depression if given in higher than recommended doses or if given to patients with compromised respiratory function.

Tramadol also may cause clinically significant hypotensive effects in some patients (probably fewer than 1%), and it may cause hallucinations in an occasional patient (also probably fewer than 1%).

VITAL SIGNS AND LABORATORY VALUES

A review of vital signs and laboratory data from the chronic U.S. trials appears as a separate report under this same section. There were no clinically significant changes in population averages of vital signs or routine laboratory values. In particular, there was no evidence of a general orthostatic effect of tramadol. Examination of patients with selected laboratory abnormalities found no case in which tramadol was the probable cause.

NON-SERIOUS ADVERSE EVENTS

A range of non-serious adverse events were captured in the U.S. short- and long-term therapeutic trials. Since the patient populations and duration of treatment were different, these two types of trials are considered separately.

Short Term Therapeutic Trials

There were 9 single-dose dental pain trials, 11 single-dose surgical pain trials, 1 short-term dental pain trial and 1 short-term surgical pain trial. There were a few small abuse liability, GI motility, PK and metabolic trials that were not included due to the difference in doses used and the fact that they were healthy volunteers instead of being part of a target treatment population.

The numbers of patients exposed to each dose are tabulated below:

Tramadol Dose (mg)	Patients
50	647
75	427
100	707
150	326
200	52

The 50 and 100 mg doses tended to be used in the dental studies, while the 75 and 150 mg doses were used mostly in the surgical studies. The proposed analgesic dose is 100 mg. For computing incidence rates, data from the 75, 100 and 150 doses were pooled to provide a group of 1460 patients. This pooling increases sample size as well as providing a better balance between surgical and dental pain models.

Table 1 shows the number and percentage of patients with at least one adverse event for each of the events listed. Although the table includes all the active comparators, the only events listed are those which occurred at least once in the tramadol or the placebo group. The table also includes a nominal p-value (corrected chi-square test) for comparing the tramadol and placebo rates; no adjustment has been made for study or site. It has been customary to use $p<.2$ as a rough guide to screen for possible relatedness.

The most common adverse events with tramadol were dizziness (14%), somnolence (17%), nausea (20%) and vomiting (10%); all of which were more frequent than in placebo. Headache was not unusual either, but occurred at about the same frequency as placebo. Some lower frequency events also appeared more common with tramadol than placebo. These were asthenia (1.7%), vasodilation (1.0%), tremor (1.1%), dry mouth (1.0%), pruritus (2.1%), sweating (2.5%), and menopausal symptoms (1.1%).

Although tabulations are not presented here, adverse event rates (for events occurring in at least 1%) were examined by dose of tramadol. Comparisons are complicated by the fact that 50 and 100 mg doses were used together in some studies, while others used 75 and 150 mg doses. Only one study used all four together. The 200 mg dose was used in only one trial. Although headache, dizziness, somnolence, nausea, vomiting and sweating appeared much more common at the highest dose, the evidence for dose-response in the vicinity of the therapeutic dose (as judged by comparing 150 to 75 mg) was weak.

Table 2 examines the adverse event rates in males vs. females for patients receiving 75 to 150 mg of tramadol. The results of PK studies have shown higher plasma concentration in females at the same doses, which might in turn result in higher toxicity. The only events included in Table 2 were those occurring to at least 1% of patients in at least one group. The table below shows the dose distribution for males and females. Females got fewer of the 100 mg doses than did males as a result of having higher representation in the surgical studies than the dental studies. One fourth of females got the 150 mg dose vs. one sixth for males.

Tramadol	Males		Females	
Dose	N	%	N	%
75	148	27%	279	31%
100	318	58%	389	43%
150	86	16%	240	26%

Nausea was more common in females (23% vs. 17%), and vomiting was also slightly more common (11% vs. 8%). Other events, notably CNS events, provided no evidence of being more common in females.

Chronic studies

The sponsor conducted 3 long-term studies: a 1-month study of pain of malignancy, and 1- and 3-month studies of other chronic pain. Each study used a different active control, and there were no placebos. A total of 503 patients were exposed to tramadol during the double-blind period of these trials.

Table 3 shows the number and percentage of patients with at least one adverse event during the double blind period for each of the events listed. The table has been edited by omitting events that occurred to fewer than 2 tramadol patients. This table shows only crude rates over the period of double-blind exposure. Lifetable rates of first occurrence of event by 30 days appear to be very similar to these crude rates. [A last minute problem with the lifetable analyses precluded their being included in this report. The results should be available for labeling day.]

The most common events were asthenia (10%), headache (26%), dizziness (28%), somnolence (21%), anorexia (6%), constipation (35%), diarrhea (6%), dyspepsia (8%), dry mouth (8%), nausea (38%), vomiting (15%), abdominal pain (5%), pruritus (9%), and sweating (7%). The main contrast with the short term studies is the appearance of a significant rate of constipation.

Table 4 compares selected event rates for males and females receiving tramadol in the double-blind period. Although nausea tended to be more common in females, vomiting was comparable, and dyspepsia was less. Women had more complaints of headache, but fewer complaints of urinary retention.

SUMMARY AND CONCLUSIONS:

Tramadol has a pattern of general adverse events (dizziness, somnolence, nausea, vomiting, constipation, sweating and pruritus) that resembles that of an opioid. The pattern was similar to that of the comparators. There have been reports of orthostatic hypotension associated with this drug; it does not appear to be a substantial problem in these studies. Females had somewhat more nausea in single-dose trials, but otherwise did not appear to be subject to significantly increased toxicity.

The labeling does not need to reflect any general effect of tramadol on vital signs or laboratory tests. This, of course, does not preclude the reporting of infrequent adverse effects on laboratory or vital signs based on spontaneous reports or adverse event reports from the trials.

The death data by themselves do not appear to require any warnings about specific lethal effects of tramadol.

The labeling should include warnings about the risk of seizure at high doses or in patients with a reduced seizure threshold. Reports of seizures with chronic therapy should be provided as alerting information, but qualified that their significance is unknown. There also should be warnings about the risk of respiratory depression at high doses or in compromised patients. Hypotension, possibly with syncope, and hallucinations should be mentioned as uncommon, probably related, adverse reactions.

John E. Hyde

John E. Hyde, Ph.D./M.D

Russ. Widerhorn 2-28-95

Table 1: Adverse Events by Drug for Short-Term Therapeutic Studies

		APAP/Prop		ASA/Codeine		Codeine		Placebo		Tramadol 75-150		p-value
BODY SYSTEM	COSTART TERM	N=324		N=319		N=710		N=899		N=1460		T vs PL
Body as a Whole	ASTHENIA			9	2.8%	8	1.1%	6	0.7%	25	1.7%	0.05
Body as a Whole	CHILLS			1	0.3%	2	0.3%	7	0.8%	4	0.3%	0.15
Body as a Whole	EDEMA			1	0.3%			1	0.1%			0.81
Body as a Whole	FEVER					2	0.3%	8	0.9%	1	0.1%	0.01
Body as a Whole	HEADACHE	8	2.5%	18	5.6%	45	6.3%	53	5.9%	94	6.4%	0.66
Body as a Whole	HOT/COLD SENSATION					4	0.6%	2	0.2%	4	0.3%	1.00
Body as a Whole	PAIN					2	0.3%	1	0.1%			0.81
Body as a Whole	PAIN, CHEST - NON SPECIFI			1	0.3%					1	0.1%	1.00
Body as a Whole	PAIN, LOWER EXTREMITIES							1	0.1%			0.81
Cardiovascular	ARRHYTHMIA									1	0.1%	1.00
Cardiovascular	HYPERTENSION							1	0.1%			0.81
Cardiovascular	HYPOTENSION					1	0.1%	1	0.1%	1	0.1%	1.00
Cardiovascular	ORTHOSTATIC HYPOTENSION									2	0.1%	0.70
Cardiovascular	PALPITATIONS									1	0.1%	1.00
Cardiovascular	SYNCOPE			2	0.6%	2	0.3%			3	0.2%	0.44
Cardiovascular	TACHYCARDIA	2	0.6%			2	0.3%	1	0.1%	1	0.1%	1.00
Cardiovascular	VASODILATION	1	0.3%			4	0.6%	4	0.4%	15	**1.0%**	0.19
Central Nervous Syst	ATAXIA							1	0.1%	1	0.1%	1.00
Central Nervous Syst	DISORDER, SLEEP									7	**0.5%**	0.09
Central Nervous Syst	DIZZINESS	11	3.4%	18	5.6%	46	6.5%	24	2.7%	200	**13.7%**	0.00
Central Nervous Syst	DREAMING ABNORMAL					1	0.1%			1	0.1%	1.00
Central Nervous Syst	NYSTAGMUS									1	0.1%	1.00
Central Nervous Syst	PARESTHESIA	3	0.9%	1	0.3%	3	0.4%	5	0.6%	7	0.5%	1.00
Central Nervous Syst	SOMNOLENCE	45	13.9%	58	18.2%	102	14.4%	65	7.2%	255	**17.5%**	0.00
Central Nervous Syst	TREMOR			4	1.3%	4	0.6%	2	0.2%	16	**1.1%**	0.03
Central Nervous Syst	VERTIGO					1	0.1%			2	0.1%	0.70
Endocrine	THIRST									1	0.1%	1.00
Gastrointestinal	ANOREXIA									1	0.1%	1.00
Gastrointestinal	BLEEDING, ORAL					3	0.4%	2	0.2%	1	0.1%	0.67
Gastrointestinal	CONSTIPATION							1	0.1%	1	0.1%	1.00
Gastrointestinal	DIARRHEA							1	0.1%	2	0.1%	1.00
Gastrointestinal	DYSPEPSIA	1	0.3%			1	0.1%	3	0.3%	7	0.5%	0.84
Gastrointestinal	DYSPHAGIA					2	0.3%			1	0.1%	1.00

Boldface = different from placebo with nominal $p < 0.20$

Table 1: Adverse Events by Drug for Short-Term Therapeutic Studies

		APAP/Prop		ASA/Codeine		Codeine		Placebo		Tramadol 75-150		p-value
BODY SYSTEM	COSTART TERM	N=324		N=319		N=710		N=899		N=1460		T vs PL
Gastrointestinal	ERUCTATIONS					1	0.1%	1	0.1%			0.81
Gastrointestinal	FLATULENCE	4	1.2%	1	0.3%	6	0.8%	1	0.1%	6	0.4%	0.36
Gastrointestinal	GASTRITIS							1	0.1%	1	0.1%	1.00
Gastrointestinal	MOUTH, DRY	3	0.9%	1	0.3%	8	1.1%	1	0.1%	15	**1.0%**	0.02
Gastrointestinal	NAUSEA	9	2.8%	35	11.0%	54	7.6%	59	6.6%	297	**20.3%**	0.00
Gastrointestinal	NAUSEA AND VOMITING			2	0.6%			2	0.2%	2	0.1%	1.00
Gastrointestinal	PAIN, ABDOMINAL	5	1.5%	3	0.9%	7	1.0%	4	0.4%	12	0.8%	0.41
Gastrointestinal	RETCHING									2	0.1%	0.70
Gastrointestinal	VOMITING	2	0.6%	3	0.9%	16	2.3%	22	2.4%	139	**9.5%**	0.00
Musculoskeletal	HYPERTONIA	1	0.3%							2	0.1%	0.70
Musculoskeletal	TWITCH, SKELETAL MUSCLE									1	0.1%	1.00
Psychiatric	AGITATION							1	0.1%			0.81
Psychiatric	CONFUSION									1	0.1%	1.00
Psychiatric	EUPHORIA									3	0.2%	0.44
Psychiatric	NERVOUS			1	0.3%	4	0.6%	3	0.3%	12	0.8%	0.24
Respiratory	BREATHING, ABNORMAL					1	0.1%			1	0.1%	1.00
Respiratory	EPISTAXIS			1	0.3%	1	0.1%	2	0.2%	2	0.1%	1.00
Respiratory	HICCUPS	1	0.3%							2	0.1%	0.70
Respiratory	PHARYNGITIS			1	0.3%	3	0.4%	1	0.1%	3	0.2%	0.98
Respiratory	POST NASAL DRIP							1	0.1%			0.81
Skin	PRURITUS	1	0.3%	1	0.3%	3	0.4%			31	**2.1%**	0.00
Skin	RASH					3	0.4%	2	0.2%	7	0.5%	0.52
Skin	SWEATING	1	0.3%	3	0.9%	4	0.6%	5	0.6%	37	**2.5%**	0.00
Special Senses	CONJUNCTIVITIS							1	0.1%			0.81
Special Senses	DISORDER, EAR	1	0.3%					1	0.1%	2	0.1%	1.00
Special Senses	DISORDER, EYE									1	0.1%	1.00
Special Senses	DISTURBANCE, VISUAL					2	0.3%	3	0.3%	7	0.5%	0.84
Special Senses	DYSGEUSIA					1	0.1%	1	0.1%	1	0.1%	1.00
Special Senses	TINNITUS			2	0.6%			2	0.2%	5	0.3%	0.90
Urogenital	BLEEDING, VAGINAL, DYSFUN							1	0.2%			0.80
Urogenital	DYSURIA					1	0.1%	2	0.2%	5	0.3%	0.90
Urogenital	HEMATURIA									1	0.1%	1.00
Urogenital	MENOPAUSAL SYMPTOMS			2	1.0%	1	0.2%			10	**1.1%**	0.03
Urogenital	POLYURIA							1	0.1%	1	0.1%	1.00
Urogenital	URINARY RETENTION									3	0.2%	0.44

Boldface = different from placebo with nominal $p < 0.20$

Table 2: Selected Adverse Events by Gender for Short-Term Therapeutic Trials

		Placebo, F		Placebo, M		Tram 75-150, F		Tram 75-150, M	
BODY SYSTEM	COSTART TERM	N=544		N=355		N=908		N=552	
Body as a Whole	ASTHENIA	5	0.9%	1	0.3%	14	1.5%	11	2.0%
Body as a Whole	FEVER	4	0.7%	4	1.1%	1	0.1%		
Body as a Whole	**HEADACHE**	33	6.1%	20	5.6%	49	5.4%	45	8.2%
Cardiovascular	VASODILATION			4	1.1%	8	0.9%	7	1.3%
Central Nervous System	DIZZINESS	17	3.1%	7	2.0%	125	13.8%	75	13.6%
Central Nervous System	PARESTHESIA	2	0.4%	3	0.8%	1	0.1%	6	1.1%
Central Nervous System	**SOMNOLENCE**	41	7.5%	24	6.8%	144	15.9%	111	20.1%
Central Nervous System	TREMOR	2	0.4%			11	1.2%	5	0.9%
Gastrointestinal	MOUTH, DRY			1	0.3%	12	1.3%	3	0.5%
Gastrointestinal	**NAUSEA**	37	6.8%	22	6.2%	205	22.6%	92	16.7%
Gastrointestinal	PAIN, ABDOMINAL	4	0.7%			10	1.1%	2	0.4%
Gastrointestinal	VOMITING	13	2.4%	9	2.5%	96	10.6%	43	7.8%
Psychiatric	NERVOUS	2	0.4%	1	0.3%	6	0.7%	6	1.1%
Skin	PRURITUS					20	2.2%	11	2.0%
Skin	**SWEATING**	4	0.7%	1	0.3%	14	1.5%	23	4.2%
Urogenital	MENOPAUSAL SYMPTOMS					10	1.1%		

Boldface = Female and male rates in tramadol group differ with nominal $p < 0.05$

Table 3: Adverse Events for Double-Blind Portion of Chronic Trials

		Tramadol		APAP/Codeine		ASA/Codeine		APAP/Oxycodone	
BODY SYSTEM	COSTART TERM	N=530		N=156		N=65		N=69	
Abnormal Lab		21	4.0%	7	4.5%			2	2.9%
	ABNORMAL LAB	3	0.6%						
	ABNORMAL LIVER FUNCTION T	2	0.4%	1	0.6%				
	CREATININE INCREASE	2	0.4%						
	HEMATOCRIT DECREASE	2	0.4%	1	0.6%			1	1.4%
	HEMOGLOBIN DECREASE	2	0.4%	1	0.6%				
	PROTEIN-UA	2	0.4%						
	S.G.O.T. INCREASE	3	0.6%	1	0.6%				
	S.G.P.T. INCREASE	2	0.4%	1	0.6%				
Body as a Whole		227	42.8%	66	42.3%	29	44.6%	32	46.4%
	ACCIDENTAL INJURY	11	2.1%	6	3.8%				
	ASTHENIA	51	9.6%	17	10.9%	7	10.8%	4	5.8%
	CHILLS	5	0.9%					3	4.3%
	DEATH	2	0.4%					1	1.4%
	EDEMA	8	1.5%	12	7.7%	6	9.2%	5	7.2%
	FEVER	8	1.5%	2	1.3%	3	4.6%	3	4.3%
	HEADACHE	138	26.0%	31	19.9%	19	29.2%	8	11.6%
	HOSPITALIZATION-CONDITION	9	1.7%	1	0.6%			9	13.0%
	HOT/COLD SENSATION	5	0.9%	2	1.3%	1	1.5%		
	INFECTION, FUNGAL	2	0.4%					2	2.9%
	INFECTION, VIRAL	10	1.9%			1	1.5%	1	1.4%
	MALAISE	7	1.3%	1	0.6%	1	1.5%	1	1.4%
	PAIN	13	2.5%	1	0.6%	1	1.5%	1	1.4%
	PAIN, CHEST - NON SPECIFI	7	1.3%	6	3.8%	1	1.5%		
	PAIN, LOWER EXTREMITIES	13	2.5%	2	1.3%	3	4.6%		
	PAIN, UPPER EXTREMITIES	8	1.5%					1	1.4%
	SUICIDAL TENDENCIES	2	0.4%						
	SYNDROME, WITHDRAWL	2	0.4%						
Cardiovascular		46	8.7%	9	5.8%	5	7.7%	2	2.9%
	ECG ABNORMAL	2	0.4%						
	HYPERTENSION	7	1.3%			1	1.5%		
	MYOCARDIAL ISCHEMIA	2	0.4%	2	1.3%				
	ORTHOSTATIC HYPOTENSION	2	0.4%	1	0.6%				

Table 3: Adverse Events for Double-Blind Portion of Chronic Trials

		Tramadol		APAP/Codeine		ASA/Codeine		APAP/Oxycodone	
BODY SYSTEM	COSTART TERM	N=530		N=156		N=65		N=69	
	PALPITATIONS	4	0.8%	1	0.6%				
	TACHYCARDIA	8	1.5%	1	0.6%				
	VASODILATION	14	2.6%	1	0.6%	4	6.2%	2	2.9%
Central Nervous System		254	47.9%	76	48.7%	30	46.2%	17	24.6%
	AMNESIA	5	0.9%	1	0.6%				
	ATAXIA	5	0.9%	2	1.3%				
	COGNITIVE DYSFUNCTION	10	1.9%	3	1.9%	1	1.5%		
	DIFFICULTY CONCENTRATING	3	0.6%	1	0.6%				
	DISORDER, SLEEP	25	4.7%	6	3.8%	2	3.1%	3	4.3%
	DIZZINESS	149	28.1%	41	26.3%	14	21.5%	8	11.6%
	MIGRAINE	5	0.9%	2	1.3%	2	3.1%		
	PARESTHESIA	13	2.5%	4	2.6%	6	9.2%	1	1.4%
	SEIZURE	2	0.4%						
	SOMNOLENCE	110	20.8%	43	27.6%	16	24.6%	6	8.7%
	TREMOR	14	2.6%	2	1.3%	1	1.5%		
	VERTIGO	15	2.8%	4	2.6%	2	3.1%		
Endocrine		16	3.0%	2	1.3%	3	4.6%	1	1.4%
	GOUT	3	0.6%						
	THIRST	2	0.4%						
	WEIGHT LOSS	8	1.5%	1	0.6%	1	1.5%		
Gastrointestinal		375	70.8%	122	78.2%	55	84.6%	44	63.8%
	ANOREXIA	32	6.0%	4	2.6%	3	4.6%	3	4.3%
	CONSTIPATION	183	34.5%	90	57.7%	32	49.2%	28	40.6%
	DIARRHEA	30	5.7%	13	8.3%	2	3.1%	5	7.2%
	DRY MUCOUS MEMBRANES	2	0.4%			3	4.6%		
	DYSPEPSIA	43	8.1%	17	10.9%	18	27.7%	3	4.3%
	FLATULENCE	15	2.8%	11	7.1%	1	1.5%	3	4.3%
	GASTROENTERITIS	4	0.8%						
	IRRITABLE BOWEL SYNDROME	2	0.4%						
	MOUTH, DRY	42	7.9%	14	9.0%	9	13.8%	3	4.3%
	NAUSEA	202	38.1%	52	33.3%	27	41.5%	20	29.0%
	NAUSEA AND VOMITING	5	0.9%						
	PAIN, ABDOMINAL	27	5.1%	17	10.9%	12	18.5%	4	5.8%

Table 3: Adverse Events for Double-Blind Portion of Chronic Trials

		Tramadol		APAP/Codeine		ASA/Codeine		APAP/Oxycodone	
BODY SYSTEM	COSTART TERM	N=530		N=156		N=65		N=69	
	STOMATITIS	7	1.3%	3	1.9%			1	1.4%
	STOOLS ABNORMAL	4	0.8%	1	0.6%				
	VOMITING	84	15.8%	10	6.4%	10	15.4%	6	8.7%
Hemic / Lymphatic		4	0.8%			1	1.5%		
	ECCHYMOSIS	2	0.4%			1	1.5%		
Musculoskeletal		52	9.8%	13	8.3%	8	12.3%	5	7.2%
	ARTHRITIS	4	0.8%					2	2.9%
	BURSITIS	3	0.6%						
	DISORDER, JOINT	4	0.8%	1	0.6%				
	FRACTURE, BONE	2	0.4%	1	0.6%				
	HYPERTONIA	14	2.6%	2	1.3%	2	3.1%	1	1.4%
	MYALGIA	4	0.8%			1	1.5%		
	PAIN, BACK	11	2.1%						
	PAIN, NECK	5	0.9%	2	1.3%				
	SWELLING, JOINT	4	0.8%	1	0.6%	2	3.1%		
	WEAKNESS OF EXTREMITIES	3	0.6%	3	1.9%			2	2.9%
Psychiatric		67	12.6%	14	9.0%	7	10.8%	5	7.2%
	ANXIETY	12	2.3%	2	1.3%	1	1.5%	1	1.4%
	CONFUSION	14	2.6%	3	1.9%	2	3.1%	1	1.4%
	DEPRESSION	11	2.1%	2	1.3%	2	3.1%		
	DISORDER, PSYCHOSEXUAL	3	0.6%			1	1.5%		
	EUPHORIA	9	1.7%			1	1.5%		
	HALLUCINATIONS	2	0.4%	1	0.6%			1	1.4%
	NERVOUS	21	4.0%	5	3.2%				
Respiratory		60	11.3%	13	8.3%	6	9.2%	8	11.6%
	BRONCHITIS	6	1.1%	1	0.6%				
	COUGH	6	1.1%	1	0.6%			5	7.2%
	DISORDER, PLEURAL	2	0.4%						
	DYSPNEA	7	1.3%	3	1.9%			3	4.3%
	EPISTAXIS	2	0.4%						
	HICCUPS	4	0.8%	2	1.3%				
	INFECTION, UPPER RESPIRAT	15	2.8%	3	1.9%	4	6.2%	1	1.4%
	NOSE-ITCHING	2	0.4%						

Table 3: Adverse Events for Double-Blind Portion of Chronic Trials

		Tramadol		APAP/Codeine		ASA/Codeine		APAP/Oxycodone	
BODY SYSTEM	COSTART TERM	N=530		N=156		N=65		N=69	
	PHARYNGITIS	5	0.9%	1	0.6%	1	1.5%	1	1.4%
	RHINITIS	4	0.8%	1	0.6%	2	3.1%	1	1.4%
	SINUSITIS	8	1.5%			3	4.6%		
Skin		104	19.6%	23	14.7%	5	7.7%	4	5.8%
	ACNE	2	0.4%						
	ERYTHEMA	2	0.4%						
	INFECTION, SKIN	3	0.6%					1	1.4%
	PRURITUS	50	9.4%	10	6.4%	3	4.6%	1	1.4%
	RASH	14	2.6%	4	2.6%	1	1.5%	1	1.4%
	SKIN IRRITATION	2	0.4%						
	SWEATING	37	7.0%	6	3.8%	1	1.5%	1	1.4%
	URTICARIA	2	0.4%						
	VESICLE	2	0.4%						
Special Senses		52	9.8%	9	5.8%	5	7.7%	4	5.8%
	CONJUNCTIVITIS	4	0.8%	1	0.6%	2	3.1%		
	DEAFNESS	4	0.8%						
	DISORDER, EYE	4	0.8%	2	1.3%	2	3.1%		
	DISTURBANCE, VISUAL	14	2.6%	2	1.3%	1	1.5%	3	4.3%
	DYSGEUSIA	9	1.7%	1	0.6%				
	EARACHE	3	0.6%	1	0.6%				
	INFECTION, EAR	2	0.4%	1	0.6%				
	KERATOCONJUNCTIVITIS	3	0.6%						
	TINNITUS	16	3.0%	2	1.3%	1	1.5%		
Urogenital		68	12.8%	16	10.3%	7	10.8%	5	7.2%
	CYSTITIS	2	0.4%	2	1.3%	1	1.5%		
	DISORDER, MENSTRUAL	2	0.6%			1	2.4%		
	DISORDER, PROSTATIC	4	1.9%						
	DISORDER, URINARY TRACT	3	0.6%						
	DYSURIA	9	1.7%					1	1.4%
	INCONTINENCE-URINARY	4	0.8%	1	0.6%				
	MENOPAUSAL SYMPTOMS	11	3.4%	1	0.9%	1	2.4%		
	POLYURIA	2	0.4%						
	URINARY FREQUENCY	8	1.5%	1	0.6%	2	3.1%		
	URINARY RETENTION	11	2.1%	5	3.2%				
	URINARY TRACT INFECTION,	13	2.5%	6	3.8%	2	3.1%	2	2.9%
	URINE OUTPUT DECREASED	2	0.4%						

Table 4: Selected Adverse Events by Gender for Patients Receiving Tramadol in Chronic Trials

	Female	Male
	N=321	N=209
ANY AE	93%	91%
NAUSEA	41%	33%
CONSTIPATION	36%	33%
DIZZINESS	29%	26%
HEADACHE	31%	18%
SOMNOLENCE	23%	18%
VOMITING	16%	15%
ASTHENIA	10%	10%
DYSPEPSIA	6%	12%
PRURITUS	12%	5%
MOUTH, DRY	9%	6%
SWEATING	5%	10%
ANOREXIA	7%	5%
DIARRHEA	7%	4%
PAIN, ABDOMINAL	6%	4%
NERVOUS	4%	4%
VASODILATION	2%	3%
URINARY RETENTION	1%	4%
URINARY TRACT INFECT	3%	1%

Boldface = Different with nominal $p < .05$

Table 5: Adverse Events in Chronic Studies by Lifetable Analysis

SYSTEM	AEGROUP	7 Days TRAM	7 Days APAP/CO	7 Days ASA/CO	7 Days APAP/OXY	30 Days TRAM	30 Days APAP/CO	30 Days ASA/CO	30 Days APAP/OXY	90 Days TRAM	90 Days ASA/CO
ANYAE	ANYAE	73%	85%	77%	62%	90%	93%	93%	89%	90%	93%
BODYASWH	BODYASWH	26%	27%	21%	28%	45%	51%	44%	62%	57%	50%
BODYASWH	ACCINJ	.6%	-	-	-	2.0%	6.1%	-	-	3.2%	-
BODYASWH	ALLERG	.2%	-	-	-	.2%	-	-	-	1.1%	-
BODYASWH	ASTHENIA	5.5%	7.6%	9.8%	4.8%	12%	15%	12%	7.8%	14%	12%
BODYASWH	CHILLS	.3%	-	-	3.2%	1.1%	-	-	6.2%	1.7%	-
BODYASWH	DENTAL	-	-	-	-	.2%	-	-	-	.5%	6.7%
BODYASWH	EDEMA	.6%	4.8%	3.2%	4.8%	3.9%	12%	11%	11%	7.1%	14%
BODYASWH	FEVER	.6%	1.4%	1.6%	3.2%	1.6%	1.4%	3.5%	6.3%	2.5%	6.8%
BODYASWH	HEADACHE	17%	16%	6.5%	9.7%	25%	23%	23%	13%	31%	35%
BODYASWH	HOTCOLD	.3%	-	1.6%	-	1.1%	2.5%	1.6%	-	1.4%	1.6%
BODYASWH	INFECT	.8%	-	-	-	2.5%	1.3%	-	9.0%	6.8%	3.4%
BODYASWH	MALAISE	.5%	-	1.6%	1.6%	1.2%	1.3%	1.6%	1.6%	2.4%	1.6%
BODYASWH	PAIN	2.6%	2.8%	1.6%	1.6%	8.8%	5.2%	5.4%	4.7%	13%	8.3%
BODYASWH	PAINCHST	.8%	.7%	-	-	2.0%	6.8%	1.9%	-	4.2%	1.0%
CARDIO	CARDIO	3.4%	2.1%	4.8%	3.2%	8.8%	8.2%	6.7%	3.2%	15%	10%
CARDIO	AVBLOCK	.3%	.7%	-	-	1.1%	2.0%	-	-	2.6%	-
CARDIO	ECGABN	.2%	-	-	-	.4%	-	-	-	.7%	-
CARDIO	HYPERTEN	.3%	-	-	-	1.5%	-	1.9%	-	3.0%	1.9%
CARDIO	HYPOTEN	-	-	-	-	.6%	1.3%	-	-	1.5%	-
CARDIO	ISCHEMIA	-	-	-	-	.4%	2.5%	-	-	1.8%	-
CARDIO	PHLEBIT	-	-	-	-	.4%	1.3%	-	-	.4%	-
CARDIO	SYNCOPE	.2%	-	-	-	.2%	-	-	-	.5%	-
CARDIO	TACHY	.5%	.7%	-	-	.9%	.7%	-	-	1.8%	-
CARDIO	VASODIL	1.9%	.7%	4.8%	3.2%	2.9%	.7%	4.8%	3.2%	3.5%	8.2%
CNS	CNS	37%	42%	33%	19%	47%	57%	41%	33%	53%	57%
CNS	AMNESIA	-	-	-	-	.6%	1.3%	-	-	1.5%	-
CNS	ANXIETY	1.1%	1.4%	-	-	1.9%	1.4%	-	3.1%	2.8%	3.4%
CNS	ATAXIA	1.1%	.7%	-	-	1.7%	3.2%	-	-	2.3%	-
CNS	CNSDEPR	18%	26%	21%	7.9%	26%	38%	26%	7.9%	30%	32%
CNS	CNSSTIM	6.8%	6.9%	3.3%	4.8%	11%	9.3%	5.1%	7.8%	14%	8.5%
CNS	COGNAT	.8%	.7%	1.6%	-	1.6%	3.2%	1.6%	-	2.5%	1.6%
CNS	CONFUSE	1.5%	1.4%	1.6%	-	2.7%	2.7%	1.6%	-	3.6%	4.9%
CNS	DEPRESS	.8%	1.4%	1.6%	-	2.4%	1.4%	1.6%	-	5.8%	4.9%
CNS	DIZZY	24%	26%	16%	8.0%	29%	31%	22%	17%	32%	29%

Table 5: Adverse Events in Chronic Studies by Lifetable Analysis

CNS	EMOTLAB	-	.7%	-	3.2%	-	.7%	-	3.2%	.6%	-
CNS	EUPHORIA	1.1%	-	-	-	1.5%	-	1.9%	-	1.5%	1.9%
CNS	MIGRAINE	.3%	.7%	-	-	.9%	2.0%	-	-	1.5%	6.8%
CNS	NERVOUS	2.6%	3.5%	-	-	4.1%	3.5%	-	-	4.6%	-
CNS	PARESTH	.8%	1.4%	6.5%	1.6%	2.2%	3.9%	8.4%	1.6%	4.7%	12%
CNS	SEIZURE	-	-	-	-	.4%	-	-	-	1.3%	-
CNS	SLEEP	2.3%	2.1%	-	1.6%	5.1%	8.2%	-	7.8%	8.5%	6.8%
CNS	SOMNOL	16%	24%	19%	7.9%	21%	34%	24%	7.9%	23%	28%
ENDOCRIN	ENDOCRIN	1.1%	.7%	3.3%	-	4.4%	2.0%	5.1%	3.1%	4.9%	5.1%
ENDOCRIN	GOUT	.2%	-	-	-	.6%	-	-	-	.6%	-
ENDOCRIN	HYPOGLYC	-	-	1.6%	-	.4%	-	1.6%	3.1%	.4%	1.6%
ENDOCRIN	THIRST	.3%	-	-	-	.5%	-	-	-	.5%	-
ENDOCRIN	WGTLOSS	.5%	-	1.6%	-	1.9%	1.3%	1.6%	-	2.2%	1.6%
GI	GI	51%	72%	71%	48%	70%	84%	87%	72%	78%	87%
GI	ABDOMIN	3.2%	6.9%	13%	4.8%	4.8%	12%	19%	7.8%	6.6%	18%
GI	ANOREXIA	3.4%	1.4%	-	3.2%	6.7%	3.9%	3.7%	6.2%	8.9%	7.1%
GI	BLEEDREC	.2%	-	-	1.6%	.6%	1.3%	1.9%	4.7%	.6%	1.9%
GI	CONSTIP	24%	51%	34%	29%	40%	69%	52%	52%	48%	56%
GI	DIARRHEA	4.2%	5.5%	1.6%	4.8%	6.4%	12%	1.6%	11%	10%	4.9%
GI	DRYMOUTH	5.0%	9.0%	16%	4.8%	8.4%	10%	18%	4.8%	10%	22%
GI	DYSPEPSI	5.1%	12%	13%	4.8%	8.7%	15%	30%	7.8%	13%	34%
GI	FLATUL	1.8%	6.9%	1.6%	4.8%	3.2%	8.1%	1.6%	4.8%	3.5%	1.6%
GI	GASTRO	.5%	-	-	-	.7%	-	-	-	1.3%	-
GI	GUM	.5%	1.4%	-	-	1.9%	2.7%	-	3.1%	1.9%	-
GI	HEMORRH	-	.7%	1.6%	-	.4%	2.0%	1.6%	-	.7%	1.6%
GI	NAUSEA	25%	29%	35%	17%	36%	38%	40%	37%	42%	47%
GI	VOMITING	10%	4.8%	6.4%	7.9%	16%	8.5%	16%	11%	20%	19%
LYMPH	LYMPH	.2%	-	-	-	1.0%	-	-	-	1.9%	3.5%
LYMPH	ANEMIA	-	-	-	-	.4%	-	-	-	1.0%	
LYMPH	PURPURA	-	-	-	-	.4%	-	-	-	.7%	3.5%
MUSCULO	MUSCULO	3.9%	4.1%	1.6%	6.4%	11%	13%	9.1%	9.5%	19%	19%
MUSCULO	ARTHRIT	.8%	.7%	-	1.6%	2.9%	3.2%	1.9%	4.7%	3.8%	8.7%
MUSCULO	FRACTURE	.2%	-	-	-	.2%	1.3%	-	-	.5%	-
MUSCULO	HYPERTON	1.3%	-	1.6%	1.6%	2.5%	2.5%	3.5%	1.6%	4.4%	3.5%
MUSCULO	MYALGIA	.5%	-	-	-	.9%	-	1.9%	-	1.2%	1.9%
MUSCULO	MYASTHEN	.2%	.7%	-	3.2%	.8%	3.2%	-	3.2%	1.4%	-
MUSCULO	SPRAIN	.2%	.7%	-	-	.4%	.7%	1.9%	-	1.3%	1.9%

Table 5: Adverse Events in Chronic Studies by Lifetable Analysis

RESPIR	RESPIR	4.8%	3.4%	3.3%	4.8%	12%	13%	5.2%	19%	21%	15%
RESPIR	BRONCH	.3%	-	-	-	.7%	1.3%	-	-	3.0%	-
RESPIR	COUGH	.3%	.7%	-	-	1.7%	.7%	-	15%	3.7%	-
RESPIR	DYSPNEA	.6%	.7%	-	1.6%	2.0%	3.2%	-	7.7%	3.4%	-
RESPIR	HICCUPS	.2%	1.4%	-	-	.8%	1.4%	-	-	1.1%	-
RESPIR	LUNG	.3%	.7%	-	-	1.3%	5.6%	-	-	1.9%	-
RESPIR	PHARYNG	.5%	.7%	-	1.6%	1.1%	.7%	-	1.6%	1.7%	3.4%
RESPIR	RHINITIS	.2%	-	-	1.6%	1.0%	2.5%	-	1.6%	3.0%	6.7%
RESPIR	SINUS	1.3%	-	1.6%	-	1.7%	2.5%	5.4%	-	3.5%	8.8%
RESPIR	UPPRESP	.6%	-	1.6%	-	2.4%	3.7%	1.6%	3.1%	5.2%	11%
SENSES	SENSES	5.0%	3.5%	3.2%	3.2%	9.7%	7.2%	5.0%	9.3%	16%	12%
SENSES	DEAFNESS	.5%	-	-	-	.7%	-	-	-	1.0%	-
SENSES	DYSGEUS	.8%	.7%	-	-	1.6%	.7%	-	-	2.2%	-
SENSES	EAR	.8%	-	-	-	1.4%	2.5%	-	-	2.3%	-
SENSES	EYE	.3%	.7%	-	-	2.1%	3.2%	1.9%	3.1%	4.1%	8.6%
SENSES	TINNITUS	1.6%	1.4%	1.6%	-	3.1%	1.4%	1.6%	-	4.2%	1.6%
SENSES	VISION	1.5%	1.4%	1.6%	3.2%	3.1%	1.4%	1.6%	6.3%	5.9%	1.6%
SKIN	SKIN	14%	11%	1.6%	3.2%	19%	17%	5.4%	9.3%	25%	8.8%
SKIN	DRY	.6%	-	-	-	.6%	-	-	-	.9%	-
SKIN	PRURITUS	6.4%	6.2%	-	-	8.5%	7.4%	5.7%	3.1%	9.6%	5.7%
SKIN	RASH	1.3%	.7%	-	1.6%	2.3%	3.2%	-	1.6%	4.8%	-
SKIN	SWEAT	6.1%	2.8%	-	1.6%	7.3%	4.1%	-	1.6%	9.3%	3.4%
UROGENIT	UROGENIT	4.8%	4.1%	1.6%	3.2%	13%	16%	7.2%	12%	21%	17%
UROGENIT	BREAST	-	-	-	-	.4%	-	-	3.1%	1.0%	-
UROGENIT	CYSTITIS	-	-	-	-	-	1.3%	-	-	.6%	3.4%
UROGENIT	DYSURIA	1.1%	-	1.6%	1.6%	2.5%	1.3%	3.5%	1.6%	3.7%	6.8%
UROGENIT	HEMATUR	-	-	-	-	-	-	-	3.1%	.6%	-
UROGENIT	INCONT	.3%	-	-	-	.7%	1.3%	-	-	1.9%	-
UROGENIT	MENOPAUS	1.1%	-	-	-	1.7%	1.3%	-	-	2.6%	3.5%
UROGENIT	PROSTATE	.2%	-	-	-	1.0%	-	-	-	1.9%	-
UROGENIT	URINRET	1.3%	2.1%	-	-	1.9%	4.5%	-	-	2.5%	-
UROGENIT	UTI	.5%	1.4%	-	1.6%	3.3%	6.3%	1.9%	4.7%	5.5%	5.3%
UROGENIT	VAGINIT	-	.7%	-	-	.6%	.7%	1.9%	-	.9%	1.9%

Tramadol Safety Summary: Deaths

MEDICAL OFFICER REVIEW

NDA #: 20-281
NAME: ULTRAM (Tramadol Hydrochloride).
SPONSOR: R.W. Johnson
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.
REVIEW DATE: January 5, 1995.
CSO: C. Moody

INTRODUCTION:

There are two sources for safety data on tramadol: the U.S. trials undertaken by the sponsor and spontaneous reports to the German manufacturer, Gruenenthal.

The safety data base in the U.S. trials consisted of three long-term studies, from which we have data on 677 patients exposed to tramadol (excluding two in Study TKB who were lost to follow-up right after enrollment). The deaths are tabulated and described in the first section below

Tramadol was introduced in Germany in 1977 and subsequently in several foreign countries. Between 1977 and 1992 Gruenenthal had collected over 400 spontaneous reports of adverse events, which included 24 deaths. These deaths are described in the second section below.

DEATHS IN U.S. TRIALS

No deaths were reported from the single-dose or short-term studies.

Among the 677 patients who received tramadol in the three long-term studies, 26 deaths were reported for patients who were currently taking tramadol or who had been taking tramadol. Ten of these were reported in the original NDA filing, and another 16 were reported in the refiling. The latter were deaths that occurred after tramadol was stopped and which appeared unrelated; most occurred several weeks after leaving the study.

Some mortality could reasonably be expected from two of the long-term studies: study TL2 (7 deaths) required patents to be at least 65, and study TKM (18 deaths) involved pain of malignancy.

A table of reviewer's grouping of cause of death is given below, followed by brief descriptions of the cases in each category:

Causes of Death in U.S. Trials	
Cancer	18
Cardiac	3
Emphysema	2
Overdose	1
Unclassified	2

Cancer: In all but one of the cases of malignancy, the disease was present at baseline and can reasonably be considered the underlying cause of death. One case was a rectal carcinoma initially diagnosed after the patient had been taking Tramadol for 12 months (see also review of serious adverse reactions), and death 4 months later was attributed the cancer.

Cardiac: The cardiac deaths were as follows:

A 70-year-old (70 yo) male S/P CABG and with a history of hypercholesterolemia was being treated with Lovistatin. Baseline ECG noted "ST abnormality." He took tramadol for 3 months for back pain and stopped treatment to have back surgery. He was off tramadol 17 days when he died. The cause was listed as cardiac arrhythmia due to coronary arteriosclerosis.

A 73 yo male had a remote history of MI. He was treated with tramadol for 13 mo for bilateral testicular pain. He died unexpectedly due to CHF.

A 49 yo male took tramadol for trigeminal neuralgia, but withdrew after 4 days due to complaints of abdominal pain and melena. He died 61 days later; autopsy attributed death to cardiomyopathy.

Emphysema: Both emphysema deaths could be attributed to pre-existing lung disease.

Overdose: The case of overdose death was as follows:

An 80 yo female was taking tramadol for OA of the hip and knee. She had been seeing a psychiatrist and had been taking anti-depressants for over 20 years. She was found dead after 5 months in the study. Autopsy listed cause of death as alcohol, temazepam and alprazolam intoxication. Tramadol was not tested for, but pill counts were appropriate to prescribed dose.

Unclassified: The unclassified deaths were as follows:

A 73 yo male took tramadol for 3 months for cancer pain. He left the study due to hospitalization for hip fracture from fall. He suffered renal failure, pulmonary edema, UTI and liver failure, and expired 36 days after leaving the study.

A 76 yo female took tramadol for 4 months for post-herpetic neuralgia. She was lost to follow-up, but it was learned she expired 39 days after leaving the study.

In the reviewer's opinion, it is unlikely that any of the deaths in U.S. trials were related to tramadol. Although little is known about the demise of the patient lost to follow-up, the time between leaving the study and death make relationship to tramadol remote.

DEATH REPORTS FROM FOREIGN EXPERIENCE

A total of 24 patient deaths associated with tramadol have been reported from foreign experience. They can be classified as follows:

Causes of Death from Foreign Reports	
Cardiac	7
Overdose	3
Allergic	3
Agranulocytosis	2
Respiratory	1
Cancer	1
Other	3
Uncertain	4

Cardiac: In 5 of the 7 CV deaths acute angina was present before tramadol was given. The cases may have been reported because deterioration or demise occurred within minutes of tramadol administration. Of the other two cases, one was a 79 yo female with multiple cardiovascular risk factors who experienced ventricular fibrillation 10-15 min after a tramadol injection. The other case was a 71 yo F who deteriorated shortly after tramadol was given. Clinical impression initially was "possible anaphylactoid shock," but autopsy found MI.

Overdose: There were 3 overdose cases:

A 40 kg female with a history of a previous suicide attempt found dead after taking an oral dose of Tramadol drops estimated to be 500 mg. The dose had to be less than 1 g based on bottle size. No other drugs were identified at autopsy.

A 32 yo male was found dead with blood alcohol of 290 mg/dL (most fatal intoxications have blood alcohol concentrations of 400 mg/dL or more) and tramadol concentration of 0.9 µg/mL (if this were a peak concentration it would correspond to an oral dose of 300 mg).

In a case of probable suicide, the blood concentration of tramadol was 1.3 µg/mL (if this were a peak concentration it would correspond to an oral dose of at least 450 mg) and stomach contents had tramadol of 100 mg/kg. No opiates, barbiturates or benzodiazepines were found.

The first overdose case implies that a dose between 12.5 and 25 mg/kg (~0.9 - 1.8 g/70 kg) could be lethal. This is about an order of magnitude greater than the recommended analgesic dose. In the other two cases the dose is not documented, however is of some concern that the plasma concentrations were only 3 to 5 fold higher than peak levels achieved with the recommended dose. In the second case, alcohol undoubtedly played a significant role. It is not clear how to interpret postmortem tramadol concentrations or relate them to ingested dose.

Allergic: The allergic cases consisted of one case of Stevens-Johnson Syndrome and two cases of toxic epidermal necrolysis. In all three cases the patients were on multiple other medications, so clear attribution is not possible. In one of the cases, symptoms reportedly improved temporarily despite continuing tramadol. In another, stopping tramadol did not lead to any improvement.

Agranulocytosis: Both of the cases of agranulocytosis were in patients receiving multiple drugs, some of which are associated with agranulocytosis. Attribution is difficult.

Respiratory: The one case of respiratory depression was in a 79 yo male who was given tramadol and chlorazepate for colonoscopy. He had to be intubated 16-20 hours later. The temporal relationship makes tramadol relationship improbable.

Cancer: The malignancy was a brain tumor in a 14 yo female. The patient was given tramadol as part of evaluation and treatment of severe headache. There seems to be no causal connection.

Other: The 3 cases are:

A 74 yo male was given 100 mg IV for acute angina and deteriorated 15-20 minutes after the dose, requiring resuscitation. He expired 14 days later of cerebral hypoxia.

A 91 yo female was operated for incarcerated hernia. Postoperatively she was given tramadol 200 mg IV and suffered severe respiratory depression. Cause of death was reported as mechanical ileus that could not be relieved surgically.

A 40 yo female was given tramadol and three other drugs following gallbladder surgery. She developed massive intravascular hemolysis and DIC.

Unclassified: The 4 Unclassified cases are:

A 50 yo female had chest pain for 3 weeks. The patient died 3-4 minutes after tramadol 100 mg IM. Physician denied MI; there was no autopsy.

A 31 yo pregnant female was being treated for malaria and acute pyelonephritis. Three hours after a second dose of tramadol 100 mg IM, she developed hypotension, restlessness and tachypnea. Symptoms were controlled for a while, but she expired 8 hrs after last dose of tramadol. A premortem blood sample showed large quantities of P. falciparum.

A 71 yo female with coronary insufficiency, hypertension and emphysema had exacerbation of respiratory symptoms after 100 mg tramadol. Death felt to be possibly MI, PE or pneumothorax.

An 82 yo male was treated in an ER with tramadol 100 mg IV for upper abdominal pain. He became hypotensive and arrested.

SUMMARY:

These reports show that tramadol can be fatal if taken in overdose. It appears that a dose an order of magnitude higher than the recommended dose has the potential to produce a fatal outcome; lower doses may contribute as part of a mixed drug overdose. Postmortem concentrations in two overdose cases were 3-5 time peak concentration with the recommended dose, but it is not clear how to interpret that data in light of the rarity of fatal overdose reports.

A few cases reported tramadol in association with agranulocytosis or fatal allergic reactions. In all cases other drugs were involved, so the evidence is inconclusive. The association should be considered an unestablished possibility of a rare event.

The associations with cardiac are not particularly suspicious given the circumstances of the cases and the prevalence of MI. Likewise, the deaths due to malignancy are not concerning for tramadol.

Of particular note is the complete lack of any clear cases of tramadol causing death from respiratory depression. Although respiratory depression was mentioned in two of the cases, they were not very indicting of tramadol.

CONCLUSIONS:

The risk of death from tramadol taken in usual oral doses (100 to 200 mg) appears to be quite low, as there is no clearly incriminating case report. Of course, rare allergic or idiopathic fatal reactions cannot be ruled out. Tramadol may be fatal if taken orally at about ten times the recommended single oral dose (possibly as little as 12 mg/kg).

The death data by themselves do not appear to require any warnings about specific lethal effects of tramadol.

John E. Hyde

John E. Hyde, PhD, MD

2-28-95

Peer Reviewer

Tramadol Safety Summary:
Serious Non-Fatal Adverse Events

MEDICAL OFFICER REVIEW

NDA #: 20-281
NAME: ULTRAM (Tramadol Hydrochloride).
SPONSOR: R.W. Johnson
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.
REVIEW DATE: January 5, 1995.
CSO: C. Moody

INTRODUCTION:

There are two sources for safety data on tramadol: the U.S. trials undertaken by the sponsor and spontaneous reports to the German manufacturer, Gruenenthal.

Most of the serious adverse events (AEs) in the U.S. trials occurred in the three long-term studies. From those studies we have data on 677 patients exposed to tramadol (excluding two in Study TKB who were lost to follow-up right after enrollment). The events are tabulated and described in the first section below.

Tramadol was introduced in Germany in 1977 and subsequently in several foreign countries. Between 1977 and 1992 Gruenenthal had collected over 400 spontaneous reports of adverse events. An extensive report on the first 344 reports (through 1990) was prepared by Gruenenthal and is the basis of the review in the second section below. Updated data through 1992 was consistent with the profile reflected in the 1990 report.

SERIOUS ADVERSE EVENTS IN U.S. TRIALS

There were 27 non-fatal serious AEs reported in the refiling of the NDA and the safety update (one patient listed in the filing was not on tramadol, one patient (128/002) was not reported under serious adverse events but was hospitalized for perforated ulcer and hypotension). The reviewer classifies them as follows:

Visual Disturbance	6
Seizure	5
Cardiac	2
Syncope	3
Overdose	2
Cancer	2
Hepatitis	1
Other*	6

* The other cases were one instance each of stroke, nephritis, venous thrombosis, perforated ulcer, hypotension and leukocytosis (hypotension and perforated ulcer were separate events in the same patient).

Three of the seizures came from abuse liability studies, and two cases of syncope came from the single-dose studies. The remainder came from the three long-term trials.

Visual Disturbances: The visual disturbances consisted of 4 cases of cataracts and 1 case of worsening of pre-existing glaucoma in patients over 60. However one case is atypical:

> A 32-year-old (32 yo) female was taking tramadol in study TKB for fibromyositis. At 100 days of therapy, moderate visual changes were noted (20/40 and 20/70 vs. 20/20 initially). Study drug and change in patient's computer screen at work were considered possibilities. Average dose had been about 100 to 150 mg/day. By day 162, visual changes were rated mild. The patient left the study after day 165 due to nausea, lightheadedness and heart racing. Ophthalmologic exam at 181 days found complete resolution of visual changes.

Seizure: The cases of seizure were as follows:

> In study TAA, a 28 yo 161 lb male former addict had a generalized seizure after receiving tramadol 700 mg PO in the third phase of a crossover study. The seizure started about 2.5 hours after the dose and lasted 90 sec. The seizure severity was rated as moderate in severity. He reported feeling "high" when his confusion cleared 25 min later. There were no abnormal findings on neurologic exam. Associated symptoms were odd feeling in stomach, dry mouth, hand tremors, sweating. Opioid-like effects lasted for 12 hours. All adverse events resolved by the next day. The treatments the subject took in the first two periods of the study were tramadol 350 mg and oxycodone 20 mg, respectively.
>
> In Study TAC, a 32 yo 16 lb male former addict had a seizure after receiving tramadol 300 mg IV in the fifth infusion of a crossover study. The seizure was rated as marked. Associated postictal symptoms were headache, sore tongue, upper back pain, restlessness, sweating, clammy hands, and sedation. Symptoms other than sore tongue resolved in two days.
>
> In Study TAC, a 33 yo 189 lb male former addict had a seizure after receiving tramadol 400 mg IV as the third infusion of a crossover study. Associated symptoms were lightheadedness, dizziness, clammy palms, nervousness, cold feet, back and right thoracic pain, sore tongue, cold symptoms, constipation, sleepiness, loss of appetite, vomiting, and facial twitching. Symptoms resolved within four days.
>
> In Study TKB, a 60 yo male taking tramadol for cervical arthritis had a grand mal seizure after 111 days of treatment. Tramadol dose averaged 300 - 400 mg/day. He had a history of diabetes and glaucoma but no seizure history, and he had been taking Glucotrol and eye drops. Head CT was normal, and EEG showed seizure activity. Tramadol was stopped, dilantin was started, and 2 weeks later EEG was normal.
>
> In Study TL2, an 83 yo female taking tramadol for OA had a generalized seizure after 40 days in the study. Tramadol dose averaged about 150 - 300 mg/day, but she did not take tramadol from days 23 to 29. She had no seizure history. She had also been taking calcium, Didronel, HCTZ and Ativan. She was hospitalized for observation for 4 days then discharged.

Cardiac: A 42 yo female with a history of "palpitations" had superventricular tachycardia 1 hr after receiving 100 mg tramadol for postoperative pain; she was given digitalis and the problem resolved in 3 days. A 62 yo female with a history of hypertension, CHD and MI had worsening angina after 120 days of tramadol and was hospitalized for atrial fibrillation after 150 days.

Syncope: Two of the cases of syncope were two young adult females in oral surgery studies who fainted briefly after a single dose of tramadol. The third case was an 84-year-old male who had several fainting spells and was hospitalized once for dehydration.

Overdose: There were two non-fatal overdoses. One was a suicide attempt, the other an accidental ingestion in a child:

> In study TKB, a 34-year-old 144 lb white man was taking tramadol for back pain. He attempted suicide on Day 74 by taking approximately 60 capsules of tramadol (3 g). According to the patient, he vomited everything after 30 minutes. No other adverse sequelae from the attempted overdose were noted by the patient. He was psychologically evaluated, but not hospitalized. The patient's average dose of tramadol had increased from about 100 mg/day to 200 mg/day but with diminishing pain relief. The patient experienced several adverse experiences before this suicide attempt, including euphoria, difficulty in urination, urinary hesitancy, sinus pain, disorientation, constipation, itchy eyes, metallic taste, neuralgia, ear infection, nausea and vomiting. The patient reported withdrawal symptoms (unspecified) on Day 76.
>
> The 18-month-old niece of a patient in Study TKB reportedly ingested "1 dose" (presumably 50 mg) of tramadol. She showed somnolence, lethargy and hematuria, all of which resolved spontaneously. The patient was discharged after 3 days in good condition.

Cancer: A gallbladder carcinoma was discovered incidentally following cholecystectomy in a 77 yo female who had been taking tramadol for 6 months. Rectal carcinoma was discovered in a 81 yo female just after completing 12 months of tramadol. She died 4 months later of the malignancy. (This case also was counted in the review of deaths.)

Hepatitis:

> A 76 yo male was withdrawn after 146 days of tramadol therapy due to hepatitis. SGPT was 213 and fell to 113 three weeks later. Concurrent NSAID use was blamed for the hepatitis.

Hallucinations:

> A 73 yo male was taking tramadol in study TL2 for postherpetic neuralgia. Average dose was about 250 mg/day. He began to experience hallucinations after four days of treatment, and they disappeared after tramadol was stopped on day 9.

Other: A **stroke** was seen after 84 days of treatment in study TL2 in a 69 yo female with a history of hypertension. A patient with **leukocytosis** had it present at baseline, had pre-existing bowel disease and received prednisone. A case of **deep vein thrombosis** occurred in a 48 yo female after

64 days of treatment in study TKB. There was a case of **nephritis** in a 21 yo female who developed hematuria and proteinuria after a single dose of tramadol, but she had received multiple doses of ketorolac IM just before entering the study. A 65 yo male had his dose reduce on day 4 due to dizziness, and was hospitalized for **perforated ulcer** on day 12 at which time tramadol was stopped; tramadol was restarted on day 25 but he was hospitalized on day 27 with severe **hypotension** and dizziness.

SERIOUS ADVERSE EVENTS FROM FOREIGN REPORTS

From 1977 to 1992 Gruenenthal received over 400 spontaneous reports of adverse reaction. Gruenenthal estimates that during that period about 12 million Germans were exposed to tramadol. The categories that include serious reactions are discussed below:

Seizures: There were 14 reports of epileptiform seizures. In 4 cases IV doses of 200 to 300 mg were given and there were no other possible explanations for seizure. There was 1 case of intoxication with 750-1000 mg taken orally. One case was reported in a fasting patient who took 50 mg tramadol drops. Neuroleptics were comedications in 4 of the cases. One had been taking orphenadrine, which reportedly can induce seizures. Two patients had coexisting medical conditions (hypertensive crisis, and acute pancreatitis with possible hypocalcemia) which might have contributed. Finally, one patient had epilepsy.

Respiratory Effects: There were 18 reports of respiratory depression. Only one involved oral administration of tramadol:

> An 82 yo female with baseline respiratory insufficiency was given 75 mg tramadol drops for fractured femoral neck. She experienced acute respiratory insufficiency with cardiac instability. Comedications were not mentioned.

The remaining cases all involved IV administration. In 3 of the reports, high doses (600 to 1000 mg) were given intraoperatively. An additional 2 cases involved high dose infusions (972 mg/day and 400 mg over 5 hours) in postoperative pain. In 3 other postoperative cases, the attribution is uncertain or information is sparse. For 3 of the reports, the patients already were compromised at the time tramadol was given. There were 4 reports of dyspnea, which is not typical of the respiratory effect of an opioid; in one of these, anaphylaxis due to dextran is a likely explanation; in another difficulty breathing started after starting 100 mg IV, and improved spontaneously after ending treatment. There was 1 report of postnatal respiratory distress: the mother received tramadol IV 10 min before birth; APGARs were 10, but 90 min later the infant had respiratory distress. Finally, 1 of the reports is incomplete and uninformative.

Cardiovascular Effects: There were 41 reports of cardiovascular reactions in 40 patients. The majority (35/41) could be classified as hypotensive

effects, ranging in severity from orthostatic hypotension to loss of consciousness and shock. However Gruenenthal related that in 1/5 of the cases tramadol did not really seem to be involved, and in another 1/5 use of comedications may have had a role. Other cases were increased diastolic pressure during anesthesia, superventricular tachycardia, ventricular fibrillation in a patient with recent MI, "disordered action of the heart" with respiratory depression when 50 mg was given with midazolam, and dyspnea, restlessness and sweating (possible orthostatic effect?) within seconds of an IV administration.

Anaphylactoid Reactions: Gruenenthal had 32 cases in the allergic/anaphylactic category, including 7 classified as anaphylaxis/anaphylactoid. Two appear to be cardiovascular reactions. In three cases attribution is difficult since other drugs were given. There was a report of anaphylactoid shock following tramadol 100 mg IV in a patient with no prior exposure to tramadol, and an allergic reaction (syncope with unconsciousness and respiratory arrest) to 50 mg tramadol drops. In the latter case, a subsequent intracutaneous test with tramadol injection was positive.

Other CNS Effects: Gruenenthal had 41 cases of CNS side effects, most of which would be expected for an opioid. There were 4 reports of hallucinations and 1 report of psychosis with aggressive behavior. There was also a report of a suicide attempt resulting in coma from which the patient recovered. There was one report of optic neuritis and one of ophthalmoplegia; Gruenenthal felt tramadol was not likely to be related in those cases.

SUMMARY:

The three seizures in patients receiving high doses of tramadol in the abuse liability studies seem readily attributable to tramadol. Seizure was seen after an oral dose of 700 mg and an IV dose as low as 200 mg. The seizure risk of tramadol is probably increased in patient taking neuroleptics. The role of tramadol is not clear in the two seizures in US patients taking the recommended dose chronically. However, no underlying cause was identified in either patient, leaving toxic/metabolic as a reasonable possibility.

The case of hallucination correlated well with the time course of therapy, making it likely that, at least for that patient, tramadol caused the reaction. There are also a few foreign reports of hallucinations.

The young female with visual disturbances is noteworthy in that symptoms completely resolved after leaving the study, however symptoms seemed to be improving in the last part of the study despite continuing treatment with tramadol. Similar effects were not seen in the foreign cases.

The few cases of syncope in US studies do not appear especially incriminating considering the contexts in which they occurred. However, there are several foreign reports that suggest tramadol can have a clinically significant hypotensive effect in a few patients.

The case of a massive overdose in Study TKB resulted in reasonably expeditious emesis and no sequelae. In a foreign case, overdose produced a coma from which the patient recovered.

The other cases from the US studies do not seem very suggestive for a causal role for tramadol, and probably represent sporadic events.

CONCLUSIONS:

It appears that tramadol can cause seizures in single high doses (which can be as low a 700 mg PO or 200 mg IV). The risk may be increased for patients taking neuroleptics. The seizure risk for chronic use of recommended doses is unclear.

Tramadol may cause respiratory depression if given in higher than recommended doses or if given to patients with compromised respiratory function.

Tramadol may cause clinically significant hypotensive effects in some patients (probably fewer than 1%).

Tramadol may cause hallucinations in an occasional patient (probably fewer than 1%).

The risk of a deliberate large overdose may be tempered somewhat by the drug's tendency to produce vomiting. Patients may be able to recover from an overdose even if it results in coma.

The labeling should include warnings about the risk of seizure at high doses or in patients with a reduced seizure threshold. Reports of seizures with chronic therapy should be provided as alerting information, but qualified that their significance is unknown. There also should be warnings about the risk of respiratory depression at high doses or in compromised patients. Hypotension, possibly with syncope, and hallucinations should be mentioned as uncommon, probably related, adverse reactions.

John E Hyde

John E. Hyde, PhD, MD

Rm. Wilmark 2-28-95

Peer Reviewer

Tramadol Safety Summary:
Vital Signs and Laboratory Values

MEDICAL OFFICER REVIEW

NDA #: 20-281
NAME: ULTRAM (Tramadol Hydrochloride).
SPONSOR: R.W. Johnson
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.
REVIEW DATE: January 10, 1995.
CSO: C. Moody

INTRODUCTION

Vital signs and clinical laboratory values were assessed at baseline and a regular intervals in the three long-term clinical trials. Population mean values over time were tabulated by the sponsor. In addition, medical summaries were provided for patients with selected laboratory abnormalities, viz., creatinine ≥ 1.8, SGPT ≥ 3 x upper limit of normal, bilirubin ≥3 mg/dL, and hemoglobin decrease from baseline ≥ 2.

VITAL SIGNS

Pulse, blood pressure, respiration rate, weight and temperature were tabulated as population averages over time. Tables 1 and 2 in the appendix to this review provide a synopsis of those tabulations by showing the absolute changes from baseline at the final visit, whenever it occurred. This skews comparisons somewhat,as the tramadol group had longer average exposure due to tne open-label extension periods. However, these values are reasonably representative of changes reflected in the more extensive tabulations. Study TKM is tabulated separately because that study involved patients with cancer pain, and greater changes might be expected in that group due to disease progression.

None of the changes in population averages of vital signs appears to be clinically significant. Although there has been some question about orthostatic changes due to tramadol, the changes in standing blood pressure on a population basis are not remarkable, and tramadol does not appear different from the comparators.

LABORATORY VALUES

Standard laboratory tests were tabulated by the sponsor as population averages over time. As for the vital signs, tables 1 and 2 in the appendix to this review provide a synopsis of those tabulations for selected tests by showing the absolute changes from baseline at the final visit. Again, these

final values are reasonably representative of the sponsor's more extensive tabulations. None of the changes population averages of the laboratory values appears to be clinically significant.

The sponsor also summarized medical data from those patients for whom selected laboratory tests showed significant abnormalities. Of the patients taking tramadol, 574 had data sufficient to be screened.

Creatinine

Twenty patients had maximum creatinine ≥1.8 at some point during treatment with tramadol. The vast majority either had a sporadic high value that resolved while tramadol was continued, or had high a baseline value and occasionally rose above 1.8 but remained essentially stable on treatment. Two patients were an exception:

A 76-year-old (76 yo) male was taking tramadol for pain due to rectal cancer. Over 113 days of tramadol therapy, his creatinine rose from 1.1 to 2.7 with a concurrent rise in BUN. Average tramadol doses increased from 75 to 137/day. During the treatment period he also received chemotherapy, he was hospitalized for intestinal blockage, and hematocrit progressively fell significantly. He quit the study due to vomiting.

A 75 yo female was in the study 343 days with average daily doses usually between 250 and 350 mg/day. Creatinine rose gradually, reached 1.9 after 210 days and stayed elevated. She was found to have right hydronephrosis.

A relationship to tramadol seems unlikely in both cases. In the first, chemotherapy and/or underlying disease may have played a role. In the second, renal insufficiency was due to an anatomic lesion that was unlikely to be related to tramadol.

Hepatic Enzymes

The were 4 patients who had maximum SGPT ≥ 3 x upper limit of normal. One patient had only SGOT measured, but it was not significantly elevated.

A 76 yo male developed hepatitis after 131 days on tramadol in average doses of 150 to 400 mg/day. The hepatitis was attributed to concurrent NSAID use.

A 66 yo female had a brief rise in SGOT and associated moderate rise in Alk. Phos. after 364 of tramadol. Average dose was 200-400 mg/day. Patient complaint mentions cholelithiasis and cholecystitis.

A 68 yo female taking averages doses of around 100 mg/day had enzymes elevated to over 5 x normal on day 368. Values fell gradually over the following ~200 days while maintaining tramadol treatment. Concurrent medication was ASA 600 mg/day.

A 69 yo had elevations of liver enzymes to just over 3 X normal between days 350 and 385 of therapy with tramadol in doses averaging 200-300 mg/day. Changes resolved while continuing tramadol. Concurrent medication included Flexeril.

Although the elevations in the last two cases are not well explained, the fact that they resolved despite continuation of tramadol makes it unlikely tramadol was contributory.

Bilirubin

No patient had a maximum bilirubin of 3 mg/dL or more. However, 4 patients had maximum bilirubin between 1.2 and 3 mg/dL. Medical synopses of those patients are pending.

Hemoglobin

Baseline values were obtained in 565 patients. Of these, 29 had a maximum decrease of 2 coupled with a fall in hematocrit of at least 5%. Most cases had stable low values that occasionally met the selection criterion, or had sporadic slightly low values that resolved while continuing tramadol. There were some cases with a progressive fall in Hgb. Most of these were in cancer patients with disease progression or who received chemotherapy; there were a few cases of falling Hgb in patients taking concurrent NSAIDs. None of the cases seemed particularly concerning to this reviewer.

CONCLUSIONS:

There were no clinically significant changes in population averages of vital signs or routine laboratory values. In particular, there was no evidence of a general orthostatic effect of tramadol. Examination of patients with selected laboratory abnormalities found no case in which tramadol was the probable cause.

The labeling does not need to reflect any general effect of tramadol on vital signs or laboratory tests. This, of course, does not preclude the reporting of infrequent adverse effects on laboratory or vital signs based on spontaneous reports or adverse event reports from the trials.

John E. Hyde

John E. Hyde, PhD, MD

Rm. Widmark 2-28-95

Peer Reviewer

Table 1
Mean Absolute Changes from Baseline
in Vital Signs and Laboratory Values
from Studies TKB and TL2 (Chronic Painful Conditions)

	Tramadol N=466-525	APAP/CO N=132-137	ASA/CO N=56-59
Pulse	1.8	-1.0	-1.3
Supine SBP	-1.5	-2.5	-3.2
Supine DBP	-0.8	-1.2	-2.1
Standing SBP	-3.3	-3.2	-5.9
Standing DBP	-1.3	-2.0	-3.9
Resp. Rate	.0	.0	.3
Weight (lb)	-3.6	0.0	-1.5
Temp (°F)	.03	.06	.01
Hgb	.1	-.2	-.1
WBC	.1	.2	.3
Plt*	9	10	-6
Sodium*	-.5	--	-.2
BUN	-1.4	-1.4	0.6
Creatinine	.0	.0	.0
Glucose	3	4	4
Calcium	-.1	.0	-.2
Albumin	-.1	.0	-.1
Cholesterol	-8	-11	-8
TG	-19	-2	-15
SGOT	.8	.6	.0
SGPT	.6	.1	-.1
Alk. Phos.	4	-1	-3
Bilirubin	.0	.0	.0
Urine Protein	.0	.8	-.1

* Measured on a subset of tramadol patients: Urine Protein N=192, Sodium N=194, Plt N=349.

Table 2
Mean Changes from Baseline in Vital Signs and Laboratory Values
from Study TKM (Pain of Malignancy)

	Tramadol N=77-113	APAP/Oxy N=46-55
Pulse	4.4	2.2
Supine SBP	-1.7	-3.7
Supine DBP	-.4	.1
Standing SBP	-3.5	-4.5
Standing DBP	-.5	.4
Resp. Rate	.7	.7
Weight (lb)	-5.1	.4
Temp (°F)	.02	-.10
Hgb	.0	-.6
WBC	.6	.1
Plt	--	--
Sodium	--	--
BUN	2.2	1.1
Creatinine	.1	.0
Glucose	10	8
Calcium	-.1	-.1
Albumin	-.1	-.1
Cholesterol	-1	-3
TG	-28	-5
SGOT	4.4	3.3
SGPT	6.3	.2
Alk Phos	21	24
Bilirubin	.0	.2
Urine Protein	.0	.1

Tramadol Effects on Respiration

Two double-blind, placebo controlled studies of tramadol effects on respiration were presented and summarized in the NDA. These could be considered pivotal studies. One examined oral drug in healthy volunteers and one evaluated intravenous drug in post-operative patients.

Oral Tramadol in Volunteers (study 53717; Gruenenthal, not published). A total of 33 healthy male volunteers (19 to 47 yrs old) were randomized into three treatment groups: placebo, 50 mg or 100 mg tramadol. In the first phase, each group received a single dose. In the second phase, the same treatment was administered every six hours for a total of 17 doses. A minimum 6-day washout period separated the phases. Blood gas parameters (pH, pO_2, pCO_2, base excess and HCO_3) were determined prior to and at 2, 4, and 6 hrs post dosing in the single dose phase, and at hrs 0, 2, 4, 6, 48, 50, 52, 54, 96, 98, 100 and 102.

In the single-dose study, tramadol had no significant effect on blood gas parameters. In the multiple dose phase, none of the blood gas parameters changed significantly except pCO_2. There were three statistically significant increases in pCO_2 (at 2 and 4 hrs after the first 50 mg dose and at 4 hrs after the 100 mg dose). Also, there was a trend for pCO_2 to increase with time in both the 50 mg and 100 mg tramadol groups. The investigators regressed pCO_2 values against elapsed time since hr 0 and found that the regression coefficients for both tramadol groups were significantly more positive than for the control group. That is, they show a trend toward significantly greater pCO_2 values over time compared to the placebo group. However, mean pCO_2 for the two tramadol groups remained within the established normal range (35 to 45 mm Hg; maximum pCO_2 after tramadol 42.3 mm Hg). [Using the 6 x half-life rule, this study should have been long enough to allow both tramadol and the M-1 metabolite to accumulate to maximum levels. PK measurements show that both tramadol and M-1 plasma concentrations doubled during chronic dosing but did not increase further than that.]

Intravenous Tramadol in Post-Operative Patients (study 500539; Dept of Anesthetics, Univ of Wales, published as part of Vickers et al., Anesthesia 47: 291-296, 1992). Thirty male and female patients (18 to 60 yrs old) scheduled for non-emergency surgery involving endotracheal intubation participated in this study. An i.v. bolus (0.1ml/kg) of placebo, tramadol (0.5, 1.0, or 2.0 mg/kg) or morphine (0.143 mg/kg) was given following induction of thiopentone anesthesia and resumption of spontaneous ventilation. Respiratory parameters were evaluated pre-dose and again at 5, 10, 15, 20, 25 and 30 minutes post-dose. Morphine caused a significant reduction in respiratory rate and a significant elevation in end-tidal CO_2. Tramadol caused a smaller but significant reduction in respiratory rate but did not cause any statistically significant increase in end-tidal CO_2. Neither morphine nor tramadol altered tidal volume or minute volume significantly. [This monitoring interval is probably too short to detect the effects on respiration of the M-1 metabolite. This difficulty is offset by other studies in post-surgical patients (49681 & 501781, as well as published reports). In these studies, pO_2 and pCO_2 remained in the normal range throughout a 6 hour treatment

period when tramadol was available via a continuous infusion or through a patient-controlled i.v. delivery system. The tramadol consumption over six hours ranged from 339 mg to 412 mg. Respiratory rate, which was elevated at baseline in these studies, dropped during the course of tramadol treatment.]

Medline Express searches ('66 through 8/94) turned up 10 prospective trials in which the effect of tramadol on respiratory parameters had been investigated. All of these reports state that patients were randomized to treatment groups. All but one compared tramadol to some other analgesic. The reports are summarized below:

1. Int J Clin Pharm Res 13: 43-51, 1993. 60 post-op patients, 30 received tramadol 100 mg/injection (type not specified). Authors evaluated respiratory rate and concluded that there were no clinically significant changes in respiration.

2. Eur J Ob Gyn Repro Biol 49: 131-135, 1993. 90 during labor, 60 received tramadol 50 or 100 mg IM. Authors evaluated neonate respiratory rate and concluded that respiratory depression less than with pethidine.

3. Anaesthesia 48: 328-331, 1993. 60 abdominal surgery, 40 received tramadol 100 mg via epidural. Authors evaluated respiratory rate and arterial gases and concluded that there was no significant change in respiratory rate or blood gases.

4. C J Anesth 40: 308-313, 1993. 20 abdominal surgery, 10 received tramadol 100 mg via epidural. Authors evaluated respiratory rate and arterial gases and concluded there was no clinically relevant effect on respiration.

5. Anesteziol-Reanimatol 2: 3-7, 1992 (Russian). 282 post-op patients dose and route of tramadol not specified in abstract. Authors concluded there was no inhibition of respiration.

6. Anesthesia 47: 291-296, 1992. This paper represents two tramadol trials - one with patient controlled analgesia and one that is the same study as the pivotal injection study described above. Only the pivotal study evaluated respiration.

7. Z Geburtshilfe-Perinatol 196: 78-82, 1992 (German). 66 during labor, 44 received tramadol 100 mg IM. Authors evaluated umbilical cord blood gases, respiratory "pattern" and APGAR scores in the neonate and concluded that tramadol produced no clinically significant change in respiration in the neonates.

8. Anaesthesist 41: 83-87, 1992 (German). 40 hysterectomy, 20 received tramadol IV via patient controlled analgesia. Authors evaluated respiratory rate and arterial oxygen saturation. No mention of respiratory results in the abstract.

9. Anesth-Anal 74: 510-514, 1992. 150 gynecol surgery, 75 received tramadol 50 mg IV up to 3 times in 6 hrs. Authors monitored oxygen saturation and concluded that there was no clinically relevant change in resp[illegible]

10. Anaesthesist 39: 513-520 , 1990 (German). 20 gynecol surgery. Two patient controlled analgesia regimens with patients receiving average of 565 or 707 mg. over 20 hrs. Authors evaluated respiratory rate and blood gases and concluded that respiratory rate was high initially and dropped "slightly".

Finally, a review of tramadol which appeared in the journal Drugs (43: 313-340, 1993) concluded that "Respiratory depression has been observed in only a few patients after tramadol infusion anesthesia. When used for pain relief during childbirth, intravenously administered tramadol did not cause respiratory depression in neonates."

Based on the data summarized above, I conclude that tramadol has minimal respiratory depression liablilty when used in therapeutic doses.

John Dailey

John E. Hyde 2-28-95
Peer

MOODY

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

Date: June 15, 1994

From: Asoke Mukherjee Ph.D., HFD-007/102

Through: Phillip G. Vincent Ph.D., HFD-102

Subject: EA for Tramadol hydrochloride, NDA 20-281

To: Corinne Moody, HFD-007

The initial review for environmental assessment of above mentioned NDA has been completed. Following recommendations and comments have been suggested by the reviewer.

For item #4:

1. Provide types of environment present around the German and Delaware facilities. Also provide EPA certificates for each incineration site. The emission from incinerators should meet local, state and federal standards.

For item #5:

2. Provide list of chemicals used in the synthesis of Tramadol hydrochloride with CAS # and physicochemical properties in this section. Also provide a list of impurities for the synthesis of Tramadol if known.

For item #6:

3. Provide estimated amount of the dust that would be released in the air and that would be washed into the waste water system from each manufacturing site in Germany, Delaware, Pennsylvania and Puerto Rico for the drug substance per year basis for the fifth year of production. If packaging materials containing polyethylene and polypropylene used for packaging, storage of drug products and any other waste are planned to be incinerated, provide the emission of its pyrolysis products per year basis. Provide state, federal and local standards for emission of these products at each incineration site.

Also provide list of chemicals other than the drug substance that would be released in the environment per year from the manufacturing of the drug substance at German and Delaware sites, and manufacturing of the drug product at the Spring House and Puerto Rico sites. Type of control institutionalized to minimize environmental exposure of these chemicals need to be discussed. Provide copy of certificates to substantiate the environmental safety for Normaco plant according to the state, local and

federal authorities.

For item #8:

4. Subacute toxicity of tramadol base in earthworm needs to be determined for predicting its impact in soil and terrestrial environment.

For item #9:

5. Provide a list of chemicals and packaging materials to justify that none of these would have any effect on the endangered species.

For item #11:

6. All solid waste and plant washing from the manufacturing of the drug substance and the drug product should be incinerated for avoiding aqueous and terrestrial effect of Tramadol. This recommendation has been made with the consideration that Tramadol would degrade slowly in the environment to generate anisole and other products that may have environmental impact. Beside this possibility, inhibitory effect of Tramadol on microorganisms may be detrimental to the environment.

For item #12:

7. Provide academic qualifications of the preparer in this section also.

For item #15:

8. Identify which charts and appendices would be considered as confidential documents and list them separately in this section.

Endorsements:

HFD-007/102 Asoke Mukherjee, Ph.D.
Pharmacologist

HFD-102/ P.G. Vincent, Ph.D.

JUN 28 1994

C.C Original NDA 20-281
EA file
Divisional file/ HFD-007
Supervisory Chemist/ HFD-007

20281E00.LAM
F/T AM

MOODY

JUN 28 1994

PILOT DRUG EVALUATION STAFF HFD-007
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-281 for 50 and 100 mg Tramadol tablets.

Tramadol hydrochloride is the cis form (hydroxyl group and

and it is currently the largest selling prescription analgesic in West Germany with an expiry date up to 5 years. Tramadol hydrochloride has bitter taste. Tramadol is sold in German market from 1977 by Grunenthal GMBH of Stolberg, Germany. Tramadol hydrochloride is a centrally acting analgesic (opiate agonist) marketed worldwide in about 40 countries in various dosage forms, such as, 50 mg capsules, 100 mg suppositories, 100 mg per ml drops, and 50 and 100 mg per ml injection. For these markets,

. The applicable US Patents assigned to Grunenthal GMBH are 3652589 (1972 year invention filing for 1-m-substituted phenyl-2-aminomethyl cyclohexanols as an analgesic drug) and 3830934 (1974 year invention filing for analgesic compositions and methods of processing). From literature, cis form of Tramadol is more active than the trans form and cis + form is more active than the cis - form; cis + form of Tramadol is about 1/3 rd active as morphine by subcutaneous injection; the therapeutic index of Tramadol is 28, that is, the ratio of LD 50 mg/kg acute toxicity s.c. to ED 50 mg/kg analgesia s.c (Tramadol, Arzneimittel Forschung, 28.1, 97-218, 1978).

For US filing the preclinical studies were exclusively conducted with Grunenthal GMBH lots (oral 1 year chronic toxicity study in dogs was conducted with lot 8607642; oral acute toxicity studies in dogs and rats was performed with lot 8707061/112 kg/mfg.9.87 produced from lot 8707018 by additional milling; drug from lot 8807409/249 kg/mfg. 10.88 compounded in HPMC suspension was administered in reproductive toxicity studies in rats and rabbits). To support stability for the clinical duration, periodic assay and dissolution tests were conducted for this drug product. lot packaged in unit dose Aclar (stability study PFB no

For the planned US market,

a

ULTRAM is the proprietary name. Ultram tablets are orange colored, coated, capsule shaped, imprinted with Ultram 100, scored, and identified as formula #18. These tablets will be supplied in HDPE bottles as 20s, 30s, 50s, 100s, 500s and 1,000s, and in unit dose blisters with paper back supported foil backing. Ultram tablets stored at 15-30 C will have an interim 2 year expiry date. Grunenthal GMBH marketed Tramadol formulations have an expiry date up to 5 years.

TRAMADOL HISTORY AT FDA: Tramadol hydrochloride was submitted to FDA in 1968 by UpJohn as INDs and discontinued by UpJohn in 1971. UpJohn had discontinued due to orthostatic hypotension in outpatients and for an increase in hepatic neoplasm, pulmonary neoplasm and histiocytic sarcoma in a 2 year mouse study. Later on the ownership had changed from UpJohn to G.H.Besselaar to R.W.Johnson Pharmaceutical Research Institute (PRI), and resubmitted to FDA as
The quantitative composition cited in

Tramadol nomenclature is confusing. European INN refers to Tramadol as trans isomer and USAN refers ~~as~~ to the cis isomer. Trans configuration refers to the phenyl group and

REVIEW # 1 DATE REVIEWED: 3.24.94, rev 6.18.94 and 6.24.94

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	9.30.1993	10.1.1993 (due date 3.30.1994	

to inform whether or not the submission is sufficiently complete to permit substantive review, as per agency's letter dated 10.25.1993).

FDA-Sponsor-Grunenthal meeting dated 12.21.1992. Disciplines represented were medical, clinical research, toxicology, drug metabolism, biostatistics, chemistry, preclinical, and regulatory.

AMENDMENT	11.24.1992	11.24.1992	

(Meeting request to discuss reasons for refusal to file this NDA.)

PREVIOUS SUBMISSION	8.28.1992	8.28.1992	9.3.1992

(Refuse to file decision was conveyed on 10.26.1992 for deficiencies in PK, clinical, abuse liability assessment and pharmacology.)

NAME & ADDRESS OF APPLICANT: The R.W.Johnson Pharmaceutical Research Institute (PRI), Division of McNeil Lab Inc., Welsh and McKean Roads, Spring House, PA 19477-0776

DRUG PRODUCT NAME
- Proprietary: Ultram Tablets 50 and 100 mg
- Established: Tramadol hydrochloride tablets 50 and 100 mg
- Code Name/#:

Chem.Type/Ther.Class:

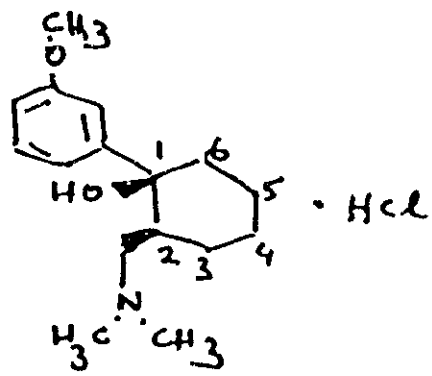
PHARMACOL. CATEGORY: Centrally acting analgesic.

DOSAGE FORM: Coated tablets
STRENGTHS: 50 and 100 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

As per USAN nomenclature, Cis-(+ and -)-2-dimethylaminomethyl-1-(m-methoxyophenyl)-cyclohexan-1-ol hydrochloride; CAS-27203-92-5 and 36282-47-0; C16H25NO2. HCl; mol.wt. 299.84;

Tramadol hydrochloride is a bitter tasting white odorless powder that exists in one crystalline form with melting point range 180-182 degrees centigrade; neither hygroscopic nor deliquescent; causes mild rusting of steel at 53% RH and severe rusting of steel at 84%RH (tablet press tooling); readily soluble in water to an extent of 295 mg per ml, with a solution pH of about 5.3; aqueous solubility was above 200 mg per ml over a pH range 1-8 buffers; In octanol to water partition experiments about 84% of total stayed in water; octanol to water partition coefficient is about 0.2; pKa is 9.4; absolute bioavailability is about : biological half life is in the range 6-9 hrs; the mono-O-desmethyl Tramadol metabolite is biologically active.



REMARKS:

In the course of Tramadol drug development several changes were made in release testing. For example, early preclinical material lots 114, 137, 142, 143 and 148 manufactured at site were released based on following release procedure - UV assay, GC trans impurity (LT 0.2%), TLC impurity 2-dimethylaminomethyl-cyclohexane-1-one, LC impurities (1,2-olefin and 1,6-olefin, and positive IR identity. Dissolution study samples of clinical supply materials were analyzed b

. Particle size study samples of clinical and preclinical drug substance materials were studied with either

Prior to drug safety evaluation studies, 10 mg capsules (batch B3813 manufactured in June 1987) were sorted by weight and content uniformity test was repeated and found to be satisfactory. This was done because initially the batch failed the content uniformity test (.
Stability data was submitted to show satisfactory stability for 12 months at 25 C in terms of assay, LC decomposition products and appearance.

Impurity profile data for 10 Tramadol lots manufactured at and 5 lots manufactured at were submitted to demonstrate process capability to produce highly pure Tramadol from lot to lot. Total impurities were in the range

CONCLUSIONS & RECOMMENDATIONS:

Recommends approval of CMC section for 100 mg Tramadol hydrochloride film coated tablets with the understanding that the sponsor will update the NDA file with information request items listed below. I also suggest the inclusion of enantiomeric assay and optical rotation test for the first 6 production batches for each site as a part of Tramadol hydrochloride release procedure for the US market.

(1) Test results for the release of most recent 3 consecutive batches of Tramadol hydrochloride produced at

(2) Real time stability test results for the active packaged in the shipping container to support the interim 2 year expiry date for the drug produced at

(3) Real time stability test results for the drug product packaged in how supplied configurations to support the interim 2 year expiry date for the drug produced

(4) Process validation documents for the drug substance and drug product produced at

(5) Resubmit CMC document for 50 mg Tramadol tablet produced with

could not locate it.

(6) Label copies for the immediate container and the secondary package for the 2 drug products, 50 and 100 mg tablets. Drug product is packaged in unit

P. Maturu 6.24.94
P Maturu, Review Chemist

6/28/94
C Yaciw, Secondary Review

CC:
Orig NDA 20-281
HFD-007/Division file
HFD-007/PMaturu,~~CYaciw~~,AMukherjee,JHyde,CWright,,RBedford CMoody
HFD-102/CKumkumian

filename: N 20-281

SATISFACTORY/ INFORMATION REQUEST/ 3.24.94/revs 6.18.94 and 6.24.94

MOODY

JUN 28 1994

PILOT DRUG EVALUATION STAFF HFD-007
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-281 for 50 and 100 mg Tramadol tablets.

50 and 100 mg Tramadol hydrochloride core tablets are compressed from the same granulation.

An in vivo bioavailability study waiver was requested for 50 mg tablet. 50 and 100 mg Tramadol tablets will be packaged in opaque HDPE bottles as 20s, 30s, 50s, 100s, 500s and 1000s, and in unit dose blisters with paper back supported foil backing. These packaged tablets will be stored at CRT with an interim 2 year expiry date (Grunenthal GMBH marketed Tramadol formulations have an expiry date up to 5 years).

REVIEW # 2 for 50 mg Tramadol tablets
DATE REVIEWED: 4.19.94 and 6.18.94 revision

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	3.11.94	3.14.94 (stability up date up to 6 months for 2 lots 50 mg Tramadol tablets and up to 24 months for 2 lots of 100 mg Tramadol tablets; process validation reports)	
AMENDMENT	3.4.94	3.7.94 (Minor modifications- annual	
AMENDMENT	1.20.94	1.25.94	
AMENDMENT	1.26.94	1.27.94 (	
AMENDMENT	12.10.93	12.13.93 (Preclinical PK of (+)-Tramadol and (-)-Tramadol enantiomers in beagle dogs and in mice following oral administration of racemic Tramadol lot 9007308 for 14 consecutive days)	
AMENDMENT	10.6.93	11.19.93	
AMENDMENT	3.15.93	3.16.93 (4.6.94 retrieval date)	

NAME & ADDRESS OF APPLICANT: The R.W.Johnson Pharmaceutical Research Institute, Division of McNeil Lab Inc., Welsh and McKean Roads, Spring House, PA 19477-0776

DRUG PRODUCT NAME

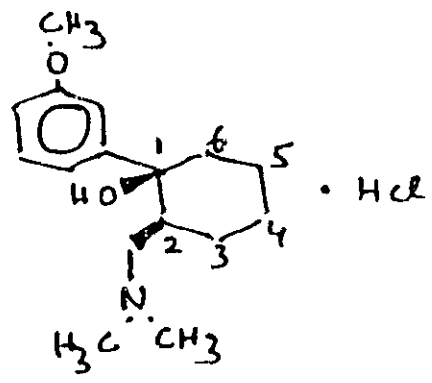
Proprietary: Ultram Tablets 50 and 100 mg
Established: Tramadol hydrochloride tablets 50 and 100 mg
Code Name/#:

Chem.Type/Ther.Class:

PHARMACOL. CATEGORY: Centrally acting analgesic (Grunenthal GMBH, Germany)

DOSAGE FORM: Coated tablets
STRENGTHS: 50 and 100 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
(+ and -)-cis-2-((dimethylamino)methyl)-1-(3-methoxyophenyl)-cyanoheanol hydrochloride, as per USAN nomenclature; C16H25NO2. Hcl; mol.wt. 299.84; exists in one crystalline form with melting point range 180-182 degrees centigrade; neither hygroscopic nor deliquescent; causes mild rusting of steel at 53% RH and severe rusting of steel at 84%RH (tablet press tooling); readily soluble in water to an extent of 200 mg per ml, with a solution Ph of about 5.3; octanol to water partition coefficient is about 0.2; pKa is 9.4; absolute bioavailability is in the range biological half life is in the range 6-9 hrs; the mono-O-desmethyl tramdaol metabolite is biologically active.



REMARKS:

Would safety of Tramadol be effected due to cis-trans isomers resolution as Materials used in preclinical studies were not produced by the

EER and MV requests were sent out from PDES in March 94 for the 100 mg tablets.

CONCLUSIONS & RECOMMENDATIONS:

Recommends approval of CMC section for 50 mg Tramadol coated tablets (100 mg tablets were recommended approval in chem review # 1 dated 3.24.94). Some of the information request items raised in chemistry review #1 were satisfactorily answered. The pending information request items are as follows.

(1). Inclusion of an enatiomeric assay and optical rotation test for the first 6 production batches for each manufacturing site,

(2) Test results for the release of most recent 3 consecutive batches of Tramadol active for each manufacturing site.

(3) Label copies for the immediate container and the secondary package for each potency and for each packaging configuration.

(4) Inclusion of stability indicative TLC method AD 91312 for tablets to monitor decomposition products. TLC can separate Tramadol (rf =1) from degradation products (RWJ-41905-002 1,2-olefin and RWJ-41906-002 1,6-olefin rf=0.9).

cc:
Orig. NDA 20-281
HFD-007/Division File
HFD-007/PMaturu,CYaciw,AMukherjee,JHyde,CWright,RBedford,CMoody

P. Maturu 6.18.94
P Maturu, Primary Review Chemist

C Yaciw 6/28/94
C Yaciw, Secondary Review Chemist

filename: N20281.942

SATISFACTORY/ REVISED INFORMATION REQUEST-4.19.94/6.18.94 revision

The original pharmacology review dated 11/29/1994 has not been finalized and has been excluded from this package.

NDA #20-281

ADDENDUM to Pharmacology Review of November 29,1994

submitted December 13, 1994
(Carcinogenicity Section)

Additional data from post-hoc 3 month mouse dose-ranging study:

There were 4 early deaths, 2 control, one from 60 mg/kg/day and one from 240 mg/kg/day group. Urethral plugs and blood collection trauma were listed as causes of death. No death was considered treatment related.

Five male and female mice per treatment group were necropsied at study completion and the other four or five mice per sex were necropsied two days later. Gross observations were recorded. No histopathological observations were associated with any treatment.

The livers and kidneys of 5 ♂ and 5♀ mice were examined for histopathological changes in the controls and high dose groups (240mg/kg/day). The lesions, mainly mild inflammatory infiltrates of kidney and liver, were considered spontaneous and not treatment related.

Harry M. Geyer III
Harry M. Geyer, III Ph.D.

In concurrence
Peer Reviewer — Dou Jean, Ph.D. — Dec. 16, 1994 — date

cc
Addendum to NDA#20-281
HFD-007/Div. File
HFD-007/HMGeyer
HFD-007/CMoody
HFD-345
R/D Init by
F/T by HMGeyer
WP#Itramaddl.213

MOODY 20281

DEC 16 1994

NDA #20-281

ADDENDUM to Pharmacology Review of November 29,1994
submitted November 29,1994

CORRECTIONS AND ADDITIONS TO THE CAC SUBMISSION

Relative AUC Values for Mice, Rats and Man After Repeated Oral Dosing

tramadol	dose (mg/kg)	dose (mg/M^2)	AUC (ng.h/ml)	AUC_{rodent} / AUC_{human}
mouse[a]	30	(x3=) 90	329 (164)$_s$	0.089 (0.06)^{sr}
rat[b]	30	(x5.9=) 177	2727 (2118)$_s$	0.741 (0.799)^{sr}
man[c]	(100/70) 1.43	(x37=) 52.9	3679 (2649)$_s$	-

a. (V1/1:3/30/94:p4-5) NMRI mice 30 mg/kg/day X 14 days [tram(+)+(-)♂+♀/2]
b. wistar rats (V19/19:p0562) DM-92337 [tram(+)+(-)♂+♀/2] - 30 mg/kg/day X 14 days
c. man 100 Q.I.D. for 29 doses (V01/0023)
s. single dose of 100 mg (V01/0022) in man and 30 mg/kg in rodents.
sr. single dose ratio

In AUC values, the rodent exposures were less than the human exposure by factors from 0.089 to 0.741. This is much less than the 25X increase stated as a general guidance. The ratio values do not change significantly when single dose values are compared.

The half-life was about 2-3 hrs in the rodents and 6 hrs in man. This indicates that the 28 days of administration to the rodents was probably only representative of multiple doses and not the

steady-state as seen in man.

Harry M. Geyer, III Ph.D.

Dec. 16, 1994
date

In concurrence
Peer Reviewer Dou Jean, Ph.D.

cc
Addendum to NDA#20-281
HFD-007/Div. File
HFD-007/HMGeyer
HFD-007/Cmoody
HFD-345
R/D Init by
F/T by HMGeyer
WP#tramadd1.cac

OCT 2 2 1992

Tramadol 100 mg oral tablet
ULTRAM
NDA 20, 281
Victoria Hale, PhD

RW Johnson
Spring House, PA
received: August 27, 1992
reviewed: October 22, 1992

Refuse to File: Pharmacokinetics

Tramadol is an opiate-like analgesic with complicated pharmacokinetics. The following are aspects of the pharmacokinetics of tramadol which were taken from the preliminary review of the August 1992 submission:

1. two enantiomers
2. the kinetics of the enantiomers has not been determined
3. active metabolite M1: relative activity unknown
4. saturable hepatic first pass clearance: fairly well characterized
5. bioavailability is absorption rate-dependent, dose-dependent and formulation-dependent.
6. difficult to determine whether changes in bioavailability alone account for the resultant nonlinear pharmacokinetics of tramadol upon multiple dosing, or whether clearance is also concentration-dependent.
7. dose-proportionality has not been examined in an acceptable manner.
8. absolute bioavailability estimates are varied
9. renal clearance decreases upon multiple dosing

The following is a brief description of the pharmacokinetics of tramadol in humans, as defined to date.

Absorption. Most of a tramadol dose is absorbed after oral administration (98% in a 14C study) and food has little effect on absorption. The absolute availability of tramadol has been investigated with the intravenous formulation. The exact value of F ranges between 68 and 88%, dependent upon protocol design.

Hepatic first pass clearance. The first pass clearance of tramadol is apparently saturable. The pharmacokinetic implications are that as increasing doses of tramadol are given orally, less is eliminated and more is bioavailable (F increases with dose). Furthermore, enhanced rates of absorption would result in increased F values. This apparent nonlinearity is problematic and requires careful examination such that adequate labeling may be prepared for this product.

Plasma protein binding. About 20% of tramadol is bound to plasma proteins; binding is linear.

Volume of distribution. The apparent volume of distribution (V/F) of tramadol is about 300 L. Without carefully designed studies, it is difficult to separate the contribution of F to apparent volume changes.

Systemic clearance. Clearance has not been fully investigated or defined; oral clearance is First pass hepatic clearance may be saturable without systemic clearance being affected post-absorption, because portal vein drug concentrations may be significantly higher than any systemic venous drug concentrations. Without carefully designed studies, it is difficult to determine the contribution of concentration-dependent changes in F to clearance.

Half-life. The elimination half-life of tramadol increases from 6 to 7 hours upon multiple dosing.

Metabolism. Tramadol is extensively metabolized upon oral administration. N- and O-demethylation, followed by glucuronidation or sulfation are the major elimination pathways. It is not known whether one enantiomer is preferentially eliminated through a specific pathway(s).

Activity of metabolites. One desmethyl metabolite is active, and it is identified as M1. Its activity has been estimated to be ?? that of tramadol. The relative activity of this metabolite was not clearly defined. It is not known whether one enantiomer is preferentially converted into M1.

Excretion. About 30% of tramadol is excreted unchanged in urine; renal clearance decreases upon multiple dosing. Most of the metabolites are recovered in urine, as well, accounting for 60% of the original dose. Little tramadol or metabolites are excreted in bile or feces.

Enantiomers. Tramadol is a racemic mixture (2 stereoisomers). Little has been done to characterize the pharmacokinetics or pharmacodynamics of the enantiomers.

Dose-proportionality. One pilot study with 3 subjects evaluated the proportionality of parameters from 100, 200, 300 and 400 mg oral doses or tramadol; due to small sample size, conclusions could not be made.

Multiple dose kinetics. Multiple dose trough concentrations are about 25-35% higher than those predicted based upon single dosing. The sponsor claims that this occurrence is attributable to saturation of first pass clearance (i.e., a change in F), but saturation of systemic clearance (CL) has yet to be ruled out in the appropriate studies.

Analytical. Tramadol and its metabolites were routinely measured in plasma and in urine. The enantiomers are presently being quantitated in one single dose study. The results of an initial survey of the methodology and validation is acceptable.

Renal dysfunction, cirrhosis. disposition studied in these subjects.

Drug interactions. effects of carbamazepine and cimetidine studied.

age, gender. studied. missing a multiple dose study in the elderly

ISSUES REMAINING TO BE ADDRESSED:

1. The sponsor has provided little or no information regarding the differential disposition (pharmacokinetics) of the enantiomers. Enantioselective analysis methods have been available for one decade and the sponsor should have been aware of the Agency's recognition of the significance of these types of studies through public statements made over the last 3 years.
   a. As this drug exhibits nonlinear kinetics, it is important to determine whether the nonlinear processes are stereoselective.
   b. The sponsor suggests that the two enantiomers possess different activities and differential nonlinear kinetics could result in the predominance of one action over another as doses increased.
   c. At present, stereospecific kinetics are available for 4 subjects in a pivotal single dose study; this study should be completed and submitted prior to acceptance for filing.
   d. A multiple dose study should be performed with stereoselective analysis to determine whether the higher than expected concentrations is attributable to one or both enantiomers.

2. Were all clinical studies performed with the same formulation ? This question is important, as the bioavailability of a drug which exhibits nonlinear first pass clearance is absorption rate- or formulation-dependent. If not, then efficacy could be formulation-dependent and bioequivalence studies would be needed for the pivotal clinical trials.

3. The pivotal dose-proportionality study had only 3 subjects, sampling was sporadic and insufficient, and the study was not of cross-over design. As multiple dose kinetics are not predicted based upon single dose kinetics, nonlinear systemic clearance must be ruled out.

4. Absolute bioavailability varies between 68 and 88%. Either another study should be performed, or the sponsor should explain the discrepant results.

a. An infusion, as opposed to a bolus should be administered, to simulate as much as possible the plasma concentration curve observed after oral administration.
b. A IV dose should be administered which provides an AUC magnitude similar to that achieved with the oral dose, until it is proven that clearance is constant.
c. Calculations should be done three ways: with tramadol, with M1 and using the sum of tramadol and M1-tramadol-equivalents. In this way, all active moieties are considered.
d. a stereoselective analysis should be performed to determine whether absorption is stereoselective.

5. The linearity of the systemic clearance of tramadol should be investigated. Various IV doses of tramadol could be administered, so as to separate the contribution of dose-dependent bioavailability.

6. The sponsor claims that there are fewer CNS and respiratory side effects from tramadol than other opiate analgesics. A PK-PD study should be performed to characterize a dose-response relationship between these effects and tramadol enantiomer plasma concentrations.

7. A multiple dose study should be performed in the elderly, quantifying tramadol and M1 excretion in urine and plasma.

The comments made above are related to development of the tramadol label and are consistent with Agency policy, HFD-007 experience/expectations and Division of Biopharmaceutics guidelines. Without this information, the tramadol submission is non-reviewable as the application lacks pivotal pharmacokinetic information. The submission does not meet the minimum requirements for filing and HFD-007 should refuse to file this new drug application.

Victoria G Hale, PhD
Pharmacokineticist
Pilot Drug Evaluation Staff

Peer Pharmacokineticist, E D Bashaw, Pharm D 10/22/92

cc: HFD-007: Hale, drug, Moody
HFD-426: reviewer, drug, chron
HFD-344: Vishwanathan
HFD-019
FT 10/22/92

Nda 20-281

JAN 6 1995

Tramadol HCl (ULTRAM^R)

50 and100 mg tablets

NDA 20-281 (Dissolution)

Reviewer: Iftekhar Mahmood, Ph. D.

R. W. Johnson Pharmaceutical Res. Institute

Welsh & Mckean Roads

Spring House, PA 19477-0776

Submission Date: September 13, 1994

Review of a NDA Supplement (Dissolution)

Background:

R. W. Johnson Pharmaceutical Research Institute, the Sponsor of tramadol HCl (ULTRAM^R) was requested to provide data for the following requests:

1. Provide complete dissolution profiles on the lot of tramadol tablets used in the comparative bioavailability study to link the US and European data. Ideally, this information should include three different media and include a recommendation for the final dissolution.

2. Provide a table that links the lots used in the comparative bioavailability study with the lots used in the clinical studies.

3. Re-analyze the data from the three way comparative study (i.e., formula 18 vs. formula 2 vs. Grunenthal). Analysis is to include 90% confidence intervals (two 1-sided t-test) on the log transformed data.

Reviewer's Comments:

1. The Sponsor's reply to request #1 is that they did not use the three different media for dissolution study because Grunenthal informed them that the release rates of tramadol HCl in artificial gastric juice (pH = 1.2), artificial intestinal juice (pH = 7.4), and demineralized water differ only slightly. Using 50 mg tramado[illegible] dissolution, [illegible] drug was released in 30 minutes in all three media. The results of this study have been presented in Appendix 1.

In the light of the report from Grunenthal, RWJPRI (Spring House) decided to perform their dissolution study only in 0.1N HCl (900 ml, 37^{0}C). The three formulations used in the

comparative bioavailability study were the 50 mg RWJPRI capsule (Formula 2, Batch # R4397), the 100 mg RWJPRI tablet (Formula 18, Batch # R4510) and the 50 mg Grunenthal capsule (Batch # 360 GH). the samples were analyzed by

The result of this study indicated that 50 mg RWJPRI and Grunenthal capsules in 30 minutes, whereas only of the 100 mg RWJPRI tablet dissolved during that time. The result of this study has been shown in Appendix 2.

In another dissolution study, at RWJPRI (Spring House), dissolution profiles using 12 dosage units were determined for the following three 100 mg strength tablet production scale batches:

(i) Uncoated core Batch No. HF1910PCO and coated tablets from two pans Batch Nos. HF1910PV1 and HF1910PV2.

(ii) Uncoated core Batch No. FS1333CO and coated tablets from two pans Batch Nos. FS1333P1 and FS1333P2.

(iii) Cores and composites from Batch Nos. FS1333CO and FS1333P, and HB 2979CO and HB2979.

The medium was 900 ml of 0.1 N HCl. The samples were collected at 10, 20, 30 and 45 minutes and analyzed by HPLC with UV detection.

The result of the study indicated that in 30 minutes all three batches showed a Q value which is reasonably satisfactory (Appendix 3).

Furthermore, a comparison was also made with

Both methods provided almost identical release rates. By 30 minutes the release rate

Therefore, the final dissolution specification of Q value with HCl media should be adequate to be discriminatory among manufacturing lots.

2. The Sponsor's reply to request #2 is in the table form in Appendix 4.

3. Re-analysis of the pharmacokinetic parameters AUC and C_{max} has been done by the Sponsor using log-transformation. Analysis of 90% confidence interval (passing criterion: 80-125%) on log transfomed data has been presented in the following tables:

TABLE 1

Parameter	Geometric mean (reference)	Geometric mean (test)	Ratio (%)	90% Confidence Interval Lower limit (%)	90% Confidence Interval Upper limit (%)
AUC (0-t)	2506.8	2377.8	94.85	88.97	101.12
AUC (0-inf)	2574.5	2441.12	94.82	89.09	100.92
C_{max}	333.5	318.8	95.58	89.86	101.65

Reference is tramadol **50 mg capsule** and test is RWJPRI **50 mg capsule**.

TABLE 2

Parameter	Geometric mean (reference)	Geometric mean (test)	Ratio (%)	90% Confidence Interval Lower limit (%)	90% Confidence Interval Upper limit (%)
AUC (0-t)	2506.8	2426.2	96.78	90.65	103.34
AUC (0-inf)	2574.5	2490.2	96.72	90.75	103.1
C_{max}	333.5	342.4	102.68	96.4	109.36

Reference is tramadol **50 mg capsule** and test is RWJPRI **100 mg tablet**.

Based on 90% confidence interval the means of AUC and C_{max} indicate that the two RWJPRI formulations are bioequivalent to the Grunenthal formulation (Appendix 5).

Comments:

Based on the informations provided by the Sponsor in reponse to FDA's request, this supplement is acceptable to the Division of Biopharmaceutics. The final dissolution specification shoul

in 30 minutes.

1/6/95

Iftekhar Mahmood, Ph. D.

Pharmacokineticist

Peer Reviewer : Ruth E. Stevens, Ph. D. Ruth E. Stevens 1-6-95

cc: NDA 20-281

HFD-007/DIV File

HFD-007/CSO/ Moody

HFD-427 (Drug, Chron, Fleischer, Chen)

HFD-007 (I. Mahmood, PK files)

HFD-344 (Viswanathan)

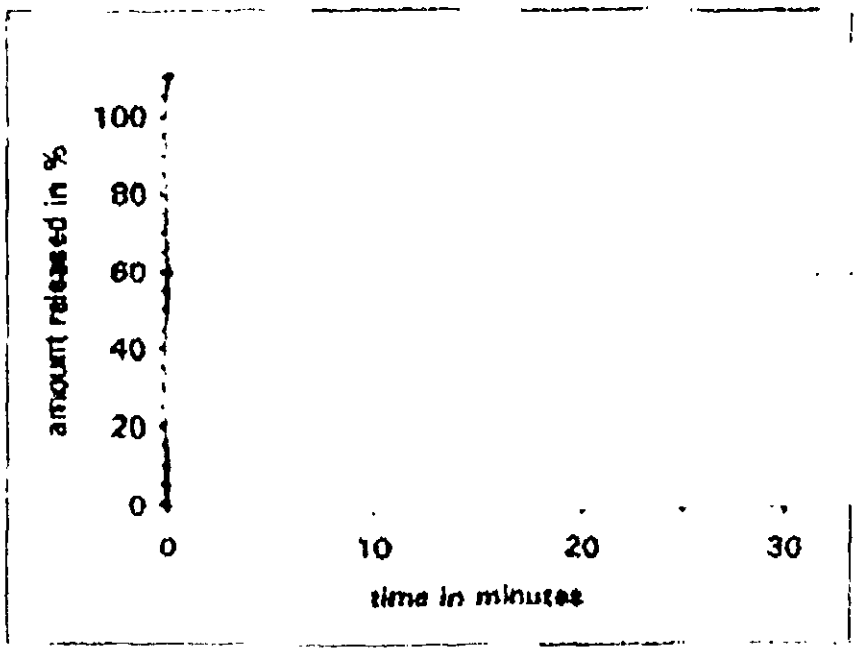
APPENDIX 1

Grünenthal GmbH, D-Aachen
Research Centre

Comparison of the in-vitro-dissolution of Tramal Capsules at pH 1.2, pH 7.4 and in demineralized water

Batch No 569 KI

time in min	amount released in % (mean values of n=6)		
	pH 1.2	pH 7.4	demineralized water
0			
2			
4			
6			
8			
10			
12			
14			
16			
18			
20			
22			
24			
26			
28			
30			



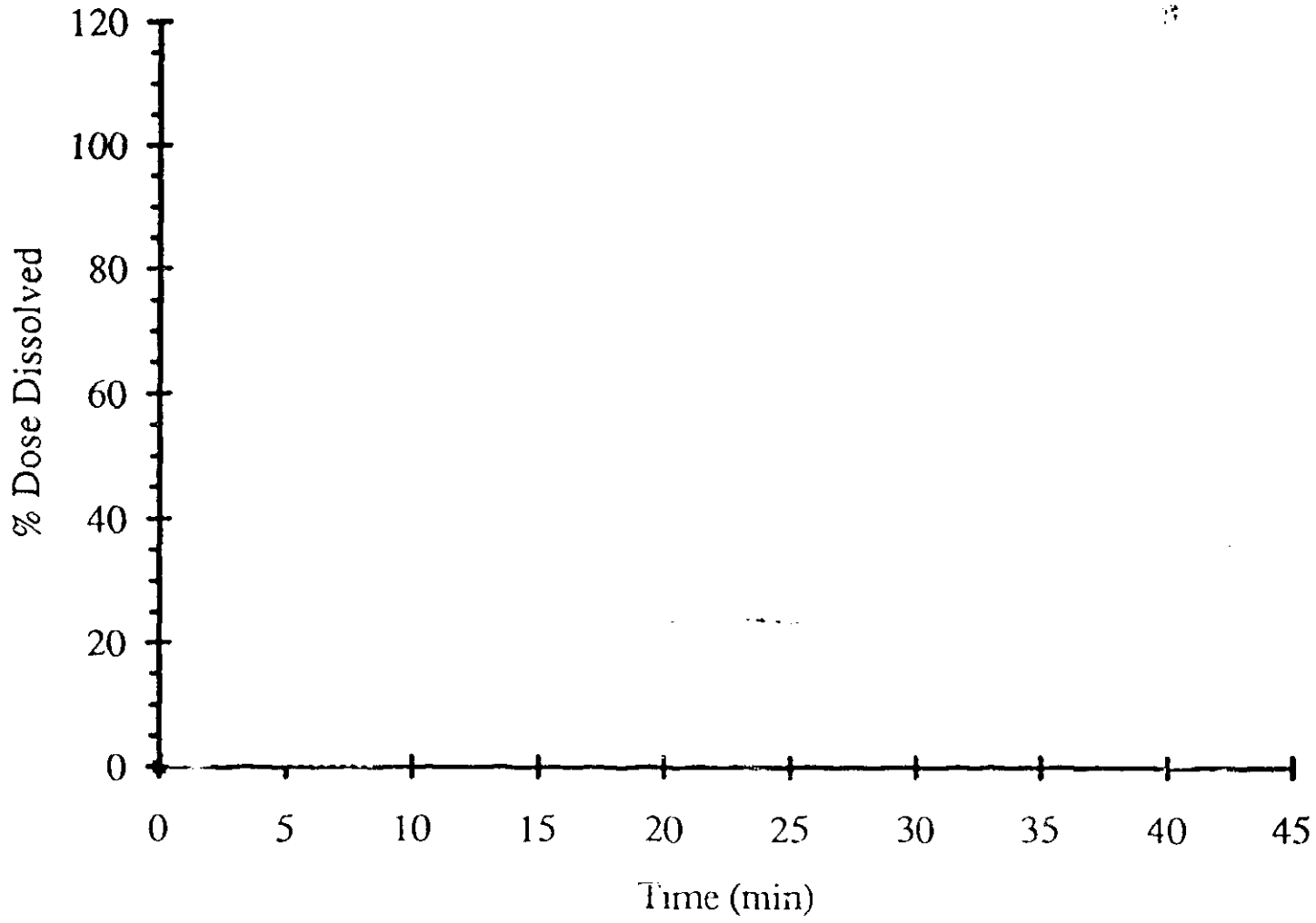
B. Wolf, PhD
Head of Analytical Department

J. Bartholomäus, PhD
Head of Pharmaceutical Development Department

19 Dec. 1994

APPENDIX 2

Dissolution Profiles of Tramadol Formulations Used in The Grunenthal Comparative Bioavailability Study Report F0-PK 326



APPENDIX 3

Table 2: Dissolution Profiles for Tramadol Hydrochloride 100 mg Tablet Validation Batch HF1910P From Cores (HF1910PCO) and coating Pans No. 1 (HF1910PV1) and No. 2 (HF1910PV2)

PD-91312

	Percent Dissolved											
	HF1910PCO (Cores)				HF1910PV1 (Coated)				HF1910PV2 (Coated)			
Min.	10	20	30	45	10	20	30	45	10	20	30	45

Table 3: Dissolution Profiles for Tramadol Hydrochloride 100 mg Tablets Batch FS1333P From Cores (FS1333CO), Coating Pans No. 1 (FS1333P1) and No. 2 (FS1333P2)

	Percent Dissolved								
	FS1333CO (Cores)			FS1333P1 (Coated)			FS1333P2 (Coated)		
Min.:	10	20	30	10	20	30	10	20	30

Table 4: Dissolution Profiles of Tramadol Hydrochloride 100 mg Tablet Validation Batches Composite Samples, Cores vs. Coated Tablets,

	Percent Dissolved					
	FS1333CO (Cores)			FS1333P (Coated)		
Min.:	1	20	30	10	20	30
	HB2979CO (Cores)			HB2979 (Coated)		

M.S. missing sample, insufficient sample volume injected into HPLC

Table 1: Dissolution Profiles of Tramadol Hydrochloride 75 mg Tablet Cores from Notebook Batches, Nos. NB 8090:19, 20, 21, 22T1 and 22T2.

	Percent Dissolved							
	Paddles, 50 rpm				Baskets 100 rpm			
Min:	10	20	30	45	10	20	30	45

APPENDIX 4

Correlation of Clinical Studies to Drug Product Batch Information

Clinical Study Designation	Drug Product Batch Information					
	Batch No.	Batch Size	Manufacturing Site	Formula No. (Strength)	In-Vitro Dissolution Results:[1] MEAN/CV	Stable for Study Duration[2]
TB, TC, TE, TJ	R4240					
AA	R4246					
TE, TE2, TKB, TKM, TL2	R4289					
TA, TB, TC, TD, TE2, TF, TF3, TG, TH, TI, TJ, TKB, TL2, TV, TW, TAA	R4315					
TF3, TQ, TR, TT2, TW2, TZA	R4381					
TKB, TL2, NS-202	R4397					
NS-201, NS-202, NS-205	R4510[3]					

(1) Dissolution results are reported as the mean and coefficient of variation determined for 6 units, except for batch nos. R4397 and R4510 where 12 units were tested. For discussion of the dissolution data, please refer to section 1.c of the CM & C reviewer guide.

(2) The stability report DO-92301 is located in Attachment 7 in Volume 5 of the NDA. Chemical assay and impurity data for R4246 and R4381 (PFBs 2654 and 2960, respectively) are provided in Appendix 1 of the CM & C reviewer guide. The Product Formula Batch number (PFB) is a code designation used to identify stability studies (specific package, formula and batch).

(3) Tablets are from production batch FS1333P. Batch FS1333P was placed on stability in various container-closure systems as described in DO-92301.

APPENDIX 5

R. W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE
PRECLINICAL BIOSTATISTICS DEPARTMENT - RARITAN
INTEROFFICE MEMO

==========

TO: S. Liao **DATE:** September 2, 1994

FROM: J. Natarajan **CC:** S. Altan

SUBJECT: Statistical Analysis of Log-Transformed Data From Three-Way Crossover Study of Tramadol.
Report # : Grunenthal FO-PK 326

This memo summarizes the results obtained in the analysis of log-transformed data from three-way crossover study of tramadol (Grunenthal Protocol #FO-PK 326).

Design and Objective

Eighteen female subjects were randomly assigned to one of six treatment sequence groups and received the following three treatments using a three-period crossover design:

R	=	Grunenthal Tramal capsules (2X 50 mg)
T	=	RWJPRI Tramadol capsule (2X 50 mg)
t	=	RWJPRI Tramadol tablets (100 mg)

Blood samples were drawn at various time points following dose administration for the determination of the pharmacokinetic parameters.

The objective of the study was to determine the bioequivalence of the two RWJPRI formulations with respect to the Grunenthal capsules (reference).

Statistical Methodology

The parameters of interest in the study were AUC to infinity (AUC_INF), AUC to the last time point (AUC_T) and the maximum concentration obtained (CMAX).

Analysis of variance models were fitted to the log-transformed data (natural logarithm) with treatment sequence group, subjects nested within treatment sequence group, treatment and period as the factors. The treatment sequence group effect was tested using the subjects nested within treatment sequence group as the error term. The period

effect was tested using a residual error term. The estimate of intrasubject variability from the analysis of variance model was used to construct 90% confidence interval for the difference in means of the log-transformed data between each test formulation and the reference. The anti-logarithms of the limits of the confidence intervals were taken as the limits of the 90% confidence interval for the ratio of the test and reference means.

Result

The raw data listing along with mean and standard deviation for the parameter are given in Tables 1-3.

Using a 10% level of significance, the analysis of variance models showed no significant treatment sequence group effect for any of the parameters of interest. The period effect was not significant for AUC to infinity and for AUC to the last time point but was significant for CMAX (p value=0.083). The estimates of intrasubject variability (MSE) were as follows:

Parameter	MSE	Root MSE
Log(AUC_INF)	0.0121	0.110
Log(AUC_T)	0.0128	0.113
Log(CMAX)	0.0119	0.109

Due to missing values for subject 15 in one of the periods, least square means were used in the estimation.

For the comparison of RWJPRI 50 mg capsule to Tramal 50 mg capsule (Table 4), the 90% confidence interval for the ratio of the means ranged from 89.1 to 100.9% for AUC_INF 89.0 to 101.1% for AUC_T, and 89.9 to 101.7% for CMAX. Thus, the 90% confidence intervals for the ratio of the means fell with the region of bioequivalence (80 to 125%) for all three parameters.

For the comparison of RWJPRI 50 mg capsule to Tramal 50 mg capsule (Table 5), the 90% confidence interval for the ratio of the means ranged from 90.7 to 103.1% for AUC_INF, 90.6 to 103.3% for AUC_T, and 96.4 to 109.4% for CMAX. Thus, the 90% confidence intervals for the ratio of the means fell with the region of bioequivalence (80 to 125%) for all three parameters.

Conclusion

Based on 90% confidence intervals for the ratios of means, it can be concluded that the two RWJPRI formulations are equivalent to the Grunenthal formulation.

TABLE 1

BIOEQUIVALENCE STUDY OF TRAMADOL

GRUNENTHAL FO-PK 326

RAW DATA LISTING FOR PARAMETER = AUC_INF

SUBJECT	R	T	t	LOG_R	LOG_T	LOG_t	DIFF (T-R)	RATIO (T/R)	DIFF (t-R)	RATIO (t/R)
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
N	18.00	18.00	17.00	18.00	18.00	17.00	18.0	18.00	17.0	17.00
MEAN	2738.94	2617.78	2633.12	7.85	7.80	7.81	-121.2	0.96	-89.4	0.98
S.D.	948.24	1017.60	942.90	0.37	0.36	0.39	384.6		414.7	

DPS94147.MC\M002\34\0994\bme

TABLE 2

BIOEQUIVALENCE STUDY OF TRAMADOL

GRUNENTHAL FC-PK 326

RAW DATA LISTING FOR PARAMETER = AUC_T

SUBJECT	R	T	t	LOG_R	LOG_T	LOG_t	DIFF (T-R)	RATIO (T/R)	DIFF (t-R)	RATIO (t/R)
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
N	18.00	18.00	17.00	18.00	18.00	17.00	18.0	18.00	17.0	17.00
MEAN	2664.61	2545.50	2563.06	7.83	7.77	7.78	-119.1	0.96	-83.5	0.96
S.D.	904.36	967.88	903.68	0.37	0.38	0.39	285.6		416.1	

TABLE 3

BIOEQUIVALENCE STUDY OF TRAMADOL

GRUNENTHAL FO-PK 326

RAW DATA LISTING FOR PARAMETER = CMAX

SUBJECT	R	T	t	LOG_R	LOG_T	LOG_t	DIFF (T-R)	RATIO (T/R)	DIFF (t-R)	RATIO (t/R)
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
N	18.000	18.000	17.000	18.00	18.00	17.00	18.0	18.00	17.0	17.00
MEAN	344.439	327.500	348.529	5.81	5.76	5.83	-16.9	0.97	4.7	1.04
S.D.	90.333	77.662	73.468	0.26	0.24	0.24	62.4		63.6	

DPS94147.MEM020347094bmm

TABLE 4

BIOEQUIVALENCE STUDY OF TRAMADOL

GRUNENTHAL FO-PK 326

90% CONFIDENCE INTERVALS FOR SCHUIRMANN'S TEST
ANALYSIS ON LOG TRANSFORMED DATA
REFERENCE IS TRAMAL 50 MG CAPSULE AND TEST IS RWJPRI 50 MG CAPSULE

PARAMETER	GEOMETRIC MEAN FOR REFERENCE	GEOMETRIC MEAN FOR TEST	SE_POOL	DF	RATIO (%)	LOWER LIMIT (%)	UPPER LIMIT (%)
AUC_T	2506.73	2377.77	0.037756	31	94.8537		
AUC_INF	2574.51	2441.12	0.036757	31	94.8188		
CMAX	333.51	318.76	0.036362	31	95.5764		

LEAST SQUARES MEANS WERE USED FOR THE ESTIMATION

OPS94147.ME/W02034709994bms

TABLE 5

BIOEQUIVALENCE STUDY OF TRAMADOL

GRUNENTHAL FO-PK 326

90% CONFIDENCE INTERVALS FOR SCHUIRMANN'S TEST
ANALYSIS ON LOG TRANSFORMED DATA
REFERENCE IS TRAMAL 50 MG CAPSULE AND TEST IS RWJPRI 100 MG TABLET

PARAMETER	GEOMETRIC MEAN FOR REFERENCE	GEOMETRIC MEAN FOR TEST	SE_POOL	DF	RATIO (%)	LOWER LIMIT (%)	UPPER LIMIT (%)
AUC_T	2506.78	2426.16	0.038631	31	96.784		
AUC_INF	2574.51	2490.19	0.037609	31	96.725		
CMAX	333.51	342.44	0.037204	31	102.677		

LEAST SQUARES MEANS WERE USED FOR THE ESTIMATION

Harter
HFD-007

Statistical Review and Evaluation

NDA: 20-281 Date: 9/28/93

Applicant: The R. W. Johnson Pharmaceutical Research Institute

Name of Drug: Ultram (Tramadol hydrochloride) tablets

Documents Reviewed: NDA Submission volumes 32 to 51 of 239, Data on floppy diskette supplied by the sponsor.

I. Background: In this NDA submission two animal carcinogenicity studies, one in mice and one in rats, were included. These two studies were intended to assess the carcinogenicity potential of Ultram in mice and rats when administered orally in drinking water at some selected dose levels. The lengths of the mouse study was 21 months for females and 24 months for males, and that of the rat study was 30 months for both sexes. Dr. Corinne P. Moody, HFD-007, requested the Division of Biometrics to perform the statistical review and evaluation of these studies. The results of the review have been discussed with the reviewing pharmacologists Dr. Asoke Mukherjee.

II. The mouse study

IIa. Design: Two separate experiments, one in male and one in female mice, were conducted. In these two experiments there were three treated groups known as low, medium, and high dose groups, and two control groups known as control 1 and control 2. Two hundred fifty male and two hundred fifty female NMRI mice were randomly divided into five groups of equal size of 50 animals to form the treatment groups. The dose levels for the treated groups were 7.5, 15.0, and 30.0 mg/kg/day for low, medium, and high dose groups, respectively. The animals in the control groups received the vehicle (sterile double-distilled water).

Water consumption was measured four times weekly up to week 4, generally every two weeks from week 4 to week 55, and generally every four weeks thereafter.

The animals were checked daily for mortality and morbidity and were examined weekly for the presence of any palpable masses. A complete histopathological examination was conducted on all animals in the control and high dose groups. Of animals belonging to the low (7.5 mg/kg) or the medium (15.0 mg/kg) dose group a complete histopathological examination was conducted on animals died or killed moribund before the scheduled terminal sacrifice, otherwise

only liver, lungs and any grossly detected abnormalities were microscopically examined.

IIb. Sponsor's analysis

Survival analysis: Tables for survival rates of male and female mice were constructed. The survival data were analyzed using the method described in the paper of Cox (Regression models and life tables, Journal of the Royal Statistical Society, B, 34, 187-220, 1972), and of Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika, 52, 203-223, 1965). The tests did not show any statistically significant positive linear trend or differences in mortality among the treatment groups.

Tumor data analyses: Tumor data were analyzed using the methods described in the paper of Peto et al. (Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980). Tests for positive linear trend were performed for tumor types found in the target organs (liver and the lungs). For tumor types found in other organs pairwise comparisons were performed to compare the incidence rate in the high dose group with those in the controls. In all his analyses the sponsor combined control 1 and control 2 to form a single control group. The tests showed statistically significant positive linear trends in hepatocellular adenoma, any liver tumors, and benign liver tumors in males and in both sexes combined. Statistically significant positive linear trends were also found in lung carcinoma and malignant lung tumors in male mice. Pairwise comparisons with the control showed statistically significantly higher incidences of hepatocellular adenoma and harderian gland adenoma in males, and generalized histiocytic sarcoma and pulmonary tumors in females in the high dose group.

IIc. Reviewer's analysis

The reviewer independently performed analyses on the survival and the tumor data. For survival data analysis the methods described in the papers of Cox (1972), and of Gehan (1965) were used. The tumor data were analyzed using the methods described in the paper of Peto et al.(1980) and the method of exact permutation trend test, developed by the Division of Biometrics. Since both of the controls were coded by 0 and were treated similarly, in order to have more powerful tests, in reviewer's analysis the two control groups were combined to form one single control group. All data used in the reviewer's analysis were provided by the sponsor on a floppy diskette, except the body weight data which were taken from the sponsor's hard copy submission.

Survival analysis: The intercurrent mortality data of mouse study are given in table 1. The plots of Kaplan-Meier estimates of the survival distributions of male and female mice are given in Figures 1a and 1b, respectively. The homogeneity of survival distributions of four groups (Control, Low, Medium, High) were tested separately for male and female mice using the Cox test and the Generalized Wilcoxon test. The tests did not show any statistically significant (at .05 level) positive linear trend in either sex. Pairwise comparisons showed statistically significantly (at .05 level) higher mortality in the low dose group in male mice when compared with the corresponding control, no such increment was found in female mice.

The p-values of the positive linear trend and the pairwise tests are given in Tables 2a and 2b, respectively.

Tumor data analyses: Since only liver and lungs of all animals were examined, the reviewer performed trend test analysis for tumor types found in these organs and pairwise comparisons of the treated groups with the control for tumor types found in other organs. Also since the sponsor did not classify the tumor types as 'cause of death', or 'not cause of death', (for all tumor types the status was reported as either 'undetermined' or 'not applicable') the reviewer applied the 'prevalence' method to test the positive linear trend in the incidence rates. All trend tests were performed using the method of exact permutation trend test, which is an extension of the Fisher exact test, and pairwise comparisons were performed using the age adjusted Fisher Exact test. The scores used for trend test were 0.00, 7.5, 15.00, and 30.00 for control, low, medium, and high dose groups, respectively. The time intervals used were 0-52, 53-78, 79-94, 95-104 weeks, and terminal sacrifice for male and 0-52, 53-78, 79-91, and terminal sacrifice for female mice.

The incidence rates of tumor types with p-values less than .05 are listed below.

Male mice	Tumor rate				P-values	
Organ/Tumor	C	L	M	H	Trend	Pairwise
	100	50	50	50		
Liver/Hepatocellular adenoma	9	6	9	12	.0081*	.0161

Female mice	Tumor rate		P-values
Organ/Tumor	C	H	Pairwise
	100	50	
Generalized/Histiocytic sarcoma	0	3	.0418*

Multiple testing adjustment: Haseman's rule states that in order to keep the false-positive rate at the nominal level of approximately five percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at .05 level, otherwise the level

should be set at .01 (Haseman, (1983), A re-examination of false-positive rates for carcinogenesis studies, Fundamental and Applied Toxicology, 3: 334-339).

On the basis of Haseman's rule the positive linear trend in Liver/Hepatocellular adenoma in male mice and the increased incidence of Generalized/Histiocytic sarcoma in female mice are considered to be statistically significant.

The incidence rates and p-values of all tumor types tested for positive linear trends and pairwise comparisons are given in Table 3.

III. The rat study

IIIa. Design: Two separate experiments, one in male and one in female rats, were conducted. In these two experiments there were three treated groups known as low, medium, and high dose groups, and two control groups known as control 1 and control 2. Two hundred fifty male and two hundred fifty female Wister rats were randomly divided into five groups of equal size of 50 animals to form the treatment groups. The dose levels for the treated groups were 7.5, 15.0, and 30.0 mg/kg/day for low, medium, and high dose groups, respectively. The animals in the control groups received the vehicle (sterile double-distilled water).

Water consumption was measured four times weekly up to week 4, once weekly from week 4 to week 61, and every two weeks thereafter.

The animals were checked daily for mortality and morbidity and were examined weekly for the presence of any palpable masses. A complete histopathological examination was conducted on all animals in the control and high dose groups. Of animals belonging to the low (7.5 mg/kg) or medium (15.0 mg/kg) dose group a complete histopathological examination was conducted on animals died or killed moribund before the scheduled terminal sacrifice, otherwise only any grossly detected abnormalities were microscopically examined. The supplied data set (in the floppy diskette) contains the incidence rates of controls and high dose groups only .

IIIb. Sponsor's analysis

Survival analysis: Tables for survival rates of male and female mice were constructed. The survival data were analyzed using the method described in the paper of Cox (1972), and of Gehan (1965).

The tests did not show any statistically significant positive linear trend or differences in mortality among the treatment groups.

Tumor data analyses: Tumor data were analyzed using the methods described in the paper of Peto et al. (1980). In his analyses only pairwise comparisons were performed to compare the incidence rate in the high dose group with that in the control. In all his analyses the sponsor combined control 1 and control 2 to form a single control group.

The tests showed statistically significantly higher increment in generalized hemangiosarcoma in both sexes, renal mesenchymal tumor, hepatocellular carcinoma, ovarian thecoma, and thyroid follicular adenoma in female rats.

IIIc. Reviewer's analysis

The reviewer independently performed analyses on the survival and the tumor data. For survival data analysis the methods described in the papers of Cox (1972) and of Gehan (1965) were used. The tumor data analyses were performed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test, developed by the Division of Biometrics. Since both of the controls were coded by 0 and were treated similarly, in order to have more powerful tests, in reviewer's analysis the two control groups were combined to form one single control group. All data used in the reviewer's analysis were provided by the sponsor on a floppy diskette, except the body weight data which were taken from the sponsor's hard copy submission.

Survival analysis: The intercurrent mortality data of the rat study are given in table 4. The plots of Kaplan-Meier estimates of the survival distributions for male and female rats are given in Figures 2a and 2b, respectively. The homogeneity of survival distributions of two groups (Control, and High) were tested separately for male and female rats using the Cox test and the Generalized Wilcoxon test. The test did not show any statistically significant (at .05 level) difference in the mortality between the control and the high dose groups in either sex.

The p-values of the test are given in table 5.

Tumor data analysis: Since tumor data of only control and high dose groups were submitted in reviewer's analyses only pairwise comparisons were performed to compare the incidence in the high dose group with that in the controls using the age adjusted Fisher exact test. Also since the sponsor did not classify the tumor types as 'cause of death', or 'not cause of death', (for all tumor types the status was reported as either 'undetermined' or 'not applicable') in reviewer's analyses all tumors were analyzed as in the incidental context (prevalence). None of the tested tumor types showed any statistically significantly (at .05 or .01 level) increased incidence in the high dose group in either sex.

The incidence rates and p-values of all tumor types tested for increased tumor incidences in the high dose group are given in Table 6.

IV. Evaluation of validity of the design

The reviewer's analysis showed that in rat study no tested tumor types had statistically significantly increased tumor incidences in the high dose group when compared with the combined control. However, before drawing the conclusion that the drug is not carcinogenic, in rats it is important to look into the following two issues as having been pointed out in the paper by Haseman (Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies, Environmental Health Perspectives, Vol. 58, pp 385-392, 1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor?
(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (Issues in carcinogenicity testing: Dose selection, Fundamental and Applied Toxicology, Vol. 5, pp 66-78, 1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Statistical Application and Research Branch, Division of Biometrics, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be consider as a sufficient number and adequate exposure.

In addition Chu, Cueto and Ward (Factors in the evaluation of 200 national cancer institute carcinogen bioassay, Journal of Toxicology and environmental Health. Vol. 8, pp 251-280, 1981), suggested that " To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of

survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy.

i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."
ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the Ultram rat carcinogenicity study, in the light of the above guidelines.

The following are summary survival data of rats in the high dose group.

	52 weeks	78 weeks	104 weeks	130 weeks
Male	96.00%	94.00%	68.00%	36.00%
Female	98.00%	90.00%	58.00%	28.00%

From the summary data, and the survival criteria mentioned above, it can be concluded that in both sexes there were enough number of rats exposed for sufficient amount of time to the drug.

The following are summary body weight gains data of the rat study.

		Mean body weight(gms) Beginning	End	Weight	Percentage of
Sex	Group	of study	of study	gain	Control
Male	Control	81.50	437.00	355.50	
	Low	80.00	424.00	344.00	96.76
	Medium	82.00	405.00	323.00	90.85
	High	81.00	403.00	322.00	90.57
Female	Control	75.00	285.00	210.00	
	Low	75.00	277.00	202.00	96.19
	Medium	77.00	297.00	220.00	104.76
	High	74.00	294.00	220.00	104.76

Therefore, relative to the control, male rats had a decrement of weight gain in the high dose group equal to 9.43% and female rats had a body weight increment of body weight gain in the high dose group equal to 4.76%.

The mortality rate at the end of the experiment are as follows:

	Control	High
Male	62.00%	64.00%
Female	70.00%	72.00%

The morality rate of the high dose group is slightly higher in both sexes than that of the control.

Thus, from the weight gain and mortality criteria it can be concluded that the high dose used may be not close to MTD. However, to draw any final conclusion in this regard all clinical signs and histopathological toxic effects must be taken into consideration.

Reviewer's comments:

The following are the reviewer's comments on the tumor data set and the review methods of review :

1) The sponsor did not classify the tumor type as 'cause of death' (fatal tumors) or 'not cause of death' (incidental tumors). In reviewer's analysis all tumors were assumed to be as not cause of death (hence the prevalence method was applied). However, as pointed out in Peto et al. (1980) " Misclassifying incidental tumors as fatal tumors tends to make the treatment of groups with poor intercurrent survival appear more carcinogenic than it really was, while, conversely, misclassifying fatal tumors as incidental tends to make the treatment of groups with poor intercurrent survival seem less carcinogenic than it really was". Since, in either the mouse or the rat study there were no differences in the survival among treatment groups (except for the low dose group in male mice when compared with the control) the probable misclassification of tumor types in reviewer's analysis may not have large implication in the results.

2) In the rat tumor data set, findings of only control and high dose groups were reported. Because of this no trend test could be performed. The data were analyzed using the age adjusted Fisher exact test. The Fisher exact test, however, is not as powerful as the trend test. Therefore, if possible, full data should be looked at and a reanalysis should be done at least for some target organs.

3) Following table shows the number of animals with at least one autolyzed organ.

		C	L	M	H
Mouse	Male	88	0	1	47
	Female	97	0	0	47
Rat	Male	89	0	0	49
	Female	92	0	0	49

The total numbers of autolysis cases in the control and the high dose groups seem too excessive.

V. Summary

Mouse study: No statistically significant (at .05 level) positive linear trend was found in either sex. Pairwise comparisons showed statistically significantly (at .05 level) higher mortality in the low dose group in male mice when compared with the corresponding control. No such increment was found in female mice.

Hepatocellular adenoma in male mice showed a statistically significant positive linear trend. Histiocytic sarcoma in general in female mice showed a statistically significantly higher incidence in the high dose group when compared with the combined control.

The rat study: Data of only control and high dose group were submitted. No statistically significant (at .05 level) difference in the mortality between the control and the high dose group was found in either sex.

None of the tested tumor types showed any statistically significantly (at .05 or .01 level) increased incidence in the high dose group in either sex.

From the weight gain and mortality criteria it can be concluded that the used high dose may not be close to MTD.

Mohammad Ataur Rahman
Mohammad A. Rahman, Ph.D.
Mathematical Statistician

Karl K. Lin 9/27/93
Concur: Karl K. Lin, Ph.D., Group Leader

cc: Original NDA 20-281
HFD-007/Dr. Harter
HFD-007 Dr. Moody
HFD-007/Dr. Mukharjee
HFD-710/Chron
HFD-715/Dr. K. Lin
HFD-715/Dr. Rahman
HFD-715/SARB Chron
HFD-715/DRU 2.1.1 NDA 20-281 Ultram (Tramadol hydrochloride) tablets Mouse and Rat carcinogenicity studies.
HFD-502/Dr. Weissinger
HFD-715/Diskette Rahman-2/ULTRAM.CAR
HFD-400/Dr. Contrera

Table 1

Intercurrent mortality rates in the mouse study

Sex	Time(wks)	Control	Low	Medium	High
MALE					
	0 - 52	6/100 (6.00)	2/ 50 (4.00)	2/ 50 (4.00)	1/ 50 (2.00)
	53- 78	8/ 94 (14.00)	7/ 48 (18.00)	7/ 48 (18.00)	10/ 49 (22.00)
	79- 94	26/ 86 (40.00)	20/ 41 (58.00)	18/ 41 (54.00)	14/ 39 (50.00)
	95-10/	18/ 60 (58.00)	9/ 21 (76.00)	5/ 23 (64.00)	8/ 25 (66.00)
	TERM. SACR	42/100 (42.00)	12/ 50 (24.00)	18/ 50 (36.00)	17/ 50 (34.00)
FEMALE					
	0 - 52	16/100 (16.00)	2/ 50 (4.00)	3/ 50 (6.00)	2/ 50 (4.00)
	53- 78	38/ 84 (54.00)	19/ 48 (42.00)	15/ 47 (36.00)	19/ 48 (42.00)
	79- 91	21/ 46 (75.00)	12/ 29 (66.00)	1?/ 32 (70.00)	13/ 29 (68.00)
	TERM. SACR	25/100 (25.00)	17/ 50 (34.00)	15/ 50 (30.00)	16/ 50 (32.00)

Note: Except the TERM. SACR. row, ar entry of this table =number of animals dying or sacrificed in the time interval/number of animals entering the time interval. An entry in parenthesis = cumulative mortality rate;i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SACR. row = number of animals surviving to terminal sacrifice / initial number of animals. An entry in parenthesis in this row = percent of animals (of the initial number) surviving to terminal sacrifice.

Table 2a

P-values of tests for positive linear trend in mortality in the mouse study

Test of homogeneity		
Sex	Test	P-value (One tail Chi-Sqr.)
Male	Cox	.1649
	Wilcoxon	.2097
Female	Cox	.3352
	Wilcoxon	.1500

Test of Positive linear trend		
Sex	Test	P-value (One tail Normal)
Male	Cox	.1472
	Wilcoxon	.1171
Female	Cox	.9097
	Wilcoxon	.9484

Table 2b

P-values of pairwise tests for the differences in mortality between treatment groups in the mouse study

Male mouse

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: B:LTA.MMS

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		3.9388	POS	4.6096	4.5865	4.2521	4.2370
	PROB	.0223*	.0472*		.0318*	.0322*	.0392*	.0396*
0 VS. 2	CHISQ		.2813	POS	.8746	.8721	1.3870	1.3838
	PROB	.2991	.5959		.3497	.3504	.2389	.2394
0 VS. 3	CHISQ		.5902	POS	1.1165	1.1149	1.6109	1.6085
	PROB	.2218	.4423		.2907	.2910	.2044	.2047
1 VS. 2	CHISQ		1.1905	NEG	.7032	.7024	.4704	.4702
	PROB	.1376	.2752		.4017	.4020	.4928	.4929
1 VS. 3	CHISQ		.7771	NEG	.5872	.5852	.3534	.3529
	PROB	.1891	.3780		.4435	.4443	.5522	.5525
2 VS. 3	CHISQ		.0000	POS	.0022	.0022	.0499	.0499
	PROB	.5000	1.0000		.9622	.9622	.8232	.8232

Female mouse

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: B:LTA.FMS

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		.9301	NEG	1.7347	1.7325	2.7662	2.7623
	PROB	.1672	.3348		.1878	.1881	.0963	.0965
0 VS. 2	CHISQ		.2088	NEG	1.3922	1.3894	3.1510	3.1443
	PROB	.3211	.6477		.2380	.2385	.0759	.0762
0 VS. 3	CHISQ		.5077	NEG	1.4169	1.4137	2.1855	2.1822
	PROB	.2367	.4762		.2339	.2344	.1393	.1396
1 VS. 2	CHISQ		.0460	POS	.0014	.0014	.0592	.0592
	PROB	.4152	.8303		.9704	.9705	.8077	.8078
1 VS. 3	CHISQ		.0000	POS	.0076	.0076	.0146	.0146
	PROB	.5000	1.0000		.9305	.9306	.9037	.9038
2 VS. 3	CHISQ		.0000	NEG	.0053	.0053	.0434	.0433
	PROB	.5000	1.0000		.9417	.9418	.8351	.8352

Table 3

Tumor rates and p-values of the tested tumor types for positive linear trend and/or pairwise comparisons for increased tumor incidence in the treated groups in mouse study[1]

Male mice	Tumor rate				P-value	
Organ/Tumor	C	L	M	H		
	100	50	50	50	Trend	Pairwise (C,H)
Adrenal-medulla/Carcinoma	4	N	N	3		.3919
Harderian gland/Adenoma	7	N	N	7		.1390
Liver/Hepatocellular adenoma	9	6	9	12	.0081*	.0161
Liver/Hepatocellular carcinoma	3	1	0	2	.4302	.4823
Lungs/Carcinoma	8	8	5	8	.1396	.1201

Male mice	Tumor rate				P-value	
Organ/Tumor	C	L	M	H		
	100	50	50	50	Trend	Pairwise
Generalized/Histiocytic sarcoma	0	N	N	3		.0418*
Harderian gland/Adenoma	9	N	N	5		.6339
Liver/Hepatocellular adenoma	0	1	2	1	.1983	.3902
Lungs/Adenoma	2	9	8	5	.0929	.0615
Lungs/Carcinoma	6	3	0	5	.4031	.4048
Mammary gland/Carcinoma	4	N	N	2		.7182
Pituitary/Adenoma	5	N	N	3		.6139

N= None were examined

Table 4

Intercurrent mortality rates in the rat study

Sex	Time(wks)	Control	High
MALE			
	0 - 52	2/100 (2.00)	2/ 50 (4.00)
	53- 78	4/ 98 (6.00)	1/ 48 (6.00)
	79-104	28/ 94 (34.00)	13/ 47 (32.00)
	05-117	18/ 66 (52.00)	10/ 34 (52.00)
	18-130	10/ 48 (62.00)	6/ 24 (64.00)
	TERM. SACR	38/100 (38.00)	18/ 50 (36.00)
FEMALE			
	0 - 52	3/100 (3.00)	1/ 50 (2.00)
	53- 78	7/ 97 (10.00)	4/ 49 (10.00)
	79-104	32/ 90 (42.00)	16/ 45 (42.00)
	05-117	12/ 58 (54.00)	11/ 29 (60.00)
	18-130	16/ 46 (70.00)	4/ 18 (72.00)
	TERM. SACR	30/100 (30.00)	14/ 50 (28.00)

Note: Except the TERM. SACR. row, an entry of this table =number of animals dying or sacrificed in the time interval/number of animals entering the time interval. An entry in parenthesis = cumulative mortality rate;i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SACR. row = number of animals surviving to terminal sacrifice / initial number of animals. An entry in parenthesis in this row = percent of animals (of the initial number) surviving to terminal sacrifice.

Table 5

P-values of tests for increased mortality in the high dose group in the rat study

Test for increased tumor incidence		
Sex	Test	P-value (One tail Normal)
Male	Cox	.5021
	Wilcoxon	.6037
Female	Cox	.3538
	Wilcoxon	.3269

Table 6

Tumor rates and p-values of the tested tumor types for pairwise comparisons for increased tumor incidence in the high dose group in mouse study

Male rats Organ/Tumor	Tumor rate C 100	 H 50	P-value
Brain/Meningioma	0	1	.3750
Generalized/Hemangiosarcoma	1	2	.3171
Kidneys/Carcinoma	1	1	.5435
Pancreas/Adenoma	3	2	.5406
Seminal vesicles/Adenocarcinoma	0	1	.3214
Female rats			
Generalized/Hemangiosarcoma	1	1	.5455
Generalized/Histiocytic sarcoma	0	1	.2000
Kidneys/Renal mesenchymal tumor	0	1	.2000
Liver/Hepatocellular carcinoma	0	2	.1739
Ovaries/Thecoma	0	2	.0636
Pancreas/Leiomyoma	0	1	.4783
Stomach/Adenocarcinoma	0	1	.4783
Thyroid/Follicular adenoma	1	2	.1939

Figure 1a

Kaplan-Meier Estimates of the survival distributions
(Male mice)

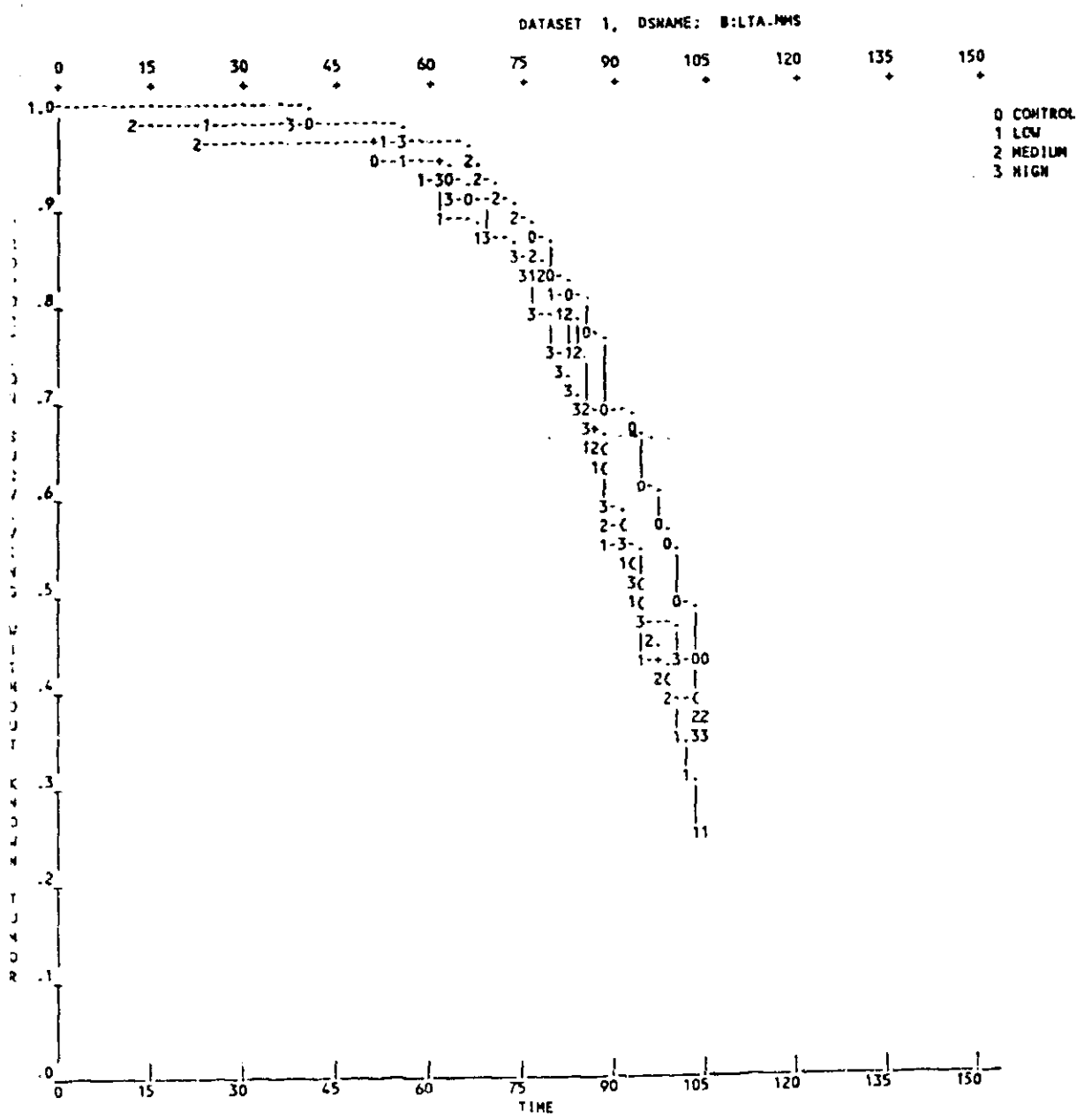


Figure 1b

Kaplan-Meier Estimates of the survival distributions (Female mice)

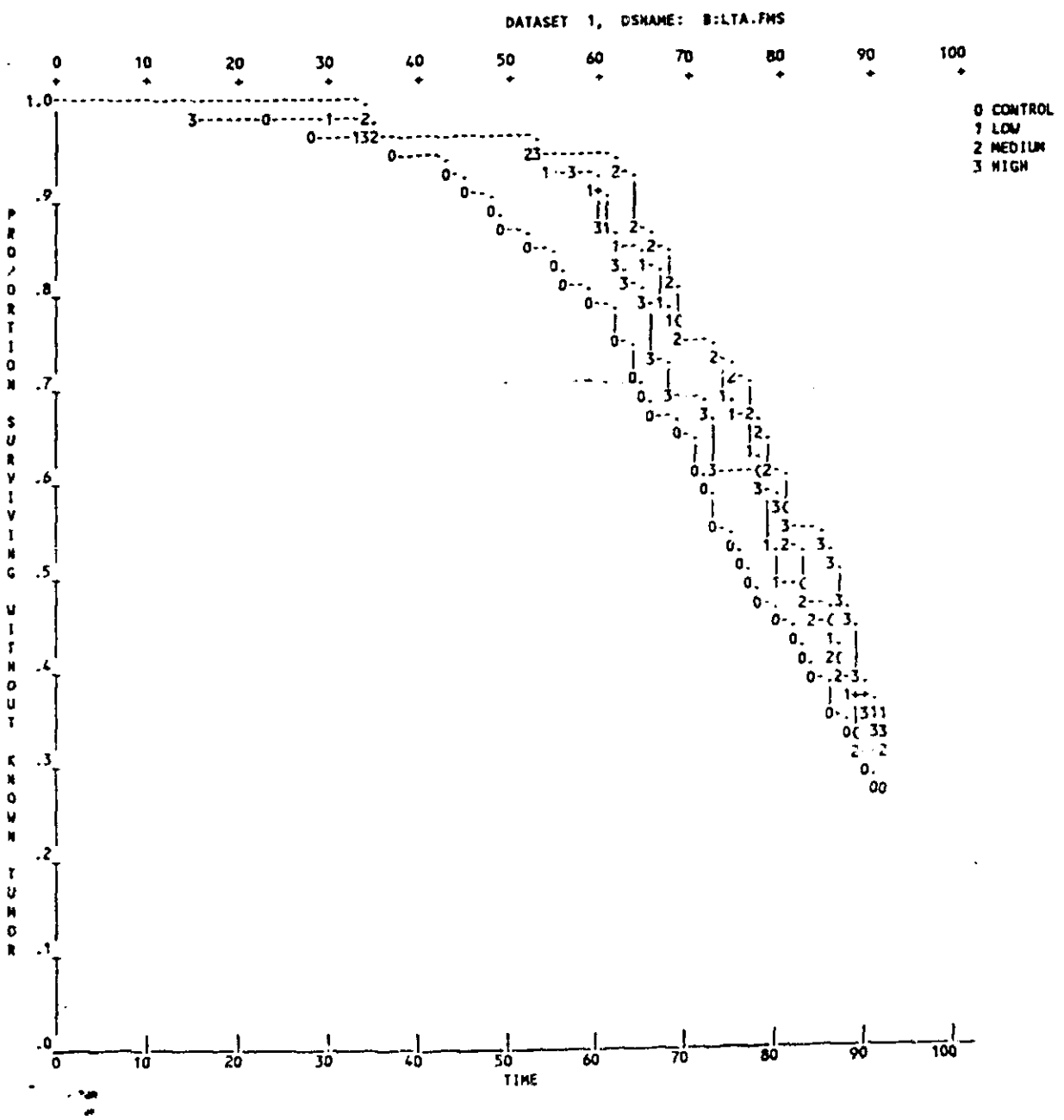


Figure 2a

Kaplan-Meier Estimates of the survival distributions
(Male rats)

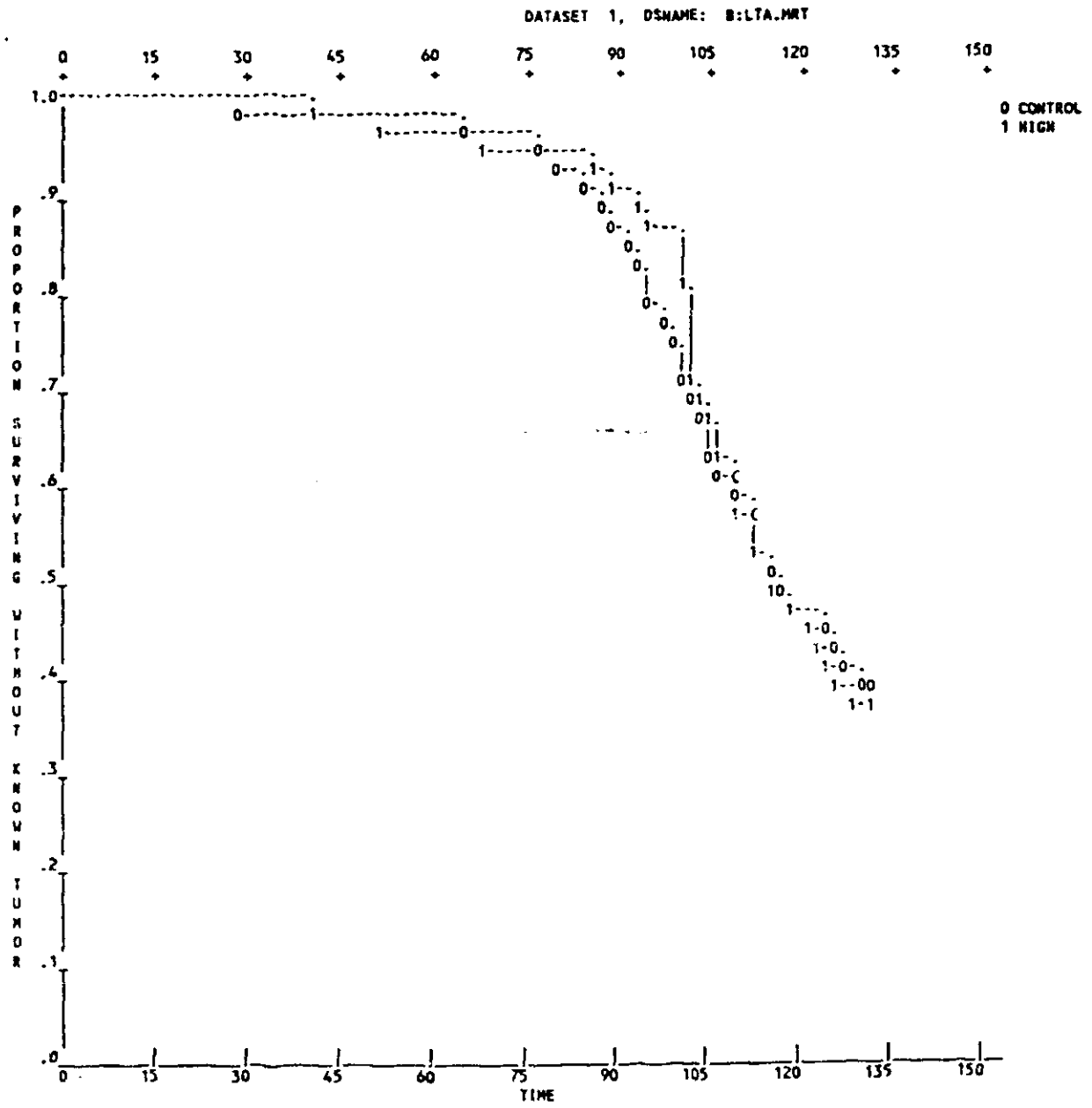
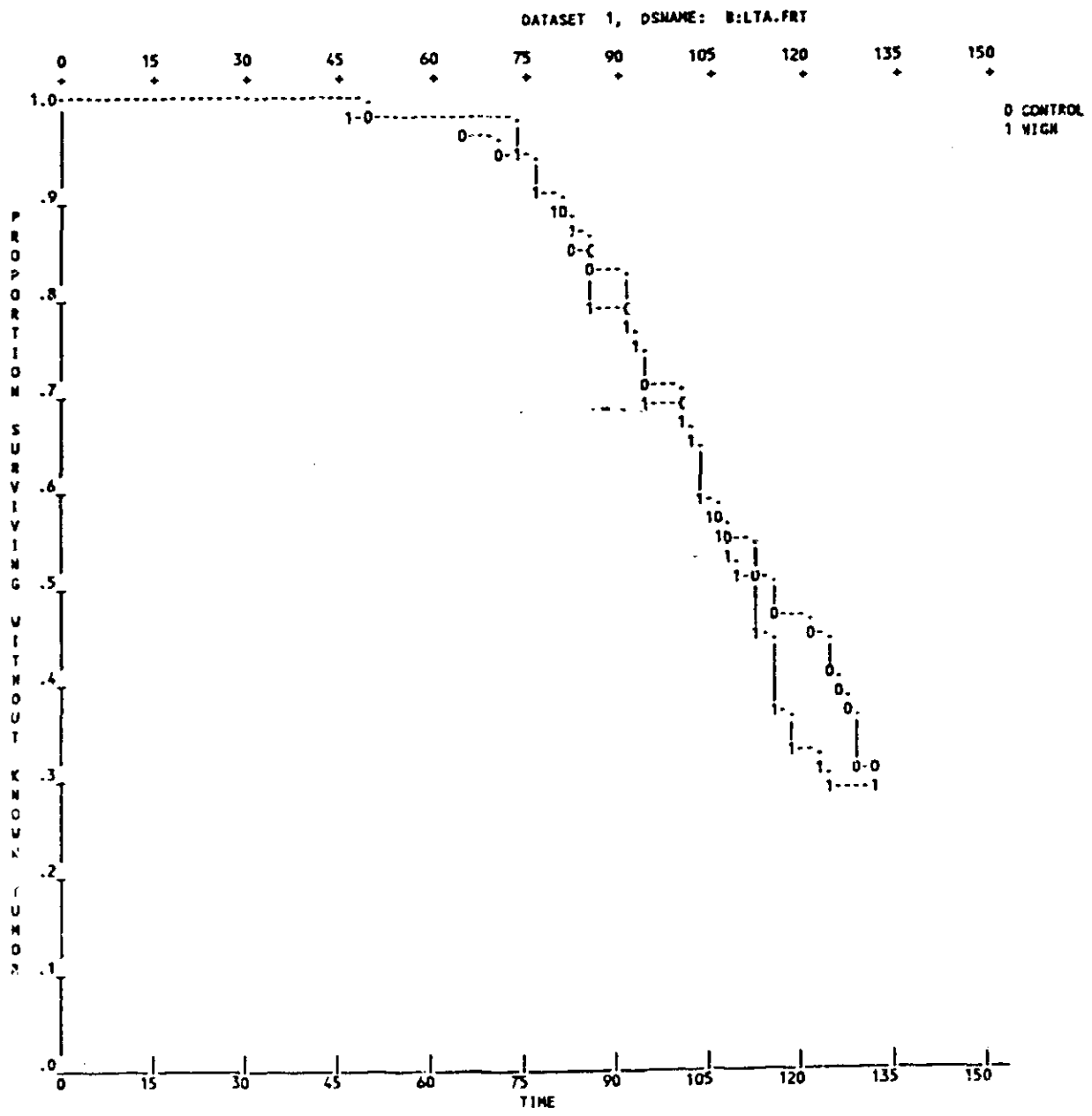


Figure 2b

Kaplan-Meier Estimates of the survival distributions
(Female rats)



Statistical Review and Evaluation

(Addendum)

NDA: 20-281 Date: OCT 19 1994

Applicant: The R. W. Johnson Pharmaceutical Research Institute

Name of Drug: Ultram (Tramadol hydrochloride) tablets

Documents Reviewed: NDA Submission volumes 32 to 51 of 239, Data on floppy diskette supplied by the sponsor.

Subj: Request for further carcinogenicity data

I. Background

A report of statistical review and evaluation on the mouse and rat carcinogenicity studies of this NDA was issued by the Division of Biometrics on 9/28/93. The submitted hard copy volumes and data in the floppy diskette of this NDA indicated that for mouse study a complete histopathological examination was conducted on all animals in the control and high dose groups. For animals belonging to the low (7.5 mg/kg) or the medium (15.0 mg/kg) dose group a complete histopathological examination was conducted on animals died or killed moribund before the scheduled terminal sacrifice, otherwise only liver, lungs and any grossly detected abnormalities were microscopically examined.

Therefore, in the previously issued report, the reviewer performed positive linear trend tests on the incidence of tumor types observed in liver and lung, and the pairwise comparisons of the high dose group with the control using the Fisher Exact test for tumor types observed in other organs. It is well known that a trend test is more powerful in detecting the effects of a treatment than pairwise comparisons. Also in case of pairwise comparisons valuable information from the low and high dose groups remains unused.

A later investigation by the reviewing pharmacologist Dr. Harry Geyer, HFD-007, revealed that complete histopathological examinations were performed on most of the animals in the low and medium dose groups.

In light of the above discussion, it is the reviewer's opinion that the full data set should be looked at and reanalysed. The sponsor should be requested to submit the full data set of all treatment groups in accordance with the Division of Biometrics data submition formats (For details sponsor is requested to see the Division of Biometrics formats for carcinogenicity data submission) along with their revised statistical analysis.

This addendum contains the names of the variables the data set

should contain and some suggested analysis methodologies. The sponsor is requested to follow the formats to prepare the new data set and if possible analyze the data using the suggested methodologies.

Data set preparation

The data set must be in a machine readable form, preferably a SAS readable form in a 3.5" diskette. There should be 13 variables separated by at least one column. The variable names and there descriptions are given in the attached page.

Analysis methodologies

For survival data analysis: The suggested methods are those described in the papers of Cox (Regression models and life tables, Journal of the Royal Statistical Society, B, 34 187-220, 1972), and of Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika, 52 203-223, 1965).

For the tumor data analysis: Two different tests namely the positive linear trend test and pairwise comparison of the incidence rate in the high dose group with that in the control are suggested. For trend test the methods described in the paper of Peto et al. (Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980) should be used. Pairwise comparisons should be performed using the one sided Fisher Exact test.

Mohammad Atiar Rahman
Mohammad A. Rahman, Ph.D.
Mathematical Statistician

Karl K. Lin 10/19/94
Concur: Karl K. Lin, Ph.D., Group Leader

cc: Original NDA 20-281
HFD-007/Dr. Harter
HFD-007/Dr. Geyer
HFD-710/Chron
HFD-715/Dr. K. Lin
HFD-715/Dr. Rahman
HFD-715/SARB Chron
HFD-715/DRU 2.1.1 NDA 20-281 Ultram (Tramadol hydrochloride) tablets Mouse and Rat carcinogenicity studies.
HFD-502/Dr. Weissinger
HFD-715/Diskette Rahman-2/ULTRAM.ADN

ANO	ANIMAL NUMBER
SEX	M MALE
	F FEMALE
DOSE	DOSE GROUP
	0 CONTROL GROUP
	1 LOW DOSE GROUP
	2 MEDIUM DOSE GROUP
	3 HIGH DOSE GROUP
WEEK	WEEK OF DEATH OR SACRIFICE
DTHST	DEATH OR SACRIFICE STATUS
	1 NATURAL DEATH
	2 TERMINAL SACRIFICE
	3 INTERMITTENT SACRIFICE
MOS	MISSING OBSERVATION STATUS
	1 AT LEAST ONE TISSUE WAS EXAMINED
	2 NO TISSUES WERE EXAMINED
NT	NUMBER OF TUMORS FOUND
TMR	TUMOR CODE
ORG	ORGAN CODE
WD	WEEK OF DETECTION
SM	MALIGNST
	1 MALIGNANT
	2 BENIGN
	3 UNDETERMINED
CAUS	CAUSE OF DEATH
	1 TUMOR CAUSED DEATH
	2 TUMOR DID NOT CAUSE DEATH
	3 UNDETERMINED
AUTO	AUTOLYSIS CODE
	1 ORGAN/TISSUE WAS USABLE
	2 ORGAN/TISSUE WAS NOT USABLE

Tramadol Single-Dose Analgesia Trials
Synopsis

MEDICAL OFFICER REVIEW

NDA #: 20-281
NAME: ULTRAM (Tramadol Hydrochloride).
SPONSOR: R.W. Johnson
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.
REVIEW DATE: January 11, 1995.
CSO: C. Moody

INTRODUCTION:
The sponsor conducted 20 single-dose pain trials for this NDA. Nine were dental pain models; 11 were surgical pain models. One of the surgical trials was not evaluated due to poor enrollment, leaving effectively 10 surgical pain trials. All were placebo- and active-controlled, randomized, parallel trials, except that the morphine comparison trial had no placebo. Two of the surgical pain trials were foreign studies.

The doses of tramadol studied ranged from 50 mg to 200 mg. The 200 mg was used in only one study. Generally, 50 and 100 mg were studied together or 75 and 150 mg were studied together; only one trial used all four doses. Codeine Sulfate 60 mg was one of the active controls in most studies, but was frequently ineffective. Aspirin 650 mg with Codeine Phosphate 60 mg was a control mainly in dental studies; Acetaminophen 650 mg with Propoxyphene 100 mg was a control mainly in surgical studies. One surgical study compared IM morphine 5 and 10 mg to tramadol 50 and 100 mg, with no placebo.

Observations were made at baseline, 1/2 hr and hourly thereafter. Pain intensity was rated on a 4-point scale and pain relief was rated on a 5-point scale. Analyses included PID (pain intensity differences from baseline at each observation time), PAR (pain relief at each observation time), PRID (sum of PID and PAR), SPID (sum of PID at halfway point or end of study), TOTPAR (sums of PAR), SPRID (sums of PRID), and time to remedication. In the following reviewer's summary assessments, the SPRID for the first three hours was emphasized by the reviewer in making final calls about the relative performance of treatments.

Short narrative summaries of the trials are provided below. The first table of the appendix shows the duration, number of sites and numbers of patients at each dose. The second table summarizes the reviewer's conclusions from each study using 3-hour SPRID as the criterion. The third table summarized conclusions based on the PRID score at 1 hour. A compilation of sponsor-generated study summaries appears in a separate appendix.

In the summaries and tables the following abbreviations are used:

Txxx - Tramadol, dose xxx.
ASA/CO - Aspirin 650 mg with Codeine Phosphate 60 mg.
APAP/PRO - Acetaminophen 650 mg with Propoxyphene 100 mg.
CO - Codeine Sulfate 60 mg.
MS xx - Morphine, dose xx.
PL - Placebo.
> - Statistically significantly better than (two-sided p<.05).

DENTAL PAIN MODELS

TE/TE2: Dental, 6 hr.
Rx: T100; T50; ASA/CO; CO; PL.
SPRID (3 hr): All > PL, and ASA/CO > T100, T50, CO.
T100, T50 and CO tended to run together with fairly flat curves. ASA/CO peaked at 1-2 hrs, then joined other for last half of period.

TF: Dental, 6 hr
Rx: T100 ; T50; ASA/CO; CO; PL.
SPRID (3 hr): ASA/CO and T100 > PL; ASA/CO > T100, T50 and CO.
No dose-response trend. T100, T50 and CO tended to run together. ASA/CO had sawtooth pattern with peak at 1 hour.

TF3: Dental, 10 hr.
Rx: T150; T100; T75; T50; CO; PL.
SPRID (3 hr): None > PL.
T100, T75, T50 and CO all cluster together but none beat placebo. T150 peaked at 3-4 hrs with flat curve; T150 > PL at 3,4 and 9 hrs.
T150 > T75, T50, PL by 10 hr SPRID; on that basis sponsor considered trial to be sensitive and positive.

TG: Dental, 6 hr.
Rx: T100; T50; ASA/CO; CO; PL.
SPRID (3 hr): ASA/CO and T100 >PL; ASA/CO > T100, T50 and CO.
No dose-response trend.
ASA/CO had sawtooth pattern with peak at 1 hour.
T100 has very flat curve with small dip at 2 hrs. A late peak at 5 hours was slightly higher than the 1 hour peak value. T100 beat CO at 3 & 5 hours

TH: Dental, 8 hr.
Rx: T100; T50; ASA/CO; CO; PL.
SPRID (3 hr): ASA/CO, CO and T100 > PL; ASA/CO > T100 > T50 and CO.
ASA/CO had peak at 1 to 2 hrs followed by rapid fall. ASA/CO beat T100 for .5 to 2 hrs.
T100 peaked at 1-2 hrs followed by slow linear fall; small bump at 6 hrs.
T50 and CO ran together.

TI: Dental, 8 hr.
Rx: T100; T50; ASA/C0; CO; PL.
SPRID (3 hr): ASA/CO > T100, T50, CO and PL.
ASA/CO peaked at 1-2 hrs.
T100 had gradually rising curve between 2 and 7 hrs, with flat peak at 6 hrs. T100 beat ASA/CO at ≥ 6 hrs.

TI2: Dental, 8 hr
Rx: T150; T75; APAP/PRO; CO; PL.
SPRID (3 hr): APAP/PRO > T150, T75, CO, and PL.
No dose-response trend.
CO resembled placebo.

TO: Dental, 8 hr.
Rx: T200; T100; CO; PL.
SPRID (3 hr): T200 > PL.
CO almost same curve as placebo. T curves showed a dose-response trend. Both T curves tended to be sustained; T200 curve dipped at 5 hours and rose again. T200 > PL at ≥ 2 hrs; T100 > PL only at ≥ 6 hrs.

TQ: Dental, 8 hr.
Rx: T150; T75; APAP/PRO; CO: PL.
SPRID (3 hr): APAP/PRO, T150 > T75, CO, and PL.
APAP/PRO > T150 at .5-2 hrs; T150 > APAP/PRO at ≥5 hrs; APAP/PRO had earlier and higher peak at 1-2 hrs, but fell off rapidly after peak. T150 flatter peak over 2-4 hrs and slower fall; showed plateau at 5-6 hrs.
T150 > CO at ≥2 hrs.

TT2: Dental, Multi-Dose (First dose analyzed as a single-dose study).
Rx: T100; T75; T50; PL.
SPRID (3 hr): T100 > T50 and PL.
All doses showed flat curves. T75 tended to be closer to T50.

DENTAL PAIN MODELS SUMMARY

Of the 10 dental pain trials, one (TF3) was insensitive using the criterion of SPRID over the first 3 hours of the trial. Based on the remaining 9 sensitive trials:

T200 was positive in 1 of 1.
T150 was positive in 1 of 2.
T100 was positive in 5 of 7.
T75 was positive in 0 of 3.
T50 was positive in 1 of 6.

T100 was surpassed (using the 3-hour SPRID criterion) by ASA/CO in all 5 trials in which the two were tested together. T100 beat CO in 1 of the 6 trials in which they were studied together.

In the dental pain models there was a tendency for tramadol to show a slower rise than ASA/CO or APAP/PRO, but more sustained activity. The

late plateau, or even a small blip, seen in several of the studies is suggestive of the effect of an active metabolite.

SURGICAL PAIN MODELS

TA: Surgical, 8 hr.
Rx: T100; T50; CO; PL.
SPRID (3 hr): None > PL.
Curves similar. No differences at any time point. No dose-response trend.

TC: Surgical, 6 hr.
Rx: T100; T 50; ASA/CO; CO; PL.
SPRID (3 hr): ASA/CO > T100, T50, CO and PL.

TJ: Surgical, 6 hr;
Rx: T 100; T50; MS10; MS5; (no PL).
SPRID (3 hr): MS10 > MS5 and T100; MS5 and T100 > T50.
Dose-response seen for both drugs.
Both MS > both T at 1 hr.
T 100 peaked at 2 hrs; tended to be flatter.

TW: Surgical, 6 hr.
Rx: T100; T50; APAP/PRO; CO; PL.
SPRID (3 hr): None > Pl.
However, T100, T50 and APAP/CO > PL by 3 hr TOTPAR and 6 hr TOTPAR and SPRID. Also T100, T50 and APAP/PRO SPRIDs beat PL at 3-5 hrs.
All four active clustered together.
There was a substantial placebo effect.

TX: Surgical, 8 hr.
Rx: T150; T75; APAP/PRO; CO; PL.
SPRID (3 hr): None > PL.
APAP/PRO and T150 > PL at 3 at 4 hrs.

TY: Surgical, 6 hr.
Rx: T150; T75; APAP/PRO; CO; PL.
SPRID (3 hr): None > PL.
Dose-response trend. T150 > CO and PL at 3 hrs, and by 6 hr SPRID.

TW2: Gyn. Surgical, 6 hr; Puerto Rico.
Rx: T150; T75; APAP/PRO; CO; PL.
SPRID (3 hr): APAP/PRO, CO, T150 and T75 > PL; APAP/PRO > CO.
All active peaked around 2-3 hrs. There was a substantial placebo effect, peaking at 2 hrs.
No dose-response trend: T150 and T75 almost identical. Both T's generally fell between CO and APAP/PRO.

TZA: Gyn. Surgical, 6 hr.
Rx: T150; T75; APAP/PRO; CO; PL.
SPRID (3 hr): APAP/PRO and T150 > T75, CO and PL.
T150 curve similar to APAP/PRO; APAP/PRO peaked at 1-2 hrs, T150 peaked at 2 hrs.
T75 curve similar to CO.
No evidence of sustained effect for either T; although T150 had short plateau at 4-5 hrs.

TR: C-section, 6 hr. Venezuela.
Rx: T150; T75; APAP/PRO; PL.
SPRID (3 hr): APAP/PRO, T150 and T75 > PL; T150 > APAP/PRO.
APAP/PRO peaked at 2 hrs.
Both T peaked at 3 hrs with more sustained activity. T150 beat APAP/PRO at ≥ 3 hrs. T75 beat APAP/PRO at 4 & 6 hrs.

TV: C-section, 6 hr.
Rx: T100; T50; ASA/CO; CO; PL.
SPRID (3 hr): ASA/CO and T100 > PL.
ASA/CO peaked at 2 hrs, others at 1 hr.
T100 similar to ASA/CO, but had dip at 2 hrs and slightly slower fall; T100 > ASA/CO at 6 hrs.
T50 curve nearly identical to CO.

TB: Cesarean, 6 hr.
Rx: T100; T50; CO; PL.
Not analyzed due to insufficient Enrollment (total N=28).

SURGICAL PAIN MODELS SUMMARY

Of the 9 placebo-controlled surgical pain studies that had adequate enrollment, 4 were insensitive using the criterion of SPRID over the first 3 hours of the trial (TA, TW, TX and TY). However, TW was borderline, as it could be considered sensitive by TOTPARs or 6-hr SPRID. The call on TW is not particularly critical to the overall conclusions. The trial that used MS but no placebo (TJ) was also sensitive since it showed a dose-response for both drugs. This study is counted as positive for T100, but is not considered part of the total for T50 since there was no clear candidate for the lower dose to beat. Of the sensitive trials:

T150 was positive in 3 of 3.
T100 was positive in 2 of 3.
T75 was positive in 2 of 3.
T50 was positive in 0 of 2.

T150 beat APAP/PRO in 1 of 3 sensitive studies in which they were studied together. They were quite similar in a second study, and T150 tended to fall below APAP/PRO in a third. T100 did not beat CO in either of the two sensitive trials in which they were studied together. The only trial that used both T100 and APAP/PRO was an insensitive study.

In the morphine study T100 was most similar to MS 5.

The suggestion of sustained activity that was seen in the dental studies was not as clearly reflected in the surgical studies. In several studies the tramadol curves were nearly parallel to the active controls. In some there was a tendency for the curves to be slightly flatter.

SUMMARY:
Pooling the studies in the two pain models gives the following by the criterion of 3-hour SPRID:

T200 was positive in 1 of 1.
T150 was positive in 4 of 5
T100 was positive in 7 of 10.
T75 was positive in 2 of 6.
T50 was positive in 1 of 8.

If one uses the PRID at 1 hour as the criterion, 7 dental and 3 surgical models were sensitive, and one arrives at the following tally:

T200 was positive in 0 of 0.
T150 was positive in 4 of 5
T100 was positive in 3 of 5.
T75 was positive in 2 of 5.
T50 was positive in 1 of 5.

The sponsor's recommended dose of 100 mg appears to be an effective analgesic dose. Although T100 tended to do better than CO, T100 beat CO in only one study (TH, Dental Pain), and its superiority over CO cannot be considered established. T100 was inferior to ASA/CO (by 3-hour SPRID) in 4 of 6 studies, but there was a suggestion of longer duration of activity. Although T150 appeared generally comparable to APAP/PRO, the T100 dose was tested against APAP/CO only in one equivocal study (TW, Surgical), so comparisons cannot be made. The relative duration of action of tramadol vs. the active controls is unclear: the suggestion of longer duration seen in dental trials was not clearly reflected in surgical trials.

CONCLUSIONS:
Tramadol 100 mg was fairly consistently shown to be an effective analgesic in the single dose models. The trials suggested, but did not establish, the superiority of this dose over Codeine 60 mg. Tramadol 100 mg appears to be less effective than ASA 650 mg with Codeine 60 mg. The relative efficacy of tramadol 100 mg vs. APAP 650 mg with Propoxyphene 100 mg cannot be determined on the basis of these studies. The late plateau, or even a small blip, seen in several of the dental studies is suggestive of the effect of an active metabolite.

John E Hyde

John E. Hyde, Ph.D., M.D

Pam. Wdmark 2-28-95

Tramadol Single-Dose Studies

						Distribution of Subjects by Treatment										
Study ID	Pain Model	Hours	No. of Sites	Total N	% Complete	T 50	T 75	T 100	T 150	T 200	APAP/PROP	ASA/CO	CO	MS 5 IM	MS 10 IM	PL
TE	Dental	6	2	285	98	51		51				52	52			52
TF	Dental	6	3	246	99	52		51				47	50			50
TF3	Dental	10	1	239	96	39	40	41	39				40			40
TG	Dental	6	2	200	96	49		49				42	33			27
TH	Dental	8	3	250	98	48		51				51	50			50
TI	Dental	8	3	251	97	51		51				49	50			50
TI2	Dental	8	1	245	93		49		47		49		50			50
TO	Dental	8	1	206	97			51		52			50			53
TQ	Dental	8	1	250	98		50		50		49		50			51
TT2	Dental	M	1	400	95	100	100	100								100
TA	Gen Surg	8	1	184	84	56		64					29			35
TC	Gen Surg	6	1	200	98	40		39				41	40			40
TJ	Gen Surg	6	1	160	99	43		38						39	40	
TW	Gen Surg	6	1	200	98	40		40			39		41			40
TX	Gen Surg	8	1	182	95		36		40		37		33			36
TY	Gen Surg	6	1	152	99		31		30		31		30			30
TW2	Gyn Surg	6	2F	201	99		41		40		39		41			40
TZA	Gyn Surg	6	2	201	99		40		40		39		40			42
TR	Cesarean	6	1F	161	100		40		40		41					40
TV	Cesarean	6	2	151	99	31		31				30	29			30
TB	Cesarean	6	1	28	96	6		10				7	2			3
			F = indicates foreign study.													

T=Tramadol, APAP=Acetaminophen 650 mg, ASA=Aspirin 650 mg, CO=Codeine 60 mg, PRO=Propoxyphene 100 mg, MS=Morphine, PL=Placebo

Tramadol Single-Dose Studies

			3-hour SPRID Results									
Study ID	Pain Model	Hours	ASA/CO	APAP/PRO	CO	T200	T150	T100	T75	T50	Comparisons	Notes
TE	Dental	6	+		+			+		+	ASA/CO > T100, T50, CO	Flat curves for T100, T50, CO
TF	Dental	6	+		-			+		-	ASA/CO > T100, T50, CO	no dose-response
TF3	Dental	10			-		-	-	-	-		T150>T75, T50 and PL by 10 hr SPRID
TG	Dental	6	+		-			+		-	ASA/CO > T100,T50, CO	T100 very flat, dip @ 2 hrs., no dose-response
TH	Dental	8	+		+			+		-	ASA/CO > T100 > T50, CO	T100 showed slow linear fall with blip at 6 hrs; T100 below ASA/CO early, above ASA/CO late
TI	Dental	8	+		-			-		-	ASA/CO > T100, T50, CO	T100 flat curve, gradual rise 2-7 hrs.
TI2	Dental	8		+	-		-		-		APAP/PRO > T150, T75, CO	
TO	Dental	8			-	+		-			Dose-response trend	Very flat curves
TQ	Dental	8		+	-		+		-		APAP/PRO, T150 > T75, CO	T150 slower onset, longer duration than APAP/PRO
TT2	Dental	M						+	-	-	T100 > T50	(First dose of Multi-Dose Study) Flat curves.
TA	Gen Surg	8			-			-		-		
TC	Gen Surg	6	+		-			-		-	ASA/CO > T100, T50, CO	
TJ	Gen Surg	6						+			Dose response for MS and T. MS 10 > T100; MS 5 > T50.	MS comparison study; no placebo used. T curves similar to, but slightly flatter than, MS
TW	Gen Surg	6		-	-			-		-		Effects only significant late, big placebo effect
TX	Gen Surg	8		-	-		-		-			
TY	Gen Surg	6		-	-		-		-		Dose-reponse trend.	T150 > CO by 6 hr SPRID.
TW2	Gyn Surg	6		+	+		+		+		No dose-response, APAP/PRO > CO	Big placebo effect. T150 and T75 both fell between APAP/PRO and CO.
TZA	Gyn Surg	6		+	-		+		-		APAP/PRO, T150 > T75, CO	T150 & APAP/PRO curves similar
TR	Cesarean	6		+			+		+		T150 > APAP/PRO	T150 and T75 had slower fall after peak than APAP/PRO
TV	Cesarean	6	+		-			+		-		T100 curve similar to ASA/CO. T100 peaked at 1 hr, dipped at 2 hrs, tended to have slower fall that ASA/CO
TB	Cesarean	6										Insufficient enrollment.
			SPRID=sum Pain Relief (0-5) and Pain Intensity (0-4) Difference Scores									
			+ = statistically different from placebo; - = not statistically different from placebo.									

T=Tramadol, APAP=Acetaminophen 650 mg, ASA=Aspirin 650 mg, CO=Codeine 60 mg, PRO=Propoxyphene 100 mg, MS=Morphine, PL=Placebo

Tramadol Single-Dose Studies

			PRID Results at 1 Hour								
Study ID	Pain Model	Hours	ASA/CO	APAP/PRO	CO	T200	T150	T100	T75	T50	Comparisons
TE	Dental	6	+		+			+		+	ASA/CO > T100, T50, CO
TF	Dental	6	+		+			-		-	ASA/CO > T100, T50, CO
TF3	Dental	10			-		-	-	-	-	
TG	Dental	6	+		+			+		+	ASA/CO > T100,T50, CO
TH	Dental	8	+		-			+		-	ASA/CO > T100 > T50
TI	Dental	8	+		-			-		-	ASA/CO > T100, T50, CO
TI2	Dental	8		+	-		-		-		APAP/PRO > T150, T75, CO
TO	Dental	8			-	-		-			Dose-response trend
TQ	Dental	8		+	-		+		-		APAP/PRO > T150, T75, CO
TT2	Dental	M						-	-	-	
TA	Gen Surg	8			-			-		-	
TC	Gen Surg	6	-		-			-		-	
TJ	Gen Surg	6						-			MS 10, MS 5 > T100, T50
TW	Gen Surg	6		-	-			-		-	
TX	Gen Surg	8		-	-		-		-		
TY	Gen Surg	6		-	-		-		-		
TW2	Gyn Surg	6		+	-		+		+		APAP/PRO > T75
TZA	Gyn Surg	6		+	-		+		-		APAP/PRO > T75, CO
TR	Cesarean	6		+			+		+		
TV	Cesarean	6	-		-			-		-	
TB	Cesarean	6									
			PRID=sum Pain Relief (0-5) and Pain Intensity (0-4) Difference Scores								
			+ = statistically different from placebo; - = not statistically different from								

T=Tramadol, APAP=Acetaminophen 650 mg, ASA=Aspirin 650 mg, CO=Codeine 60 mg, PRO=Propoxyphene 100 mg, MS=Morphine, PL=Placebo

Tramadol Single-Dose Studies

						Duration in Hours (Time until 50% Remedicate)										
Study ID	Pain Model	Hours	No. of Sites	Total N	% Complete	T 50	T 75	T 100	T 150	T 200	APAP/PROP	ASA/CO	CO	MS 5 IM	MS 10 IM	PL
TE	Dental	6	2	285	98	2.5		2.7				4.5	2.9			1.7
TF	Dental	6	3	246	99	3.4		3.4				4.3	3.4			3.1
TF3	Dental	10	1	239	96	2.8	2.9	3.0	3.9				2.6			2.5
TG	Dental	6	2	200	96	3.5		3.1				3.9	2.8			2.3
TH	Dental	8	3	250	98	3.1		6.3				4.8	3.9			2.6
TI	Dental	8	3	251	97	1.8		2.4				3.9	2.4			2.0
TI2	Dental	8	1	245	93		2.5		2.9		3.3		2.6			2.5
TO	Dental	8	1	206	97			2.6		5.0			2.6			2.5
TQ	Dental	8	1	250	98		2.7		6.0		4.1		2.9			2.4
TT2	Dental	M	1	400	95	1.8	1.9	2.3								1.8
TA	Gen Surg	8	1	184	84	7.0		6.5					6.6			5.3
TC	Gen Surg	6	1	200	98	3.0		2.9				5.3	3.5			2.8
TJ	Gen Surg	6	1	160	99	3.5		4.7						4.1	4.8	
TW	Gen Surg	6	1	200	98	5.5		6+			5.6		4.5			3.5
TX	Gen Surg	8	1	182	95		3.5		4.0		3.6		3.4			2.8
TY	Gen Surg	6	1	152	99		4.8		6+		5.1		4.3			4.2
TW2	Gyn Surg	6	2F	201	99		6+		6+		6+		6+			5.0
TZA	Gyn Surg	6	2	201	99		2.9		4.3		4.3		2.6			2.0
TR	Cesarean	6	1F	161	100		6+		6+		6+					6+
TV	Cesarean	6	2	151	99	3.5		5.1				4.4	3.4			2.7
TB	Cesarean	6	1	28	96	6.0		10.0				7.0	2.0			3.0
			F = indicates foreign study.													

T=Tramadol, APAP=Acetaminophen 650 mg, ASA=Aspirin 650 mg, CO=Codeine 60 mg, PRO=Propoxyphene 100 mg, MS=Morphine, PL=Placebo

Appendix: Single-Dose Study Summaries

The pages which follow are the individual study summaries prepared by the sponsor for the single-dose studies. No report is included for Study TB, since it was aborted, and the sample is too small for meaningful analysis. A report for study TT2, in single-dose format, is also is included for the first dose given in this multi-dose dental study. Studies have been grouped by type, as in the results tables above, and the reports appear in the following order:

TE	Dental
TF	Dental
TF3	Dental
TG	Dental
TH	Dental
TI	Dental
TI2	Dental
TO	Dental
TQ	Dental
TT2	Dental
TA	Gen Surg
TC	Gen Surg
TJ	Gen Surg
TW	Gen Surg
TX	Gen Surg
TY	Gen Surg
TW2	Gyn Surg
TZA	Gyn Surg
TR	Cesarean
TV	Cesarean

Study: TE/TE2	Pain Model: Dental Pain Study Design: si, ts, sd, db ,r ,p* Duration: 6 hours Tx: Tramadol (TR) 100 and 50 mg Aspirin 650 mg/codeine phosphate 60 mg (ASA/Codeine) Codeine Sulfate 60 mg (Codeine) Placebo
A single investigator, two-site, randomized, double-blind, single-dose, parallel group study of tramadol hydrochloride 100 mg and 50 mg (tramadol), aspirin 650 mg with codeine phosphate 60 mg (ASA/codeine), codeine sulfate 60 mg (codeine) and placebo in patients with moderate or severe baseline pain following extraction of impacted third molars.	
TR 100 mg: 51 pts. ASA/Codeine: 52 pts. Codeine: 52 pts. Placebo: 52 pts. TR 50 mg: 51pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, and 6 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* si = single investigator; ts=two-site; sd = single-dose; db = double-blind; r = randomized; p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

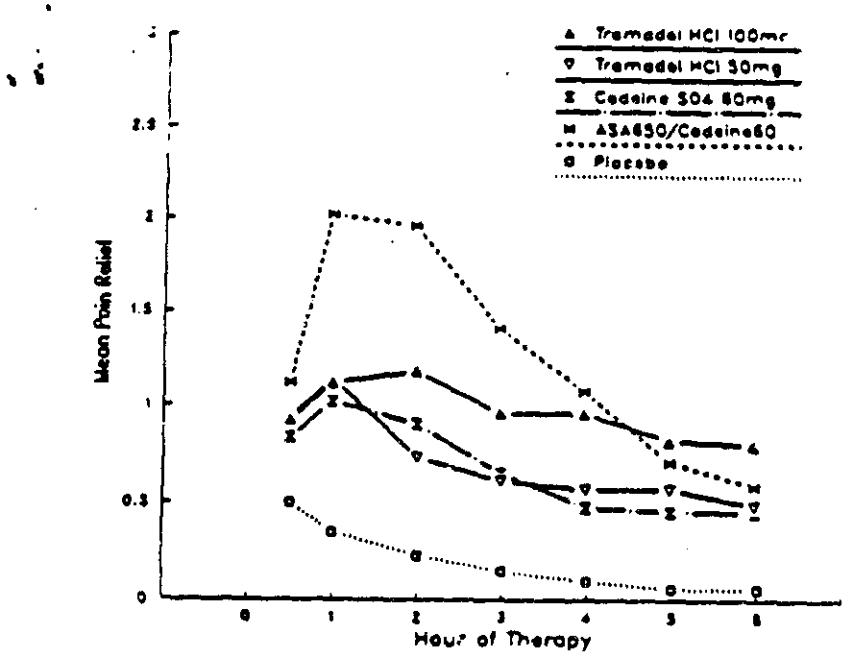
Of the 258 patients enrolled, 252 patients (98%) completed the study either by finishing the 6-hour protocol or by taking a rescue analgesic, and six patients (2%) discontinued the study prematurely. One ASA/codeine patient and two placebo patients were excluded from the analyses of efficacy because the last evaluation was done at less than 60 minutes after the study drug was administered, and one ASA/codeine patient was excluded from efficacy analyses because no post-dose data were available.

ASA/codeine was statistically superior compared to placebo for all efficacy variables. Codeine was statistically superior to placebo for all efficacy variables with the exception of SPID (Sum of the Pain Intensity Differences; 0 - 3 and 0 - 6 hour interval scores). Tramadol 100 mg and 50 mg were statistically superior compared to placebo with respect to all efficacy variables. A tramadol dose-response was observed for the 0 - 6 hour time interval for SPID scores.

Comparing the four active treatment groups, tramadol 100 mg and ASA/codeine were numerically favored over the other treatments for TOTPAR (Total Pain Relief 0 - 3 and 0 - 6 hour interval scores) and SPID (0 - 3 and 0 - 6 hour interval scores). These two treatments were not statistically different except for TOTPAR (0 - 3 hour interval score) where ASA/codeine was statistically superior. Mean TOTPAR and SPID scores were not statistically different for the tramadol 50 mg and codeine treatment groups.

This study showed model sensitivity and demonstrated statistically superior pain relief for tramadol 100 mg and 50 mg to that of placebo. In this study, the relative efficacy ordering was ASA/codeine > tramadol 100 mg > tramadol 50 mg > codeine > placebo.

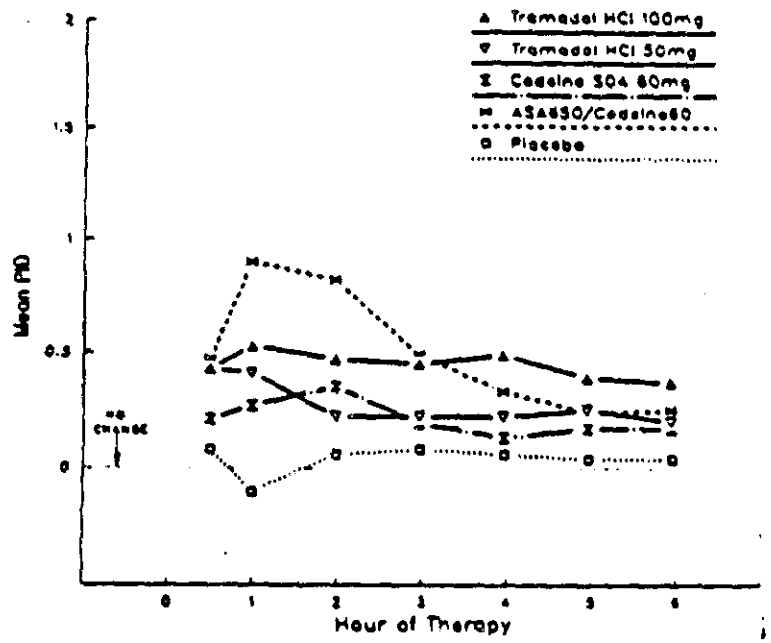
MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TE/TE2



Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 100mg	3.16(3.29) B	5.75(7.03) AB
TR 50mg	2.37(2.77) B	4.00(5.69) B
ASA/COD	5.04(3.44) A	7.46(6.62) A
CO 60mg	2.48(2.55) B	3.88(4.62) B
Placebo	0.84(1.57) C	1.06(2.63) C
P-VALUE	0.000	0.000
RMS ERROR	2.803	5.549

Treatment	Assessment Time-Points (in hours) 1/2	1	2	3	4	5	6
TR 100mg	0.92(0.98) 51 A	1.12(1.18) 51 B	1.18(1.31) 36 B	0.96(1.34) 21 B	0.96(1.37) 19 AB	0.82(1.38) 17 A	0.80(1.39) 17 A
TR 50mg	0.94(0.99) 51 A	1.14(1.20) 51 B	0.73(1.11) 33 C	0.61(1.08) 19 B	0.57(1.12) 14 BC	0.57(1.14) 14 A	0.49(1.07) 13 A
ASA/COD	1.14(1.20) 50 A	2.06(1.36) 50 A	2.00(1.41) 44 A	1.44(1.42) 36 A	1.10(1.33) 31 A	0.72(1.36) 19 A	0.60(1.23) 13 A
CO 60mg	0.83(0.83) 52 AB	1.02(0.94) 52 B	0.90(1.09) 36 BC	0.65(1.01) 25 B	0.48(0.90) 19 CD	0.46(0.96) 14 AB	0.46(1.00) 11 AB
Placebo	0.52(0.81) 50 B	0.36(0.69) 50 C	0.24(0.62) 15 D	0.16(0.51) 8 C	0.10(0.46) 3 D	0.06(0.42) 3 B	0.06(0.42) 1 B
P-VALUE	0.030	0.000	0.000	0.000	0.000	0.007	0.013
RMS ERROR	0.970	1.099	1.143	1.117	1.087	1.108	1.073

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TE/TE2



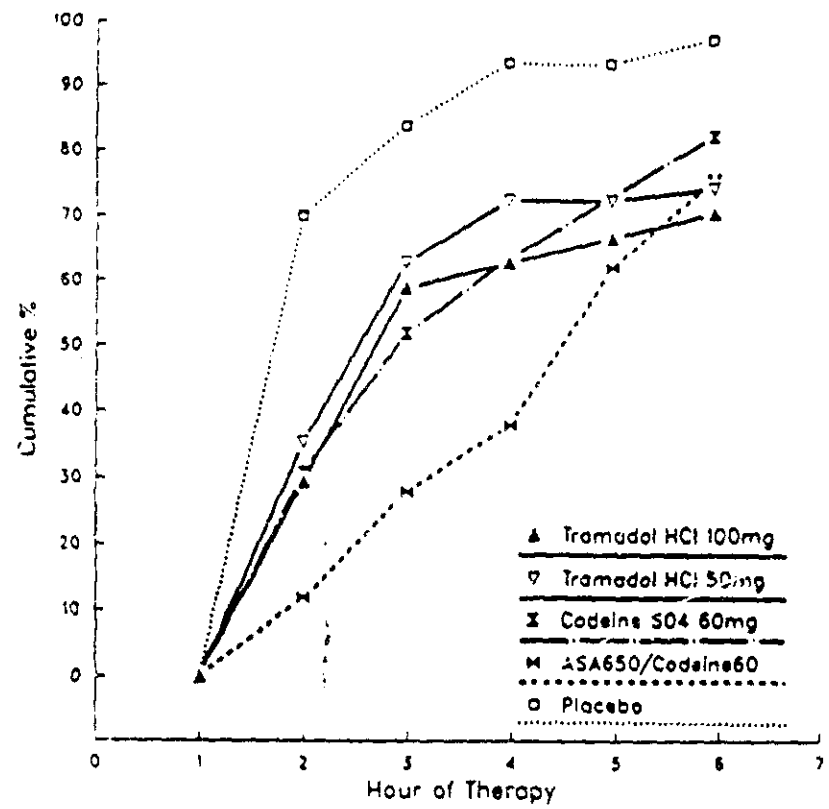
Treatment	SPID (extrapolated) 3-hour	6-hour
TR 100mg	1.40(1.96) AB	2.66(4.08) AB
TR 50mg	0.85(1.54) B	1.52(2.63) BC
ASA/COD	2.04(2.12) A	2.88(3.66) A
CO 60mg	0.78(1.46) BC	1.26(2.11) CD
Placebo	0.14(1.22) C	0.28(1.95) D
P-VALUE	0.000	0.000
RMS ERROR	1.692	3.007

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	0.43(0.70) 51 A	0.53(0.73) 51 B	0.47(0.8?) 36 B	0.45(0.76) 21 AB	0.49(0.81) 19 A	0.39(0.80) 17 A	0.37(0.80) 17 A
TR 50mg	0.43(0.64) 51 A	0.41(0.85) 51 B	0.22(0.67) 33 BC	0.22(0.54) 19 BC	0.22(0.46) 14 BC	0.25(0.52) 14 AB	0.20(0.49) 13 AB
ASA/COD	0.48(0.84) 50 A	0.92(0.78) 50 A	0.84(0.89) 44 A	0.50(0.86) 36 A	0.34(0.72) 31 AB	0.24(0.72) 19 AB	0.26(0.66) 13 AB
CO 60mg	0.21(0.67) 52 AB	0.27(0.72) 52 B	0.35(0.62) 36 B	0.19(0.53) 25 C	0.13(0.40) 19 BC	0.17(0.43) 14 AB	0.17(0.43) 11 AB
Placebo	0.08(0.75) 50 B	-.08(0.75) 50 C	0.06(0.37) 15 C	0.08(0.34) 8 C	0.06(0.31) 3 C	0.04(0.28) 3 B	0.04(0.28) 1 B
P-VALUE	0.023	0.000	0.000	0.003	0.002	0.046	0.054
RMS ERROR	0.722	0.767	0.696	0.632	0.572	0.582	0.563

CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TE/TE2

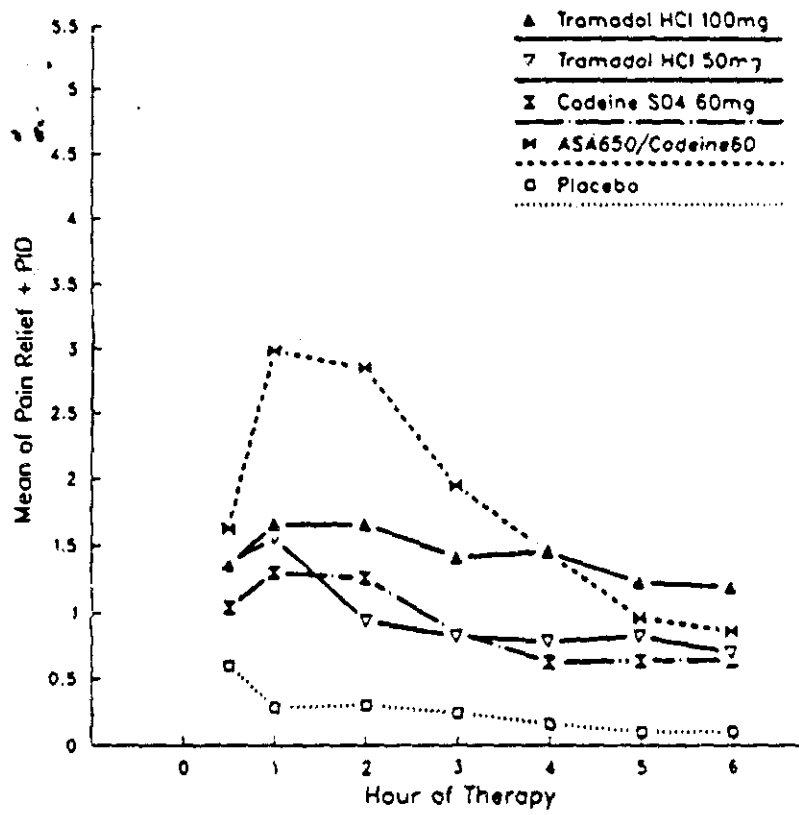
Cumulative Percent of Patients Terminating Prematurely



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour
TR 100mg	51(100.0%)	36(70.6%)	21(41.2%)	19(37.3%)	17(33.3%)	15(29.4%)
TR 50mg	51(100.0%)	33(64.7%)	19(37.3%)	14(27.5%)	14(27.5%)	13(25.5%)
ASA/COD	50(100.0%)	44(88.0%)	36(72.0%)	31(62.0%)	19(38.0%)	12(24.0%)
CO 60mg	52(100.0%)	36(69.2%)	25(48.1%)	19(36.5%)	14(26.9%)	9(17.3%)
Placebo	50(100.0%)	15(30.0%)	8(16.0%)	3(6.0%)	3(6.0%)	1(2.0%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TE/TE2



Treatment	SPRID (extrapolated) 3-hour	6-hour
TR 100mg	4.56(5.13) B	8.40(10.91) AB
TR 50mg	3.23(4.06) B	5.52(8.07) BC
ASA/COD	7.08(5.31) A	10.34(9.97) A
CO 60mg	3.26(3.84) B	5.14(6.57) C
Placebo	0.98(2.68) C	1.34(4.51) D
P-VALUE	0.000	0.000
RMS ERROR	4.310	8.331

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	1.35(1.61) 51 A	1.65(1.84) 51 B	1.65(2.04) 36 B	1.41(2.05) 21 AB	1.45(2.14) 19 A	1.22(2 14) 17 A	1.18(2.14) 17 A
TR 50mg	1.37(1.50) 51 A	1.55(1.93) 51 B	0.94(1.68) 33 CD	0.82(1.55) 19 BC	0.78(1.55) 14 B	0.82(1.62) 14 A	0.69(1.53) 13 AB
ASA/COD	1.62(1.97) 50 A	2.98(2.06) 50 A	2.84(2.16) 44 A	1.94(2.18) 36 A	1.44(1.96) 31 A	0.96(2.01) 19 A	0.86(1.85) 13 A
CO 60mg	1.04(1.34) 52 AB	1.29(1.53) 52 B	1.25(1.63) 36 BC	0.85(1.47) 25 BC	0.62(1.21) 19 B	0.63(1.36) 14 AB	0.63(1.40) 11 AB
Placebo	0.60(1.47) 50 B	0.28(1.33) 50 C	0.30(0.93) 15 D	0.24(0.82) 8 C	0.16(0.77) 3 B	0.10(0.71) 3 B	0.10(0.71) 1 B
P-VALUE	0.018	0.000	0.000	0.000	0.000	0.012	0.018
RMS ERROR	1.590	1.756	1.742	1.684	1.604	1.648	1.602

PROTOCOL TE/TE2

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	22	17	33
TR 50mg	22	17	31
ASA/COD	19	14	28
CO 60mg	29	21	45
Placebo	50	30	163

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	2:35	2:05	3:40
TR 50mg	2:25	1:55	2:55
ASA/COD	4:20	3:20	4:55
CO 60mg	2:40	2:00	3:45
Placebo	1:35	1:25	1:50

Tramadol Protocol TE

Demographic Frequencies and Means

07:45 Friday, June 3, 1994 1

	Sex		Race					Baseline Pain				Surgical Procedure	Reason for Discontinuation			
Drug	M	F	Wht	Blk	Oth	Mean Age	Mean Weight	None	Slight	Moderate	Severe	Dental Surgery	Adv Exp	Patient Choice	Protocol Violation	Other
Tramadol 100 MG	23	28	39	9	7	24.20	147.59	0	0	39	12	51	2	1	0	0
Tramadol 50 MG	20	31	37	7	7	25.06	146.59	0	0	41	10	51	0	0	0	0
Codeine SO4	20	32	39	9	4	24.25	146.83	0	0	42	10	52	0	0	0	0
ASA / Codeine	16	36	36	12	4	23.77	136.72	0	0	42	10	52	0	2	0	0
Placebo	25	27	43	8	1	23.85	147.27	0	0	40	12	52	0	1	0	0

This display includes all patients, including those who were not included in the analysis.

Study: TF	Pain Model: Dental Pain Study Design: si, ms, sd, db, r, p* Duration: 6 hours Tx: Tramadol (TR) 100 and 50 mg Aspirin 650 mg/Codeine phosphate 60 mg (ASA/Codeine) Codeine Sulfate 60 mg (Codeine) Placebo
This was a single investigator, three-site, randomized, double-blind, single-dose, parallel group study of tramadol hydrochloride 100 mg and 50 mg (tramadol), aspirin 650 mg with codeine phosphate 60 mg (ASA/codeine), codeine sulfate 60 mg (codeine) and placebo in outpatients with moderate or severe baseline pain following extraction of third molars.	
TR 100 mg: 51 pts. ASA/Codeine: 47pts. Codeine: 50pts. Placebo: 50 pts. TR 50 mg: 52 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, and 6 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* si = single investigator; ms=multi-site; sd = single-dose; db = double-blind; r = randomized; p = parallel

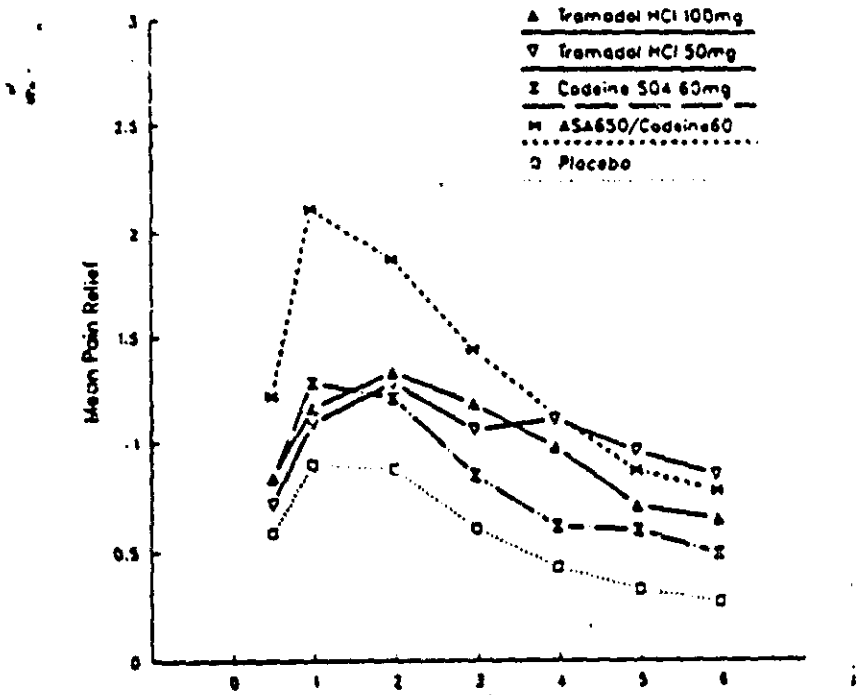
NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

Of the 246 patients enrolled who had post-baseline data recorded, 244 (99%) completed the study either by finishing the six hours of evaluations or receiving a rescue analgesic, and two (1%) discontinued the study prematurely. Nine additional patients were excluded from the analyses of efficacy: one patient (tramadol 100 mg) because of a significant protocol violation, one patient (codeine) because no baseline pain was recorded and seven patients (four tramadol 50 mg, one ASA/codeine, one codeine 60 mg, one placebo) for not completing one hour (60 minutes) of evaluation.

ASA/codeine was statistically superior to placebo with respect to all efficacy variables except for time to remedication. Codeine was numerically favored over placebo with respect to all efficacy variables, but was statistically superior to placebo only with respect to SPID (Sum of Pain Intensity Differences; 0 - 3 hour scores). Tramadol 100 mg was statistically superior to placebo with respect to all efficacy variables except for time to remedication. Tramadol 50 mg was numerically favored over placebo with respect to all efficacy variables, but was statistically superior to placebo with respect to TOTPAR (Total Pain Relief; sum of 0 - 6 hour scores) and SPID (0 - 6 hour scores). During the 0 - 3 hour time period, ASA/codeine was statistically superior to the other active treatments with respect to TOTPAR. There were no statistically significant differences among tramadol 100 mg, tramadol 50 mg and codeine. During the 0 - 6 hour time period, ASA/codeine was statistically superior to codeine, but was not statistically different from tramadol 100 mg and tramadol 50 mg with respect to TOTPAR. There were no statistically significant differences among tramadol 100 mg, tramadol 50 mg and codeine. ASA/codeine was statistically superior to tramadol 50 mg, but was not statistically different from tramadol 100 mg and codeine with respect to SPID (0 - 3 hour scores).

This study showed model sensitivity, and tramadol 100 mg provided pain relief statistically superior to that of placebo. In this study, the order of relative efficacy over all variables was ASA/codeine > tramadol 100 mg and tramadol 50 mg > codeine > placebo.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TF

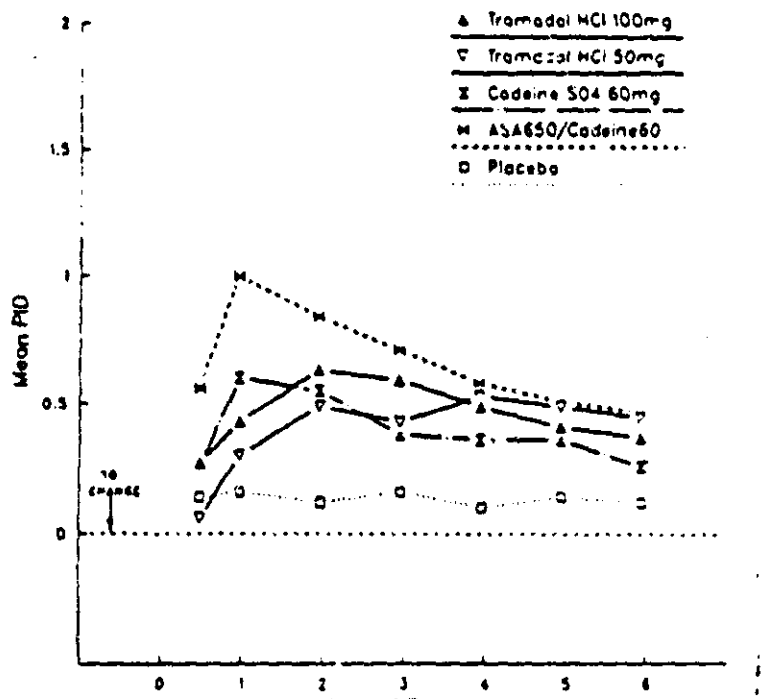


Treatment	TOTPAR (extrapolated) 3-hour		6-hour	
TR 100mg	3.51(3.46)	B	5.86(6.83)	AB
TR 50mg	3.24(3.63)	B	6.16(7.45)	AB
ASA/COD	4.98(3.31)	A	7.76(6.56)	A
CO 60mg	3.12(2.98)	B	4.82(5.70)	BC
Placebo	2.23(2.71)	B	3.26(4.86)	C
P-VALUE	0.002		0.013	
RMS ERROR	3.235		6.335	

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	0.84(0.94) 49 AB	1.16(1.20) 49 A	1.33(1.33) 39 B	1.18(1.50) 28 AB	0.98(1.45) 19 A	0.71(1.34) 14	0.65(1.38) 10
TR 50mg	0.72(1.04) 47 B	1.09(1.32) 47 B	1.28(1.39) 40 B	1.06(1.45) 25 ABC	1.11(1.52) 19 A	0.96(1.43) 18	0.85(1.40) 15
ASA/COD	1.22(1.11) 45 A	2.11(1.28) 45 A	1.87(1.44) 41 A	1.44(1.37) 31 A	1.13(1.34) 25 A	0.87(1.36) 17	0.78(1.38) 14
CO 60mg	0.83(0.92) 47 AB	1.28(1.12) 47 B	1.21(1.23) 41 B	0.85(1.22) 27 BC	0.62(1.19) 18 AB	0.60(1.17) 12	0.49(0.93) 11
Placebo	0.59(0.96) 49 B	0.90(1.07) 49 B	0.88(1.07) 41 B	0.61(0.95) 25 C	0.43(0.94) 16 B	0.33(0.92) 9	0.27(0.81) 9
P-VALUE	0.037	0.000	0.008	0.028	0.028	0.119	0.125
RMS ERROR	0.992	1.198	1.297	1.311	1.303	1.255	1.204

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TF

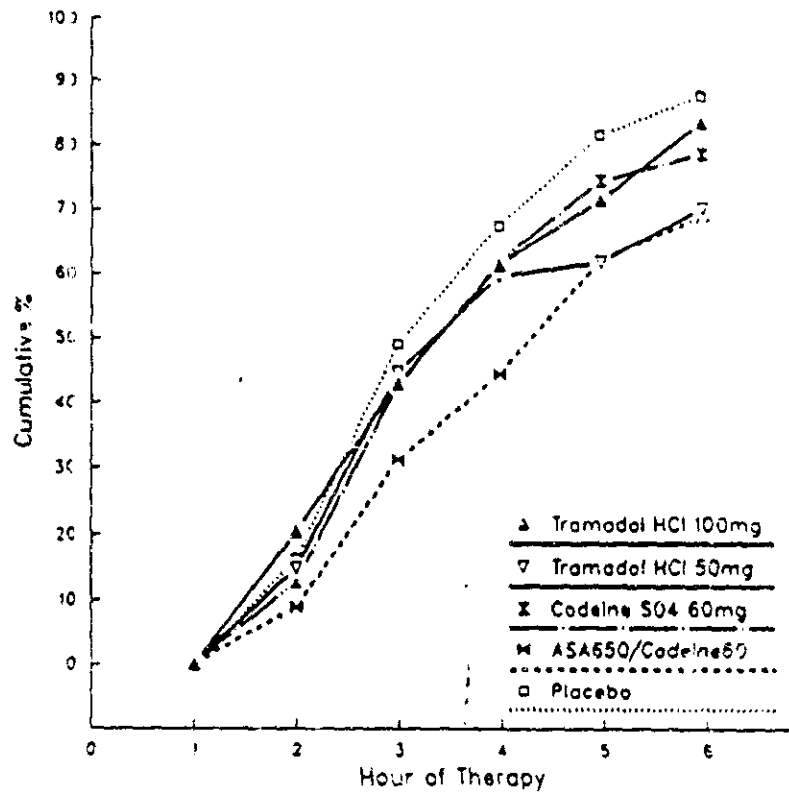


Treatment	SPID (extrapolated) 3-hour	6-hour
TR 100mg	1.57(2.21) AB	2.84(4.52) A
TR 50mg	1.10(2.27) BC	2.56(4.51) A
ASA/COD	2.33(2.43) A	3.89(4.88) A
CO 60mg	1.36(2.03) B	2.34(3.63) AB
Placebo	0.44(1.62) C	0.81(2.84) B
P-VALUE	0.001	0.010
RMS ERROR	2.122	4.132

Treatment	Assessment Time-Points (in hours) 1/2	1	2	3	4	5	6
TR 100mg	0.27(0.70) 49 B	0.43(0.91) 49 BC	0.63(0.88) 39 A	0.59(0.91) 28 A	0.49(0.92) 19 A	0.41(0.89) 14	0.37(0.88) 10
TR 50mg	0.06(0.53) 47 B	0.30(0.88) 47 BC	0.49(0.98) 40 AB	0.43(0.90) 26 AB	0.53(0.88) 19 A	0.49(0.91) 18	0.45(0.88) 15
ASA/COD	0.56(0.84) 45 A	1.00(1.02) 45 A	0.84(1.13) 41 A	0.71(0.99) 31 A	0.58(0.99) 25 A	0.51(0.99) 17	0.47(0.92) 14
CO 60mg	0.26(0.61) 47 B	0.60(0.80) 47 B	0.55(0.88) 41 A	0.38(0.77) 27 AB	0.36(0.79) 18 AB	0.36(0.76) 12	0.26(0.61) 11
Placebo	0.14(0.54) 49 B	0.16(0.72) 49 C	0.12(0.73) 41 B	0.16(0.59) 25 B	0.10(0.55) 16 B	0.14(0.58) 9	0.12(0.53) 9
P-VALUE	0.005	0.000	0.005	0.021	0.042	0.207	0.170
RMS ERROR	0.651	0.871	0.924	0.842	0.836	0.835	0.778

CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TF

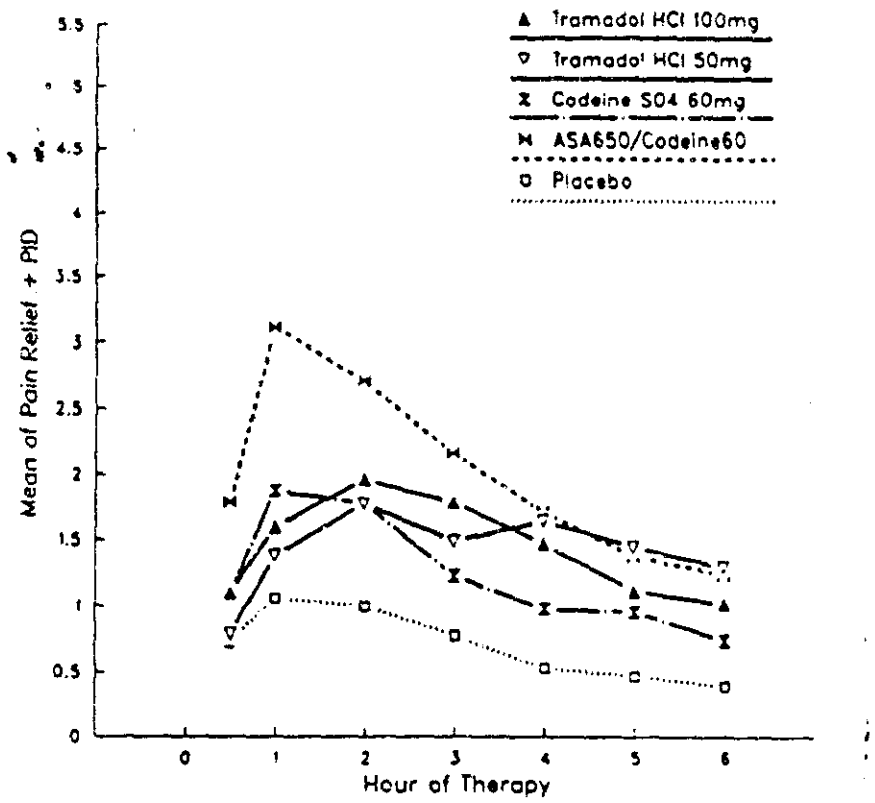
Cumulative Percent of Patients Terminating Prematurely



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour
TR 100mg	49(100.0%)	39(79.6%)	28(57.1%)	19(38.8%)	14(28.6%)	8(16.3%)
TR 50mg	47(100.0%)	40(85.1%)	26(55.3%)	19(40.4%)	18(38.3%)	14(29.8%)
ASA/COD	45(100.0%)	41(91.1%)	31(68.9%)	25(55.6%)	17(37.8%)	14(31.1%)
CO 60mg	47(100.0%)	41(87.2%)	27(57.4%)	18(38.3%)	12(25.5%)	10(21.3%)
Placebo	49(100.0%)	41(83.7%)	25(51.0%)	16(32.7%)	9(18.4%)	6(12.2%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TF



Treatment	SPRID (extrapolated) 3-hour	6-hour
TR 100mg	5.08(5.43) B	8.69(11.02) AB
TR 50mg	4.34(5.64) BC	8.72(11.65) AB
ASA/COD	7.31(5.51) A	11.64(11.13) A
CO 60mg	4.48(4.78) BC	7.16(9.15) BC
Placebo	2.67(4.13) C	4.06(7.43) C
P-VALUE	0.001	0.009
RMS ERROR	5.123	10.175

Treatment	Assessment Time-Points (in hours) 1/2	1	2	3	4	5	6
TR 100mg	1.10(1.53) 49 B	1.59(1.96) 49 BC	1.96(2.10) 39 AB	1.78(2.33) 28 AB	1.47(2.29) 19 A	1.12(2.19) 14	1.02(2.20) 10
TR 50mg	0.79(1.43) 47 B	1.38(2.10) 47 BC	1.77(2.27) 40 BC	1.49(2.26) 26 ABC	1.64(2.34) 19 A	1.45(2.28) 18	1.30(2.23) 15
ASA/COD	1.78(1.82) 45	3.11(2.19) 45 A	2.71(2.48) 41 A	2.16(2.27) 31 A	1.71(2.24) 25 A	1.38(2.30) 17	1.24(2.26) 14
CO 60mg	1.09(1.40) 47 B	1.87(1.81) 47 B	1.77(1.99) 41 BC	1.23(1.90) 27 BC	0.98(1.95) 18 AB	0.96(1.90) 12	0.74(1.47) 11
Placebo	0.73(1.40) 49 B	1.06(1.69) 49 C	1.00(1.70) 41 C	0.78(1.43) 25 C	0.53(1.40) 16 B	0.47(1.46) 9	0.39(1.27) 9
P-VALUE	0.009	0.000	0.004	0.018	0.027	0.139	0.123
RMS ERROR	1.519	1.954	2.117	2.063	2.071	2.014	1.927

PROTOCOL TF

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	27	19	45
TR 50mg	38	25	81
ASA/COD	17	13	24
CO 60mg	28	20	44
Placebo	41	26	69

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	3:10	2:30	4:00
TR 50mg	3:05	2:30	5:00
ASA/COD	4:05	3:00	5:00
CO 60mg	3:10	2:35	4:00
Placebo	2:55	2:25	3:40

Tramadol Protocol TF 10:37 Friday, June 3, 1994 1

Demographic Frequencies and Means

	Sex		Race					Baseline Pain				Surgical Procedure	Reason for Discontinuation			
Drug	M	F	Wht	Blk	Oth	Mean Age	Mean Weight	None	Slight	Moderate	Severe	Dental Surgery	Adv Exp	Patient Choice	Protocol Violation	Other
Tramadol 100 MG	19	32	38	11	2	25.98	163.80	0	0	26	24	51	0	0	1	1
Tramadol 50 MG	19	33	35	12	5	24.37	152.84	0	0	28	23	52	0	0	0	1
Codeine 304	21	29	33	15	2	25.34	149.04	0	0	21	27	50	0	0	0	2
ASA / Codeine	18	29	35	9	3	23.74	148.53	0	0	24	22	47	0	0	0	1
Placebo	18	32	43	3	4	24.14	146.58	0	0	36	14	50	0	0	0	0

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This display includes all patients, including those who were not included in the analysis.

Study: TF3	Pain Model: Dental-Extraction Pain Study Design: si, sd, db, r, p* Duration: 10 hours Tx: Tramadol (TR) 150 mg, 100 mg, 75 mg, and 50 mg Codeine Sulfate 60 mg (Codeine) Placebo
A randomized, double-blind, single-dose, parallel group, inpatient study of tramadol hydrochloride 150 mg, 100 mg, 75 mg and 50 mg (tramadol), codeine sulfate 60 mg (codeine) and placebo in patients with moderate or severe baseline pain following dental surgery.	
TR 150 mg: 39 pts. TR 75 mg: 40 pts. Codeine: 40 pts. Placebo: 40 pts. TR 100 mg: 41 pts. TR 50 mg: 39 pts.	
Time-observation points: 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* si = single investigator; sd = single-dose; db = double-blind; r = randomized; p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

Of the 239 patients enrolled, 230 (96%) completed the study either by finishing the 10-hour protocol or by receiving a rescue analgesic, and nine patients (4%) discontinued the study prematurely.

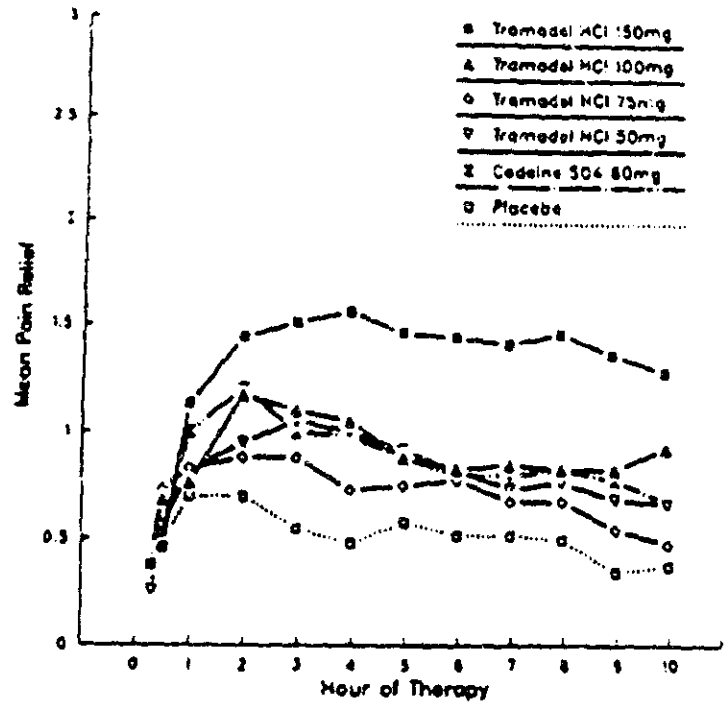
Codeine was numerically favored over placebo with respect to all efficacy variables, although this was not statistically significant. A significant linear tramadol dose response was observed for TOTPAR (Total Pain Relief; sum of 0 - 10 hour scores), SPID (Sum of the Pain Intensity Differences; 0 - 10 hour scores) and time to remedication, thus establishing model sensitivity. There was no significant difference among the treatment groups for TOTPAR (sum of 0 - 3, 0 - 5, and 0 - 6 hour scores) and SPID (0 - 3, 0 - 5, and 0 - 6 hour scores); therefore, no further tests were performed.

Tramadol 150 mg was statistically superior to placebo with respect to TOTPAR (sum of 0 - 10 hour scores), SPID (0 - 10 hour scores) and time to remedication. Tramadol 100 mg, tramadol 75 mg and tramadol 50 mg were not statistically superior to placebo with respect to any efficacy variables.

Comparing the five active treatment groups with respect to all efficacy variables, tramadol 150 mg was numerically superior to the other treatments. Tramadol 150 mg was statistically superior to tramadol 75 mg but was not statistically different from tramadol 100 mg, tramadol 50 mg and codeine with respect to TOTPAR (sum of 0 - 10 hour scores). Tramadol 150 mg was statistically superior to tramadol 75 mg and tramadol 50 mg, but was not statistically different from tramadol 100 mg and codeine with respect to SPID (0 - 10 hour scores).

This study demonstrated model sensitivity, and tramadol 150 mg provided statistically superior pain relief to that of placebo.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TF3

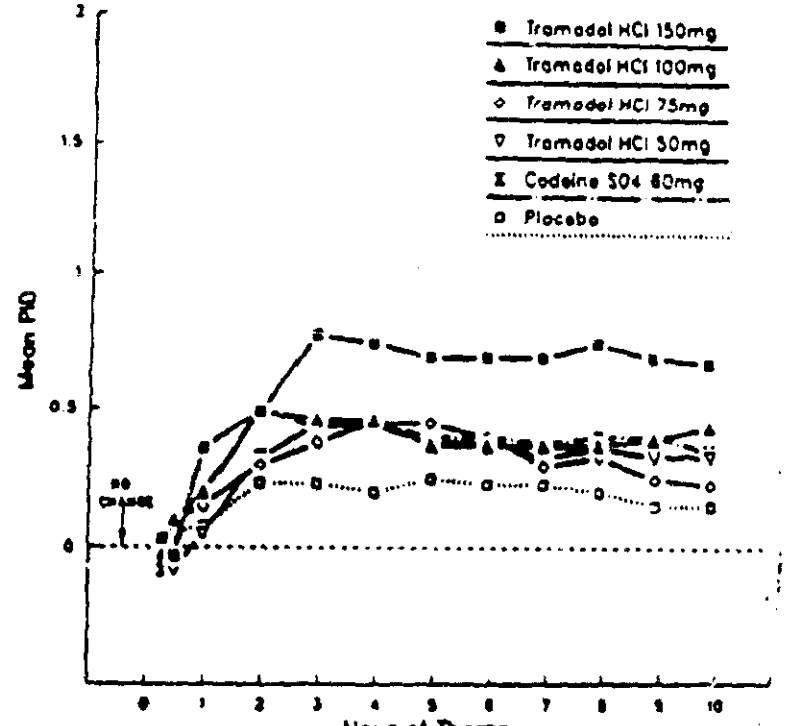


Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 150mg	3.72(3.27)	8.19(7.55)
TR 100mg	2.91(2.88)	5.66(6.58)
TR 75mg	2.44(2.82)	4.69(6.56)
TR 50mg	2.62(3.12)	5.36(6.86)
CO 60mg	2.93(3.18)	5.58(7.12)
Placebo	1.82(2.62)	3.39(6.03)
P-Value	0.122	0.065
RMS ERROR	2.985	6.796

MEAN SCORES OF PAIN RELIEF (Extrapolated)
Assessment Time-Points (in hours)

Treatment	1/4	1/2	1	2	3	4	5	6	7	8	9	10
TR 150mg	0.38(0.49) 39	0.46(0.60) 39	1.13(1.10) 39	1.44(1.31) 37	1.51(1.50) 24	1.56(1.67) 19 A	1.46(1.60) 18	1.44(1.62) 18	1.41(1.67) 18	1.46(1.80) 16	1.36(1.77) 15 A	1.28(1.76) 14
TR 100mg	0.37(0.54) 41	0.68(0.76) 41	0.76(0.92) 41	1.17(1.16) 33	1.10(1.27) 20	1.05(1.43) 16 AB	0.88(1.40) 14	0.83(1.41) 11	0.85(1.44) 11	0.83(1.41) 11	0.83(1.45) 11 AB	0.93(1.57) 11
TR 75mg	0.40(0.63) 40	0.73(0.91) 40	0.83(1.13) 40	0.88(1.11) 30	0.88(1.28) 19	0.73(1.28) 12 B	0.75(1.43) 10	0.78(1.44) 10	0.68(1.33) 9	0.68(1.35) 9	0.55(1.24) 8 B	0.46(1.22) 6
TR 50mg	0.26(0.50) 39	0.56(0.76) 39	0.82(1.00) 39	0.95(1.26) 30	1.05(1.41) 17	1.00(1.45) 14 AB	0.92(1.44) 13	0.82(1.50) 11	0.74(1.41) 9	0.77(1.46) 9	0.69(1.45) 8 B	0.67(1.46) 7
CO 60mg	0.30(0.70) 40	0.55(0.88) 40	1.00(1.01) 40	1.20(1.26) 29	1.00(1.45) 15	0.90(1.48) 13 AB	0.88(1.45) 13	0.80(1.44) 11	0.80(1.49) 10	0.83(1.57) 9	0.78(1.58) 8 AB	0.68(1.49) 7
Placebo	0.40(0.63) 40	0.48(0.64) 40	0.70(0.99) 40	0.70(1.04) 29	0.55(1.15) 11	0.48(1.15) 7 B	0.58(1.30) 7	0.52(1.20) 7	0.52(1.20) 7	0.50(1.18) 7	0.35(0.98) 5 B	0.38(1.03) 5
P-Value	0.893	0.667	0.434	0.089	0.069	0.026	0.138	0.128	0.118	0.089	0.052	0.071
RMS ERROR	0.589	0.764	1.027	1.195	1.367	1.418	1.439	1.439	1.428	1.472	1.431	1.449

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TF3



Treatment	SPID (extrapolated) 3-hour	6-hour
TR 150mg	1.44(2.19)	3.56(4.30)
TR 100mg	1.07(1.63)	2.26(3.27)
TR 75mg	0.79(2.11)	2.09(4.23)
TR 50mg	0.78(1.76)	1.99(3.51)
CO 60mg	1.02(1 76)	2.27(3.57)
Placebo	0.51(1.51)	1.19(2.74)
P-Value	0.327	0.123
RMS ERROR	1.838	3.639

Assessment Time-Points (in hours)

Treatment	1/4	1/2	1	2	3	4	5	6	7	8	9	10
TR 150mg	0.03(0.54) 39	-.03(0.67) 39	0.36(0.87) 39	0.49(0.94) 37	0.77(0.81) 24 A	0.74(0.85) 19 A	0.69(0.83) 19	0.69(0.83) 18	0.69(0.86) 18	0.74(0.94) 16 A	0.69(0.92) 15 A	0.67(0.96) 14 A
TR 100mg	-.02(0.42) 41	0.10(0.58) 41	0.20(0.75) 41	0.49(0.68) 33	0.46(0.67) 20 AB	0.46(0.67) 16 AB	0.37(0.66) 14	0.37(0.66) 11	0.37(0.66) 11	0.37(0.66) 11 B	0.39(0.70) 11 AB	0.44(0.78) 11 AB
TR 75mg	0.05(0.50) 40	0.10(0.81) 40	0.15(1.00) 40	0.30(0.82) 30	0.38(0.84) 19 B	0.45(0.81) 12 AB	0.45(0.88) 10	0.40(0.78) 10	0.30(0.65) 9	0.33(0.69) 9 B	0.25(0.67) 8 B	0.23(0.66) 6 B
TR 50mg	0.03(0.48) 39	-.08(0.66) 39	0.05(0.72) 39	0.33(0.74) 30	0.44(0.88) 17 B	0.44(0.72) 14 AB	0.38(0.71) 13	0.38(0.78) 11	0.33(0.70) 9	0.36(0.74) 9 B	0.33(0.77) 6 B	0.33(0.77) 7 B
CO 60mg	-.08(0.66) 40	0.10(0.71) 40	0.18(0.84) 40	0.50(0.68) 29	0.43(0.71) 15 B	0.45(0.71) 13 AB	0.40(0.71) 13	0.40(0.74) 11	0.38(0.77) 10	0.40(0.81) 9 B	0.40(0.84) 8 AB	0.35(0.80) 7 AB
Placebo	0.06(0.58) 40	0.06(0.60) 40	0.08(0.76) 40	0.23(0.73) 29	0.23(0.48) 11 B	0.20(0.52) 7 B	0.25(0.59) 7	0.23(0.53) 7	0.23(0.53) 7	0.20(0.52) 7 B	0.15(0.43) 5 B	0.15(0.43) 5 B
P-Value	0.886	0.781	0.640	0.456	0.032	0.050	0.167	0.127	0.070	0.038	0.035	0.046
RMS ERROR	0.539	0.676	0.831	0.770	0.708	0.722	0.736	0.727	0.703	0.737	0.738	0.749

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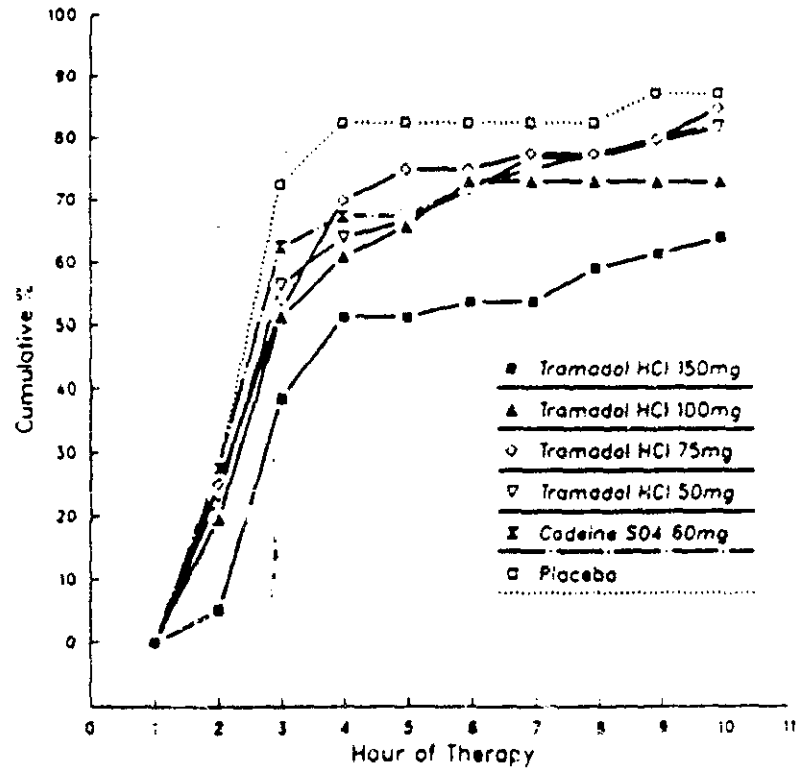
CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TF3

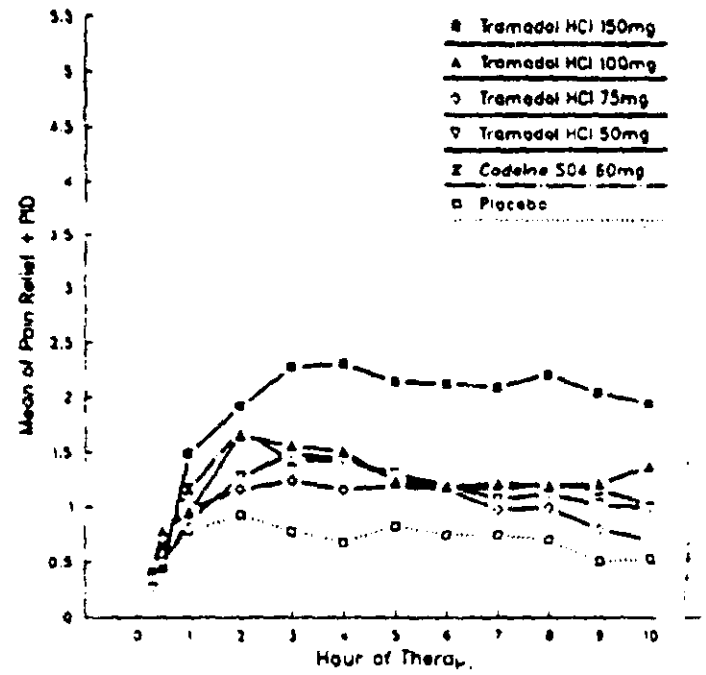
Cumulative Percent of Patients Terminating Prematurely



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour	7-hour	8-hour	9-hour	10-hour
TR 150mg	39(100.0%)	37(94.9%)	24(61.5%)	19(48.7%)	19(48.7%)	18(46.2%)	18(46.2%)	16(41.0%)	15(38.5%)	14(35.9%)
TR 100mg	41(100.0%)	33(80.5%)	20(48.8%)	16(39.0%)	14(34.1%)	11(26.8%)	11(26.8%)	11(26.8%)	11(26.8%)	11(26.8%)
TR 75mg	40(100.0%)	30(75.0%)	19(47.5%)	12(30.0%)	10(25.0%)	10(25.0%)	9(22.5%)	9(22.5%)	8(20.0%)	6(15.0%)
TR 50mg	39(100.0%)	30(76.9%)	17(43.6%)	14(35.9%)	13(33.3%)	11(28.2%)	9(23.1%)	9(23.1%)	8(20.5%)	7(17.9%)
CO 60mg	40(100.0%)	29(72.5%)	15(37.5%)	13(32.5%)	13(32.5%)	11(27.5%)	10(25.0%)	9(22.5%)	8(20.0%)	7(17.5%)
Placebo	40(100.0%)	29(72.5%)	11(27.5%)	7(17.5%)	7(17.5%)	7(17.5%)	7(17.5%)	7(17.5%)	5(12.5%)	5(12.5%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TF3



Treatment	SPRID (extrapolated) 3-hour	6-hour
TR 150mg	5.16(5.33)	11.75(11.66)
TR 100mg	3.98(4.41)	7.93(9.72)
TR 75mg	3.23(4.81)	6.78(10.62)
TR 50mg	3.40(4.74)	7.35(10.21)
CO 60mg	3.95(4.81)	7.85(10.54)
Placebo	2.33(3.94)	4.58(8.64)
P-Value	0.161	0.075
RMS ERROR	4.687	10.265

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated)
Assessment Time-Points (in Hours)

Treatment	1/4	1/2	1	2	3	4	5	6	7	8	9	10
TR 150mg	0.41(0.91) 39	0.44(1.17) 39	1.49(2.90) 39	1.92(2.19) 37	2.28(2.26) 24 A	2.31(2.48) 19 A	2.15(2.39) 19	2.13(2.41) 18	2.10(2.59) 18	2.21(2.73) 16	2.05(2.67) 16 A	1.95(2.69) 14
TR 100mg	0.36(0.82) 41	0.78(1.26) 41	0.95(1.60) 41	1.66(1.74) 33	1.56(2.01) 20 AB	1.51(2.08) 16 AB	1.24(2.03) 14	1.20(2.05) 11	1.22(2.08) 11	1.20(2.06) 11	1.22(2.13) 13 AB	1.37(2.33) 11
TR 75mg	0.45(1.04) 40	0.83(1.62) 40	0.98(2.06) 40	1.17(1.86) 30	1.26(2.07) 19 B	1.17(2.06) 12 B	1.20(2.28) 10	1.17(2.19) 10	0.98(1.95) 9	1.00(2.03) 9	0.80(1.88) 8 B	0.70(1.86) 6
TR 50mg	0.28(0.89) 39	0.49(1.30) 39	0.87(1.63) 39	1.29(1.95) 30	1.49(2.06) 17 AB	1.44(2.14) 14 AB	1.31(2.12) 13	1.21(2.26) 11	1.08(2.08) 9	1.13(2.18) 9	1.03(2.21) 8 B	1.00(2.21) 7
CO 60mg	0.30(1.24) 40	0.65(1.48) 40	1.17(1.77) 40	1.70(1.88) 29	1.43(2.12) 15 AB	1.43(2.17) 13 AB	1.28(2.14) 13	1.20(2.15) 11	1.17(2.24) 10	1.22(2.36) 9	1.17(2.41) 8 AB	1.03(2.28) 7
Placebo	0.45(1.06) 40	0.52(1.11) 40	0.78(1.66) 40	0.93(1.67) 29	0.78(1.61) 11 B	0.68(1.65) 7 B	0.83(1.88) 7	0.75(1.72) 7	0.75(1.72) 7	0.70(1.68) 7	0.50(1.40) 5 B	0.52(1.45) 5
P-Value	0.954	0.718	0.536	0.166	0.046	0.031	0.149	0.120	0.093	0.064	0.042	0.058
RMS ERROR	1.004	1.332	1.774	1.885	2.030	2.109	2.144	2.140	2.108	2.191	2.161	2.172

PROTOCOL TF3

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	69	37	478
TR 100mg	38	26	77
TR 75mg	36	22	95
TR 50mg	62	33	414
CO 60mg	45	27	164
Placebo	57	34	172

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	3:35	2:40	9:30
TR 100mg	2:50	2:20	4:20
TR 75mg	2:40	2:05	3:30
TR 50mg	2:40	2:10	3:50
CO 60mg	2:30	2:00	2:55
Placebo	2:20	2:00	2:45

Tramadol Protocol TF3 11:13 Friday, June 3, 1994 1

Demographic Frequencies and Means

	Sex		Race					Baseline Pain				Surgical Procedure	Reason for Discontinuation		
Drug	M	F	Wht	Blk	Oth	Mean Age	Mean Weight	None	Slight	Moderate	Severe	Dental Surgery	Patient Choice	Protocol Violation	Other
Tramadol 150 MG	16	23	30	4	5	25.21	157.10	0	0	26	13	39	2	0	0
Tramadol 100 MG	20	21	32	1	8	22.93	150.54	0	0	27	14	41	0	0	0
Tramadol 75 MG	17	23	33	1	6	25.35	162.50	0	0	27	13	40	1	0	0
Tramadol 50 MG	20	19	27	3	9	23.46	157.54	0	0	26	13	39	2	0	0
Codeine 504	18	22	34	4	2	25.35	147.70	0	0	26	14	40	2	0	0
Placebo	23	17	33	0	7	24.88	150.70	0	0	27	13	40	1	0	0

This display includes all patients, including those who were not included in the analysis.

Study: TG	Pain Model: Dental Study Design: ti, sd, db, r, p* Duration: 6 hours Tx: Tramadol (TR) 100 and 50 mg Aspirin 650 mg /Codeine Phosphate 60 mg (ASA/codeine) Codeine Sulfate 60 mg (Codeine) Placebo
This was a two investigator, randomized, double-blind, single-dose, parallel group, outpatient study of tramadol hydrochloride 100 mg and 50 mg (tramadol), aspirin 650 mg with codeine phosphate 60 mg (ASA/codeine), codeine sulfate 60 mg (codeine) and placebo in patients with moderate or severe baseline pain following extraction of third molars.	
TR 100 mg: 49 pts. ASA/Codeine: 42 pts. Codeine: 33 pts. Placebo: 27 pts. TR 50 mg: 49 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, and 6 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* ti = two investigators; sd = single-dose; db = double-blind; r = randomized; p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

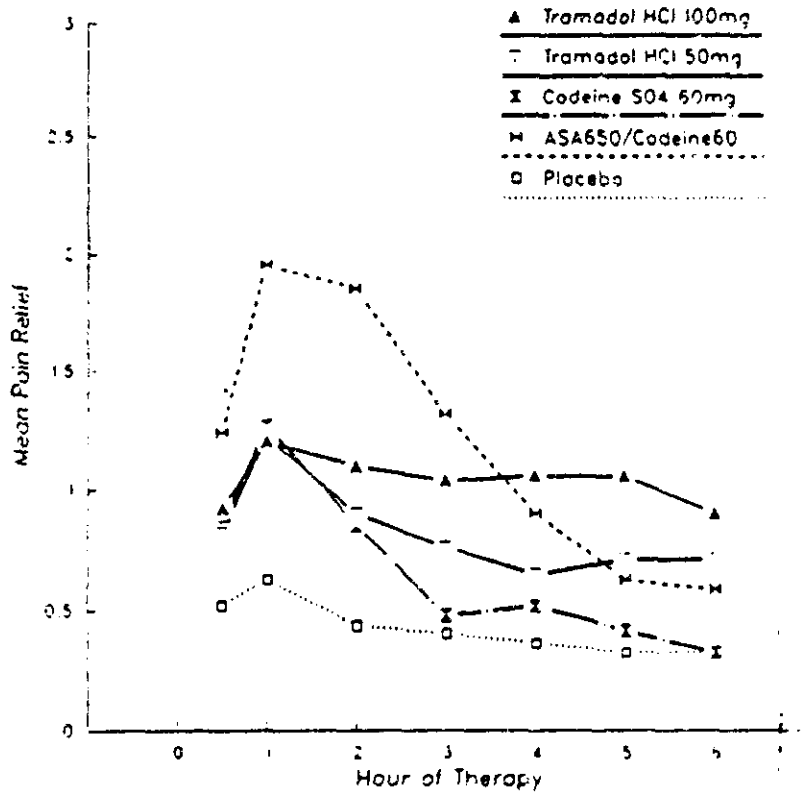
Of the 200 patients enrolled, 192 (96.0%) completed the study either by finishing the 6-hour protocol or by receiving a rescue analgesic, seven patients (3.5%) discontinued the study prematurely and one patient (0.5%) was lost to follow-up. One ASA/codeine-treated patient was lost to follow-up with no efficacy and safety data recorded, and therefore this patient did not contribute data for the analyses of demographic characteristics, efficacy and safety.

ASA/codeine was statistically superior to placebo with respect to all efficacy variables. Codeine was numerically favored over placebo with respect to all efficacy variables, although this was not statistically significant. Tramadol 100 mg was statistically superior to placebo with respect to TOTPAR (Total Pain Relief; sum of 0 - 3 and 0 - 6 hour scores), SPID (Sum of the Pain Intensity Difference; 0 - 3 and 0 - 6 hour scores) and time to remedication. Tramadol 50 mg was numerically favored over placebo with respect to all efficacy variables, but was statistically superior to placebo only with respect to time to remedication.

Comparing the four active treatment groups with respect to all efficacy variables, tramadol 100 mg and ASA/codeine were numerically superior to the other treatments. These two treatments were not statistically different with respect to any efficacy variable except TOTPAR (sum of 0 - 3 hour scores), where ASA/codeine was statistically superior to tramadol 100 mg. Mean TOTPAR scores favored ASA/codeine over tramadol 100 mg and tramadol 50 mg over codeine during both time intervals. Tramadol 50 mg and codeine were not statistically different during either time interval. Mean SPID scores favored ASA/codeine over tramadol 100 mg during the 0 - 3 hour time interval, while tramadol 100 mg was favored over ASA/codeine during the 0 - 6 hour time interval. Mean SPID scores favored tramadol 50 mg over codeine during both time periods, although this was not statistically significant.

This study showed model sensitivity, and tramadol 100 mg provided pain relief statistically superior to that of placebo. In this study, the order of relative efficacy over all variables was ASA/codeine > tramadol 100 mg > tramadol 50 mg > codeine > placebo.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TG

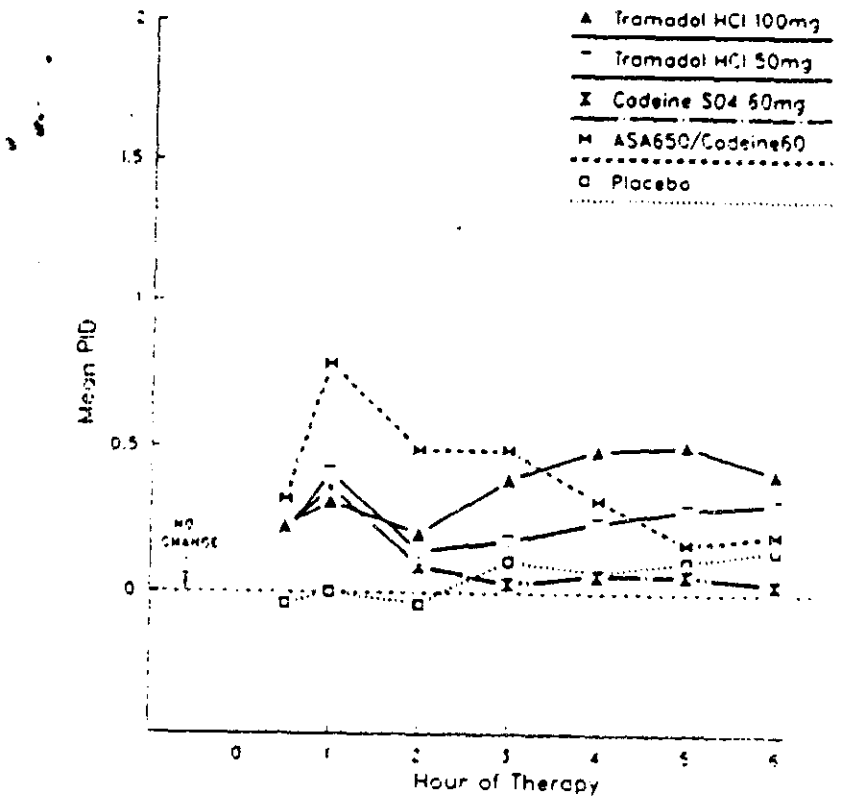


Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 100mg	3.20(3.27) B	6.22(7.49) AB
TR 50mg	2.67(2.86) BC	4.76(6.12) ABC
ASA/COD	4.77(2.91) A	6.89(5.37) A
CO 60mg	2.39(2.46) BC	3.67(4.37) BC
Placebo	1.43(1.97) C	2.46(3.85) C
P-VALUE	0.000	0.012
RMS ERROR	2.817	5.851

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	0.92(1.17) 49	1.20(1.21) 49 B	1.10(1.29) 42 B	1.04(1.41) 25 AB	1.06(1.53) 20	1.06(1.60) 17	0.90(1.56) 13
TR 50mg	0.82(0.97) 49	1.22(1.28) 49 B	0.90(1.12) 41 BC	0.76(1.15) 30 BC	0.65(1.25) 18	0.71(1.37) 15	0.71(1.41) 14
ASA/COD	1.24(1.11) 41	1.95(1.20) 41 A	1.85(1.24) 40 A	1.32(1.31) 29 A	0.90(1.28) 19	0.63(1.22) 13	0.59(1.18) 10
CO 60mg	0.85(0.97) 33	1.27(1.04) 33 B	0.85(1.06) 27 BC	0.48(0.64) 13 C	0.52(0.97) 10	0.42(0.90) 7	0.33(0.78) 6
Placebo	0.52(0.80) 27	0.63(1.04) 27 C	0.44(0.80) 16 C	0.41(0.80) 8 C	0.37(0.88) 6	0.33(1.00) 4	0.33(1.00) 4
P-VALUE	0.076	0.000	0.000	0.006	0.113	0.113	0.228
RMS ERROR	1.034	1.178	1.147	1.185	1.252	1.293	1.272

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TG



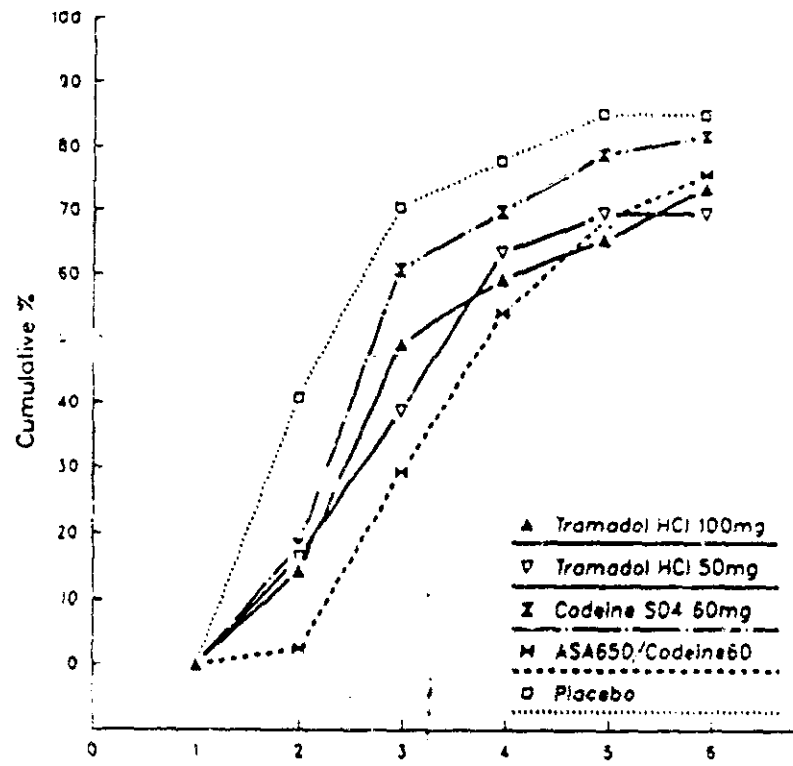
Treatment	SPID (extrapolated) 3-hour	6-hour
TR 100mg	0.86(2.12) AB	2.27(4.25) A
TR 50mg	0.63(1.73) BC	1.47(3.28) AB
ASA/COD	1.52(1.96) A	2.21(2.87) A
CO 60mg	0.41(1.46) BC	0.56(1.75) B
Placebo	0.06(1.07) C	0.39(1.73) B
P-VALUE	0.009	0.025
RMS ERROR	1.752	3.121

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	0.22(0.69) 49	0.31(0.82) 49 BC	0.20(0.96) 42	0.39(0.86) 25 AB	0.49(0.89) 20 A	0.51(0.84) 17 A	0.41(0.81) 13
TR 50mg	0.20(0.61) 49	0.41(0.81) 49 B	0.14(0.76) 41	0.18(0.75) 30 ABC	0.24(0.63) 18 AB	0 29(0.68) 15 AB	0.31(0.74) 15
ASA/COD	0.32(0.72) 41	0.78(0.69) 41 A	0.49(0.93) 40	0.49(0.71) 29 A	0.32(0.65) 19 AB	0.17(0.54) 13 B	0.20(0.51) 10
CO 60mg	0.21(0.55) 33	0.36(0.70) 33 B	0.09(0.80) 27	0.03(0.47) 13 C	0.06(0.43) 10 B	0.06(0.24) 7 B	0.03(0.17) 6
Placebo	-.04(0.44) 27	0.00(0.55) 27 C	-.04(0.59) 16	0.11(0.42) 8 BC	0.07(0.38) 6 B	0.11(0.42) 4 B	0.15(0.53) 4
P-VALUE	0.252	0.001	0.104	0.026	0.024	0.009	0.080
RMS ERROR	0.625	0.742	0.837	0.699	0.658	0.620	0.630

CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TG

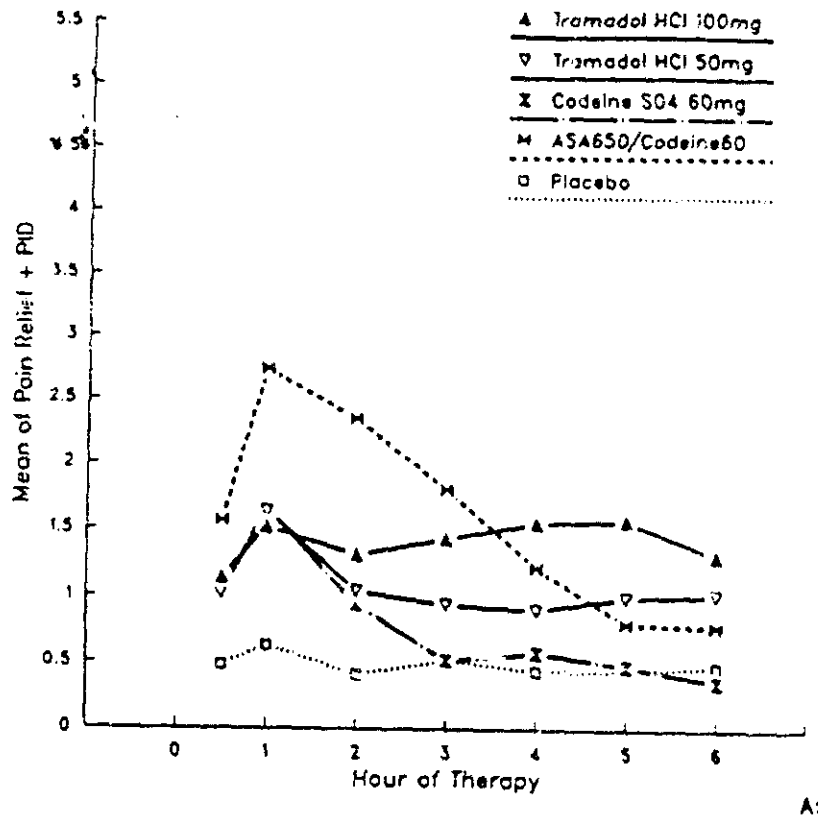
Cumulative Percent of Patients Terminating Prematurely



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour
TR 100mg	49(100.0%)	42(85.7%)	25(51.0%)	20(40.8%)	17(34.7%)	13(26.5%)
TR 50mg	49(100.0%)	41(83.7%)	30(61.2%)	18(36.7%)	15(30.6%)	15(30.6%)
ASA/COD	41(100.0%)	40(97.6%)	29(70.7%)	19(46.3%)	13(31.7%)	10(24.4%)
CO 60mg	33(100.0%)	27(81.8%)	13(39.4%)	10(30.3	7(21.2%)	6(18.2%)
Placebo	27(100.0%)	16(59.3%)	8(29.6%)	6(22.2%)	4(14.8%)	4(14.8%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TG



Treatment	SPRID (extrapolated) 3-hour	6-hour
TR 100mg	4.06(5.22) B	8.49(11.50) A
TR 50mg	3.31(4.34) BC	6.22(9.20) AB
ASA/COD	6.29(4.54) A	9.10(7.91) A
CC 60mg	2.60(3.68) BC	4.23(5.72) B
Placebo	1.48(2.46) C	2.85(5.15) B
P-VALUE	0.000	0.012
RMS ERROR	4.325	8.687

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	1.14(1.73) 49	1.51(1.93) 49 B	1.31(2.16) 42 B	1.43(2.20) 25 AB	1.55(2.37) 20	1.57(2.41) 17 A	1.31(2.30) 13
TR 50mg	1.02(1.38) 49	1.63(1.97) 49 B	1.04(1.77) 41 BC	0.94(1.80) 30 BC	0.90(1.82) 18	1.00(2.02) 15 AB	1.02(2.12) 14
ASA/COD	1.56(1.66) 41	2.73(1.75) 41 A	2.34(2.07) 40 A	1.80(1.93) 29 A	1.22(1.85) 19	0.80(1.68) 13 AB	0.78(1.62) 10
CO 60mg	1.06(1.39) 33	1.64(1.56) 33 B	0.94(1.73) 27 BC	0.52(1.28) 13 C	0.58(1.30) 10	0.48(1.06) 7 B	0.36(0.90) 6
Placebo	0.48(1.09) 27	0.63(1.47) 27 C	0.41(1.05) 16 C	0.52(0.98) 8 C	0.44(1.19) 6	0.44(1.40) 4 B	0.48(1.50) 4
P-VALUE	0.075	0.000	0.000	0.006	0.057	0.048	0.149
RMS ERROR	1.502	1.787	1.858	1.776	1.839	1.863	1.843

PROTOCOL TG

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	26	18	46
TR 50mg	30	22	49
ASA/COD	19	14	29
CO 60mg	28	19	52
Placebo	62	33	476

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	2:55	2:30	4:25
TR 50mg	3:15	2:35	3:50
ASA/COD	3:40	3:00	4:35
CO 60mg	2:35	2:10	3:20
Placebo	2:05	1:35	2:45

Tramadol Protocol TG

13:40 Friday, June 3, 1994

Demographic Frequencies and Means

	Sex		___Race____					_____Baseline Pain_____				Surgical Procedure	_Reason for Discontinuation_			
Drug	M	F	Wht	Blk	Oth	Mean Age	Mean Weight	None	Slight	Moderate	Severe	Dental Surgery	Adv Exp	Patient Choice	Protocol Violation	Other
Tramadol 100 MG	16	33	45	3	1	24.76	157.00	0	0	40	9	49	0	0	0	1
Tramadol 50 MG	21	29	47	1	2	24.34	155.72	0	0	41	9	50	0	0	0	1
Codeine SO4	16	17	32	0	1	23.70	155.76	0	0	27	6	33	0	1	0	2
ASA / Codeine	22	20	40	1	1	23.64	155.83	0	0	38	4	42	0	0	0	4
Placebo	10	17	24	1	2	24.96	146.65	0	0	21	6	27	0	0	0	0

6500 0059

This display includes all patients, including those who were not included in the analysis.

Study: TH Investigators:	Pain Model: Dental Study Design: mi, sd, db, r, p* Duration: 8 hours Tx: Tramadol (TR) 100 and 50 mg Aspirin 650 mg/Codeine Phosphate 60 mg (ASA/Codeine) Codeine Sulfate 60 mg (Codeine) Placebo
A multiple investigator, randomized, double-blind, single-dose, parallel group, outpatient study of tramadol hydrochloride, ASA/codeine, codeine and placebo in patients with moderate or severe baseline pain following extraction of third molars.	
TR 100 mg: 51 pts. ASA/Codeine: 51 pts. Codeine: 50 pts. Placebo: 50 pts. TR 50 mg: 48 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* mi = multiple investigator; sd = single-dose; db = double-blind; r = randomized; p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

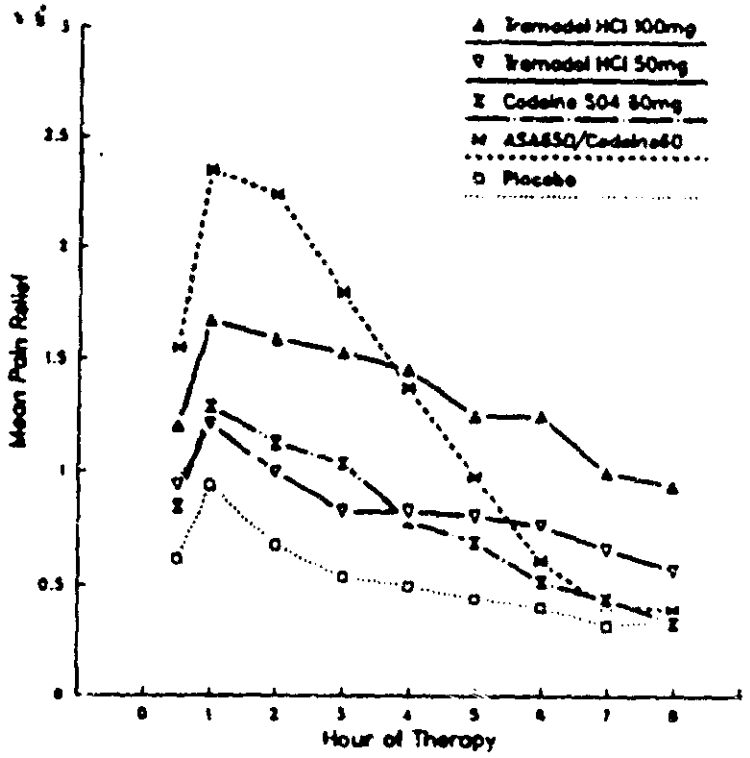
Of the 250 patients enrolled, 244 (98%) completed the study by either finishing the 8-hour protocol or by receiving a rescue analgesic, and six patients (2%) discontinued the study prematurely. Three patients were excluded from the analyses of efficacy: one tramadol 50 mg patient for a significant protocol violation and two codeine patients for not completing one hour (60 minutes) of evaluation.

ASA/codeine was statistically superior to placebo with respect to all efficacy variables. Codeine was numerically favored over placebo with respect to all efficacy variables, but was statistically superior to placebo with respect to TOTPAR (Total Pain Relief; sum of 0 - 3 and 0 - 4 hour scores) and time to remedication. Tramadol 100 mg was statistically superior to placebo with respect to all efficacy variables. Tramadol 50 mg was numerically favored over placebo with respect to all efficacy variables, but was statistically superior to placebo only with respect to SPID (0 - 6 hour scores). A significant tramadol does-response was observed for all of the efficacy variables.

Comparing the four active treatment groups with respect to all efficacy variables, tramadol 100 mg and ASA/codeine were numerically superior to the other treatments. These two treatments were statistically different with respect to TOTPAR (sum of 0 - 3 hour scores) and SPID (Sum of the Pain Intensity Difference; 0 - 3 hour scores). Mean TOTPAR scores numerically favored codeine over tramadol 50 mg during the 0 - 3 and 0 - 4 hour time intervals, while tramadol 50 mg was favored over codeine during the 0 - 6 and 0 - 8 hour time intervals. These two treatments were not statistically different with respect to TOTPAR scores. Mean SPID scores numerically favored tramadol 50 mg over codeine during all four time periods, although this was not statistically significant. The time to remedication for all active treatment groups was not statistically different.

This study showed model sensitivity, and tramadol 100 mg provided statistically superior pain relief to that of placebo. In this study, the order of relative efficacy over all variables was ASA/codeine and tramadol 100 mg > tramadol 50 mg > codeine > placebo. In comparing tramadol 100 mg and ASA/codeine, ASA/codeine had statistically significantly superior pain relief initially (0 - 3 hours). However, the overall profile of pain relief (0 - 8 hours) suggests a more prolonged effect for tramadol 100 mg over the entire study.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TH

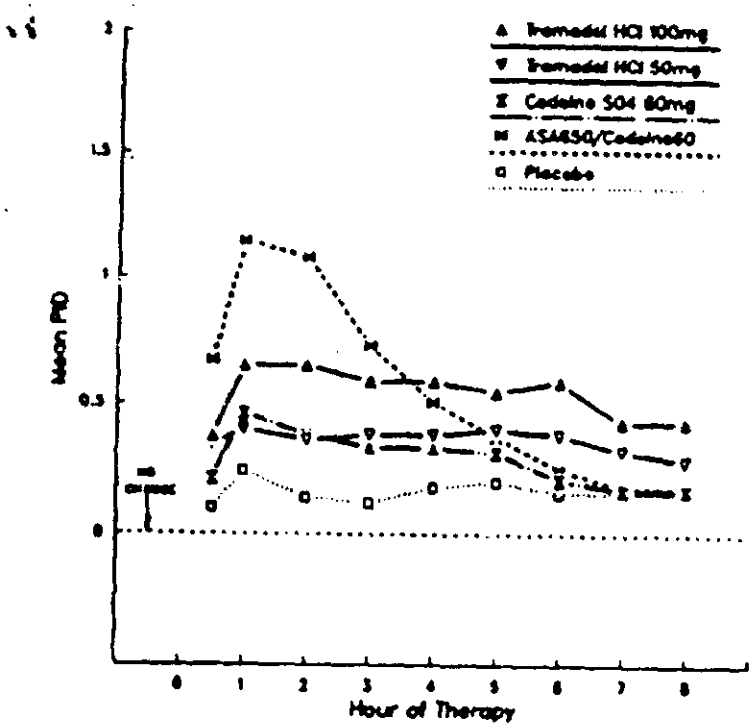


Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 100mg	4.55(3.25) B	8.51(7.01) A
TR 50mg	2.90(2.76) CD	5.31(5.97) B
ASA/COD	5.99(2.78) A	8.95(5.87) A
CO 60mg	3.24(3.12) C	5.24(6.05) B
Placebo	2.00(2.14) D	3.34(4.51) B
P-VALUE	0.000	0.000
RMS ERROR	2.837	5.939

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 100mg	1.20(0.96) 51 AB	1.67(1.11) 51 B	1.59(1.24) 44 B	1.53(1.39) 37 A	1.45(1.43) 33 A	1.25(1.43) 29 A	1.25(1.47) 27 A	1.00(1.39) 21 A	0.94(1.41) 19 A
TR 50mg	0.94(0.87) 47 BC	1.21(1.06) 47 C	1.00(1.06) 35 CD	0.83(1.13) 24 BC	0.83(1.29) 19 B	0.81(1.38) 16 ABC	0.77(1.42) 12 B	0.66(1.36) 10 AB	0.57(1.28) 9 AB
ASA/COD	1.55(1.14) 51 A	2.35(1.15) 51 A	2.24(1.14) 48 A	1.80(1.30) 44 A	1.37(1.36) 37 A	0.98(1.32) 23 AB	0.61(1.20) 14 B	0.41(1.08) 9 B	0.39(1.06) 7 B
CO 60mg	0.85(0.97) 48 BC	1.29(1.11) 48 C	1.13(1.14) 40 C	1.04(1.29) 30 B	0.79(1.15) 23 B	0.69(1.19) 18 BC	0.52(1.03) 14 B	0.44(0.99) 10 B	0.33(0.97) 6 B
Placebo	0.62(0.78) 50 C	0.94(0.84) 50 C	0.68(0.87) 32 D	0.54(0.89) 20 C	0.50(0.99) 13 B	0.44(0.93) 12 C	0.40(0.95) 9 B	0.32(0.91) 7 B	0.34(0.94) 7 B
P-VALUE	0.000	0.000	0.000	0.000	0.000	0.020	0.006	0.027	0.041
RMS ERROR	0.952	1.059	1.098	1.212	1.256	1.261	1.230	1.160	1.147

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TH

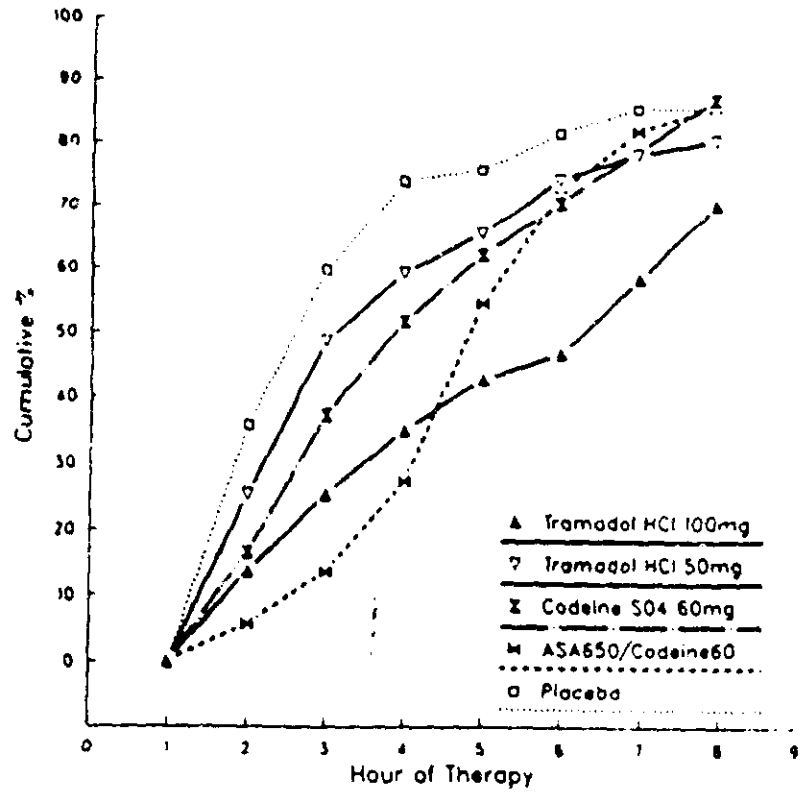


Treatment	SPID (extrapolated) 3-hour	6-hour
TR 100mg	1.75(1.63) B	3.47(3.35) AB
TR 50mg	1.12(1.83) BC	2.29(2.67) BC
ASA/COD	2.71(2.07) A	3.84(3.52) A
CO 60mg	1.04(2.06) BC	1.90(3.41) CD
Placebo	0.43(1.29) C	0.97(2.49) D
P-VALUE	0.000	0.000
RMS ERROR	1.796	3.309

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 100mg	0.37(0.60) 51 B	0.65(0.72) 51 B	0.65(0.69) 44 B	0.59(0.75) 37 AB	0.59(0.75) 33 A	0.55(0.76) 29	0.59(0.75) 27 A	0.43(0.70) 21	0.43(0.73) 19
TR 50mg	0.34(0.67) 47 B	0.40(0.77) 47 BC	0.36(0.76) 35 BC	0.38(0.64) 24 BC	0.38(0.77) 19 AB	0.40(0.80) 16	0.38(0.77) 12 AB	0.32(0.73) 10	0.28(0.71) 9
ASA/COD	0.67(0.74) 51 A	1.14(0.85) 51 A	1.08(0.84) 48 A	0.73(0.90) 44 A	0.51(0.86) 37 A	0.37(0.69) 23	0.25(0.59) 14 B	0.18(0.52) 9	0.18(0.52) 7
CO 60mg	0.21(0.82) 48 B	0.46(0.85) 48 BC	0.38(0.73) 40 BC	0.33(0.75) 30 BC	0.33(0.60) 23 AB	0.21(0.62) 18	0.21(0.50) 14 B	0.17(0.48) 10	0.17(0.52) 6
Placebo	0.10(0.61) 50 B	0.24(0.66) 50 C	0.14(0.61) 32 C	0.12(0.52) 20 C	0.18(0.52) 13 B	0.20(0.49) 12	0.16(0.47) 9 B	0.16(0.51) 7	0.16(0.51) 7
P-VALUE	0.001	0.000	0.000	0.000	0.043	0.134	0.006	0.086	0.120
RMS ERROR	0.693	0.772	0.731	0.726	0.711	0.681	0.629	0.594	0.605

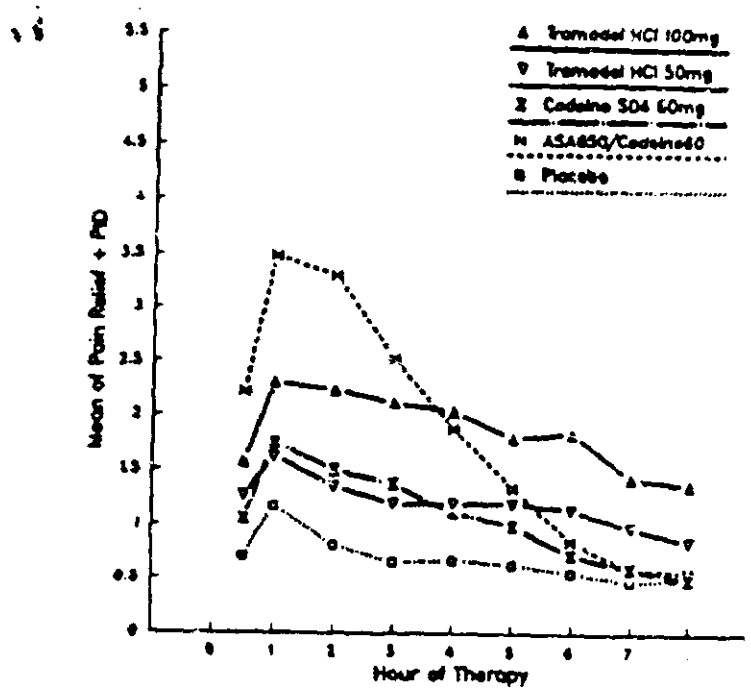
CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TH



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour	7-hour	8-hour
TR 100mg	51(100.0%)	44(86.3%)	38(74.5%)	33(64.7%)	29(56.9%)	27(52.9%)	21(41.2%)	15(29.4%)
TR 50mg	47(100.0%)	35(74.5%)	24(51.1%)	19(40.4%)	16(34.0%)	12(25.5%)	10(21.3%)	9(19.1%)
ASA/COD	51(100.0%)	48(94.1%)	44(86.3%)	37(72.5%)	23(45.1%)	14(27.5%)	9(17.6%)	7(13.7%)
CO 60mg	48(100.0%)	40(83.3%)	30(62.5%)	23(47.9%)	18(37.5%)	14(29.2%)	10(20.8%)	6(12.5%)
Placebo	50(100.0%)	32(64.0%)	20(40.0%)	13(26.0%)	12(24.0%)	9(18.0%)	7(14.0%)	7(14.0%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TH



Treatment	SPRID (extrapolated) 3-hour		6-hour	
TR 100mg	6.29(4.63)	B	11.98(9.97)	A
TR 50mg	4.02(4.43)	CD	7.60(9.45)	B
ASA/COD	8.70(4.61)	A	12.79(9.11)	A
CO 60mg	4.28(4.89)	C	7.14(9.15)	B
Placebo	2.43(3.22)	D	4.31(6.79)	B
P-VALUE	0.000		0.000	
RMS ERROR	4.392		8.959	

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 100mg	1.57(1.45) 51 B	2.31(1.73) 51 B	2.24(1.81) 44 B	2.12(2.05) 37 A	2.04(2.10) 33 A	1.80(2.09) 29 A	1.84(2.16) 27 A	1.43(2.01) 21 A	1.37(2.07) 19 A
TR 50mg	1.28(1.44) 47 BC	1.62(1.75) 47 C	1.36(1.74) 35 C	1.21(1.69) 24 B	1.21(2.01) 19 BC	1.21(2.14) 16 AB	1.15(2.16) 12 AB	0.98(2.06) 10 AB	0.85(1.97) 9 AB
ASA/COD	2.22(1.77) 51 A	3.49(1.90) 51 A	3.31(1.88) 48 A	2.53(2.10) 44 A	1.88(2.13) 37 AB	1.35(1.96) 23 AB	0.86(1.77) 14 B	0.59(1.58) 9 B	0.57(1.55) 7 B
CO 60mg	1.06(1.68) 48 BC	1.75(1.82) 48 BC	1.50(1.76) 40 C	1.38(1.93) 30 B	1.13(1.68) 23 C	1.00(1.76) 18 B	0.73(1.50) 14 B	0.60(1.41) 10 B	0.50(1.47) 6 B
Placebo	0.72(1.29) 50 C	1.18(1.37) 50 C	0.82(1.37) 32 C	0.66(1.32) 20 B	0.68(1.46) 13 C	0.64(1.40) 12 B	0.56(1.39) 9 B	0.48(1.40) 7 B	0.50(1.43) 7 B
P-VALUE	0.000	0.000	0.000	0.000	0.002	0.035	0.005	0.035	0.053
RMS ERROR	1.537	1.722	1.721	1.843	1.897	1.886	1.821	1.715	1.719

PROTOCOL TH

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	19	15	26
TR 50mg	24	18	35
ASA/COD	14	11	17
CO 60mg	28	19	52
Placebo	42	28	85

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	6:00	3:45	7:10
TR 50mg	2:50	2:15	4:20
ASA/COD	4:40	4:10	5:20
CO 60mg	3:30	2:40	4:50
Placebo	2:25	1:50	3:00

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Demographic Frequencies and Means

Drug	Sex M	Sex F	Race Wht	Race Blk	Race Oth	Mean Age	Mean Weight	Baseline Pain None	Slight	Moderate	Severe	Surgical Procedure Dental Surgery	Reason for Discontinuation: Adv Exp	Patient Choice	Protocol Violation	Other
Tramadol 100 MG	25	26	49	0	2	19.84	143.37	0	0	33	18	51	0	0	0	2
Tramadol 50 MG	22	26	47	0	1	20.33	144.38	0	0	30	18	48	0	0	1	1
Codeine SO4	23	27	45	0	1	20.56	145.34	0	0	33	17	50	0	0	0	0
ASA / Codeine	25	26	48	0	3	20.76	143.47	0	0	34	17	51	0	0	0	1
Placebo	23	27	50	0	0	19.40	146.94	0	0	35	15	50	1	0	0	0

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This display includes all patients, including those who were not included in the analysis.

Study: TI Investigators:	Pain Model: Dental Study Design: mi, sd, db, r, p* Duration: 8 hours Tx: Tramadol (TR) 100 and 50 mg Aspirin 650mg/Codeine Phosphate 60 mg (ASA/Codeine) Codeine Sulfate 60 mg (Codeine) Placebo
A multiple investigator, randomized, double-blind, single-dose, parallel group, outpatient study of tramadol hydrochloride, ASA/codeine, codeine and placebo in patients with moderate or severe baseline pain following extraction of third molars.	
TR 100 mg: 51 pts. ASA/Codeine: 49 pts. Codeine: 50 pts. Placebo: 50 pts. TR 50 mg: 51 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* mi = multiple investigator; sd = single-dose; db = double-blind; r = randomized; p = parallel

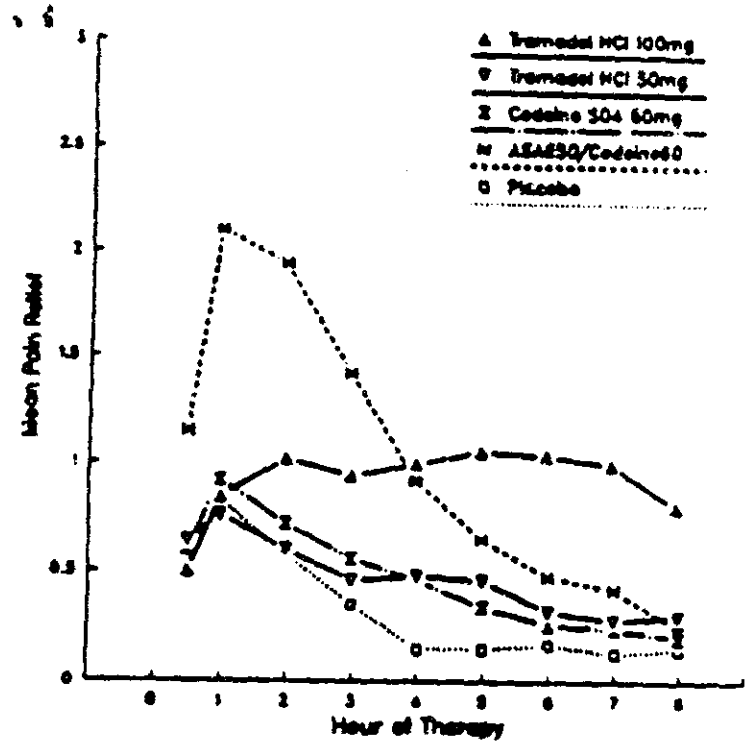
NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

Of the 251 patients enrolled, 244 (97%) completed the study by either finishing the 8-hour protocol or by receiving a rescue analgesic, and seven patients (3%) discontinued the study prematurely. Five patients were excluded from the analyses of efficacy: one tramadol 100 mg patient, one tramadol 50 mg patient, one placebo patient for not completing one hour (60 minutes) of evaluation, one ASA/codeine patient for a significant protocol violation and one placebo patient because no baseline pain was recorded.

ASA/codeine was statistically superior to placebo with respect to all efficacy variables. Codeine was numerically favored over placebo with respect to all efficacy variables except SPID (Sum of Pain Intensity Difference; 0 - 3 hour scores), although this was never statistically significant. Tramadol 100 mg was statistically superior to placebo with respect to TOTPAR (Total Pain Relief; sum of 0 - 4, 0 - 6, and 0 - 8 hour scores) and SPID (0 - 4, 0 - 6, and 0 - 8 hour scores). Tramadol 50 mg was not statistically superior to placebo with respect to any efficacy variables. There was a statistically significant tramadol dose-response for all of the efficacy variables except TOTPAR (sum of 0 - 3 hour scores) and SPID (0 - 3 and 0 - 4 hour scores). Comparing the four active treatment groups with respect to all efficacy variables, tramadol 100 mg and ASA/codeine were numerically superior to the other treatments. ASA/codeine was statistically superior to all of the other active treatment groups with respect to TOTPAR (sum of 0 - 3 and 0 - 4 hour scores) and SPID (0 - 3 and 0 - 4, hour scores). During the 0 - 6 and 0 - 8 hour time periods, tramadol 100 mg and ASA/codeine were not statically different, and both were statistically superior to tramadol 50 mg and codeine with respect to TOTPAR and SPID. Mean TOTPAR scores numerically favored codeine over tramadol 50 mg during the 0 - 3, 0 - 4, and 0 - 6 hour time intervals, while tramadol 50 mg was favored over codeine during the 0 - 8 hour time interval. These two treatments were not statistically different with respect to TOTPAR scores. Mean SPID scores numerically favored tramadol 50 mg over codeine during both time periods, although this was not statistically significant. ASA/codeine was not statistically different from tramadol 100 mg with respect to time to remedication, but was statistically superior to tramadol 50 mg codeine.

This study showed model sensitivity, and tramadol 100 mg provided pain relief statistically superior to that of placebo. In this study, the order of relative efficacy over all variables was ASA/codeine > tramadol 100 mg > tramadol 50 mg and codeine > placebo.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TI



Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 100mg	2.63(2.90) B	5.73(7.05) A
TR 50mg	1.76(2.61) B	3.02(5.38) B
ASA/COD	4.98(3.55) A	7.02(6.68) A
CO 60mg	2.04(2.54) B	3.10(4.80) B
Placebo	1.61(2.27) B	2.07(3.79) B
P-VALUE	0.000	0.000
RMS ERROR	2.803	5.672

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 100mg	0.50(0.76) 50 B	0.84(0.93) 50 B	1.02(1.22) 29 B	0.94(1.32) 19 A	1.00(1.46) 18 A	1.06(1.54) 18 A	1.04(1.60) 17 A	1.00(1.62) 16 A	0.80(1.48) 13 A
TR 50mg	0.64(0.88) 50 B	0.76(1.04) 50 B	0.60(1.03) 20 B	0.46(1.05) 11 C	0.48(1.11) 10 BC	0.46(1.11) 8 BC	0.32(0.87) B	0.28(0.86) 6 B	0.30(0.93) 5 B
ASA/COD	1.15(1.03) 48 A	2.10(1.31) 48 A	1.94(1.44) 40 A	1.42(1.54) 35 A	0.92(1.43) 22 AB	0.65(1.34) 14 AB	0.48(1.20) 7 B	0.42(1.11) 7 B	0.25(0.91) 6 B
CO 60mg	0.60(0.81) 50 B	0.92(0.99) 50 B	0.72(1.03) 30 B	0.56(0.97) 17 BC	0.46(1.03) 9 BC	0.34(0.92) 7 BC	0.26(0.83) 6 B	0.24(0.82) 4 B	0.20(0.73) 4 B
Placebo	0.52(0.77) 48 B	0.83(0.95) 48 B	0.58(1.01) 24 B	0.35(0.86) 13 C	0.15(0.65) 5 C	0.15(0.65) 5 C	0.17(0.66) 5 B	0.13(0.64) 4 B	0.15(0.65) 4 B
P-VALUE	0.001	0.000	0.000	0.000	0.002	0.002	0.001	0.001	0.008
RMS ERROR	0.855	1.052	1.155	1.174	1.175	1.158	1.088	1.066	0.988

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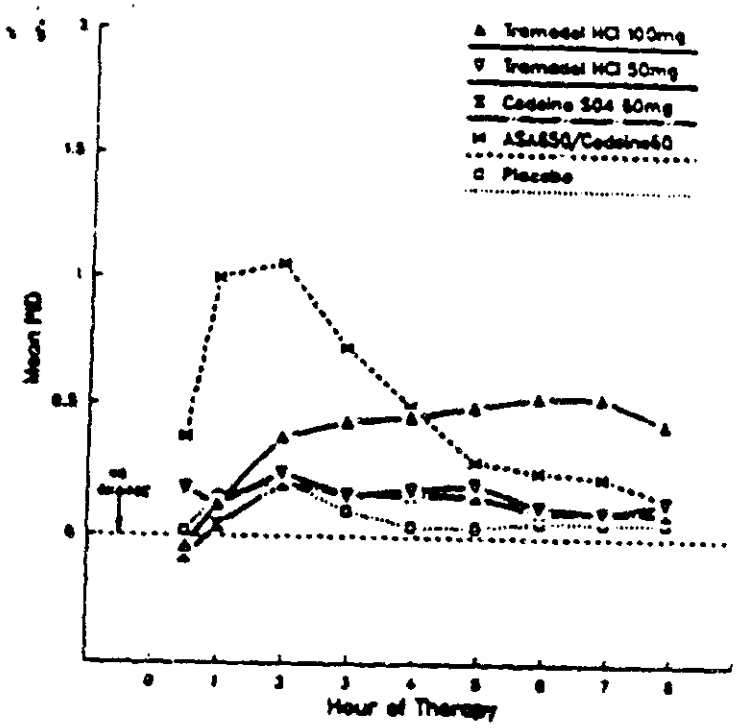
MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TI

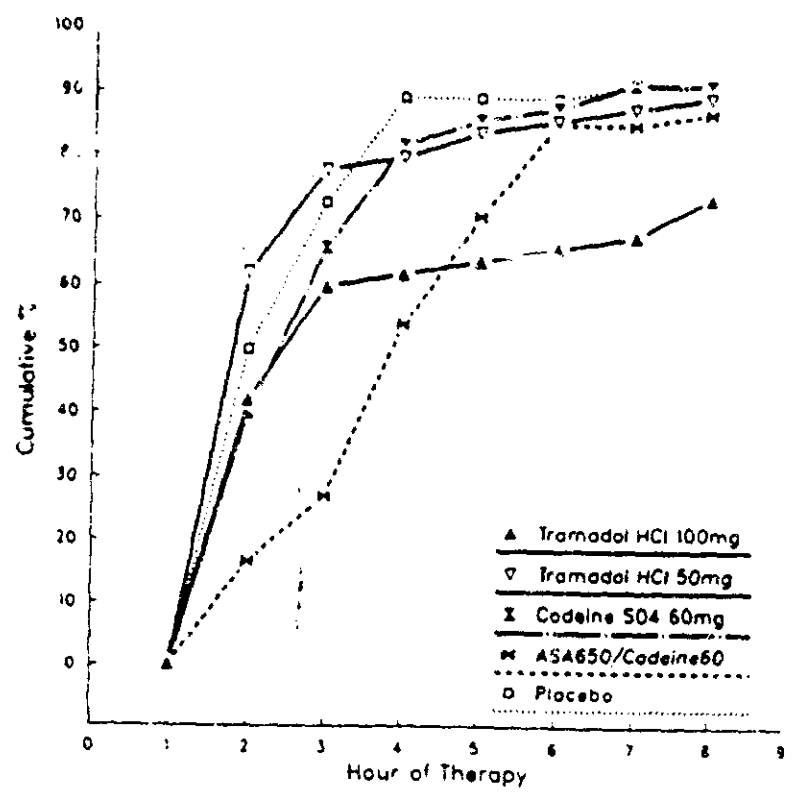


Treatment	SPID (extrapolated) 3-hour	6-hour
TR 100mg	0.86(1.91) B	2.36(4.25) A
TR 50mg	0.55(1.17) B	1.05(2.22) B
ASA/COD	2.48(2.65) A	3.52(4.48) A
CO 60mg	0.34(1.48) B	0.76(2.55) B
Placebo	0.40(1.17) B	0.54(1.85) B
P-VALUE	0.000	0.000
RMS ERROR	1.760	3.252

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 100mg	-.04(0.49) 50 C	0.12(0.77) 50 B	0.38(0.83) 29 B	0.44(0.73) 19 B	0.46(0.81) 18 A	0.50(0.86) 18 A	0.54(0.93) 17 A	0.54(0.93) 16 A	0.44(0.91) 13 A
TR 50mg	0.18(0.56) 50 AB	0.12(0.77) 50 B	0.24(0.48) 20 B	0.16(0.37) 11 C	0.18(0.48) 10 B	0.20(0.49) 8 BC	0.12(0.39) 7 B	0.10(0.42) 6 B	0.14(0.45) 5 B
ASA/COD	0.38(0.64) 48 A	1.00(0.97) 48 A	1.06(1.14) 40 A	0.73(1.11) 35 A	0.50(0.92) 22 A	0.29(0.82) 14 AB	0.25(0.67) 7 B	0.23(0.66) 7 B	0.15(0.50) 6 B
CO 60mg	-.08(0.53) 50 C	0.04(0.78) 50 B	0.20(0.73) 30 B	0.16(0.51) 17 C	0.16(0.47) 9 B	0.16(0.47) 7 BC	0.10(0.42) 6 B	0.10(0.36) 4 B	0.10(0.46) 4 B
Placebo	0.02(0.53) 48 BC	0.15(0.80) 48 B	0.21(0.50) 24 B	0.10(0.37) 13 C	0.04(0.29) 5 B	0.04(0.29) 5 C	0.06(0.32) 5 B	0.06(0.32) 4 B	0.06(0.32) 4 B
P-VALUE	0.000	0.000	0.000	0.000	0.001	0.006	0.000	0.000	0.009
RMS ERROR	0.551	0.821	0.772	0.675	0.639	0.628	0.590	0.586	0.568

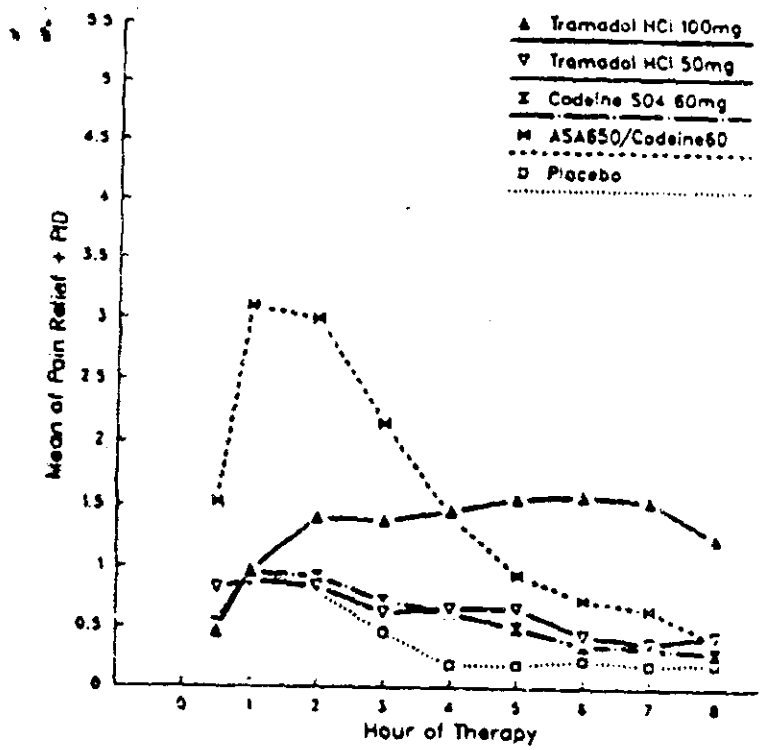
CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TI



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour	7-hour	8-hour
TR 100mg	50(100.0%)	29(58.0%)	20(40.0%)	19(38.0%)	18(36.0%)	17(34.0%)	16(32.0%)	13(26.0%)
TR 50mg	50(100.0%)	19(38.0%)	11(22.0%)	10(20.0%)	8(16.0%)	7(14.0%)	6(12.0%)	5(10.0%)
ASA/COD	48(100.0%)	40(83.3%)	35(72.9%)	22(45.8%)	14(29.2%)	7(14.6%)	7(14.6%)	6(12.5%)
CO 60mg	50(100.0%)	30(60.0%)	17(34.0%)	9(18.0%)	7(14.0%)	6(12.0%)	4(8.0%)	4(8.0%)
Placebo	48(100.0%)	24(50.0%)	13(27.1%)	5(10.4%)	5(10.4%)	5(10.4%)	4(8.3%)	4(8.3%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TI



Treatment	SPRID (extrapolated) 3-hour		6-hour	
TR 100mg	3.48(4.57)	B	8.09(10.95)	A
TR 50mg	2.31(3.66)	B	4.07(7.46)	B
ASA/COD	7.46(5.95)	A	10.54(10.86)	A
CO 60mg	2.38(3.81)	B	3.86(7.13)	B
Placebo	2.01(3.28)	B	2.61(5.49)	B
P-VALUE	0.000		0.000	
RMS ERROR	4.351		8.656	

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 100mg	0.46(1.09) 50 B	0.95(1.58) 50 B	1.40(1.96) 29 B	1.38(1.98) 19 B	1.46(2.19) 18 A	1.56(2.35) 18 A	1.58(2.49) 17 A	1.54(2.50) 16 A	1.24(2.35) 13 A
TR 50mg	0.32(1.34) 50 B	0.88(1.71) 50 B	0.84(1.45) 20 B	0.62(1.40) 11 C	0.66(1.56) 10 B	0.66(1.59) 8 BC	0.44(1.21) 7 B	0.38(1.24) 6 B	0.44(1.37) 5 B
ASA/COD	1.52(1.58) 48 A	3.10(2.17) 48 A	3.00(2.47) 40 A	2.15(2.56) 35 A	1.42(2.27) 22 A	0.94(2.13) 14 AB	0.73(1.85) 7 B	0.65(1.74) 7 B	0.40(1.38) 6 B
CO 60mg	0.52(1.18) 50 B	0.96(1.64) 50 B	0.92(1.66) 30 B	0.72(1.39) 17 BC	0.62(1.46) 9 B	0.50(1.36) 7 BC	0.36(1.21) 6 B	0.34(1.17) 4 B	0.30(1.15) 4 B
Placebo	0.54(1.17) 48 B	0.98(1.63) 48 B	0.79(1.46) 24 B	0.46(1.18) 13 C	0.19(0.91) 5 B	0.19(0.91) 5 C	0.23(0.97) 5 B	0.19(0.96) 4 B	0.21(0.97) 4 B
P-VALUE	0.000	0.000	0.000	0.000	0.001	0.002	0.009	0.000	0.007
RMS ERROR	1.282	1.755	1.836	1.771	1.750	1.748	1.647	1.624	1.526

PROTOCOL TI

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	65	39	198
TR 50mg	37	25	68
ASA/COD	20	15	28
CO 60mg	58	35	162
Placebo	55	34	146

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	2:10	1:45	3:25
TR 50mg	1:40	1:30	1:55
ASA/COD	3:40	3:05	4:20
CO 60mg	2:10	1:45	2:45
Placebo	1:50	1:35	2:25

Tramadol Protocol TI

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Demographic Frequencies and Means

Drug	Sex M	Sex F	Race Wht	Race Blk	Race Oth	Mean Age	Mean Weight	Baseline Pain None	Slight	Moderate	Severe	Surgical Procedure Dental Surgery	Reason for Discontinuation: Adv Exp	Patient Choice	Protocol Violation	Other
Tramadol 100 MG	26	25	38	1	12	24.45	154.24	0	0	36	15	51	0	2	0	1
Tramadol 50 MG	23	28	44	0	7	23.16	153.02	0	0	29	22	51	0	0	0	0
Codeine SO4	21	29	37	1	12	23.04	142.62	0	0	40	10	50	1	0	0	0
ASA / Codeine	14	35	34	1	14	23.73	144.61	0	0	32	17	49	0	0	1	0
Placebo	28	22	40	1	9	22.44	151.02	0	0	32	17	50	0	0	0	2

This display includes all patients, including those who were not included in the analysis.

Study: TI2 Investigators:	Pain Model: Dental Study Design: si, r, db, sd, p* Duration: 8 hours Tx: Tramadol (TR) 150 mg and 75 mg Acetaminophen 650 mg/Propoxyphene napsylate 100 mg (APAP/propoxyphene) Codeine Sulfate 60 mg (Codeine) Placebo
A single investigator, randomized, double-blind, single-dose, parallel group study of tramadol hydrochloride 150 mg and 75 mg (tramadol), acetaminophen 650 mg with propoxyphene napsylate 100 mg (APAP/propoxyphene), codeine sulfate 60 mg (codeine) and placebo in outpatients with moderate or severe baseline pain following dental extractions.	
TR 150 mg: 47 pts. APAP/propoxyphene: 49 pts. Codeine: 50 pts. Placebo: 50 pts. TR 75 mg: 49 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* si = single investigator, r = randomized, db = double-blind, sd = single-dose, p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

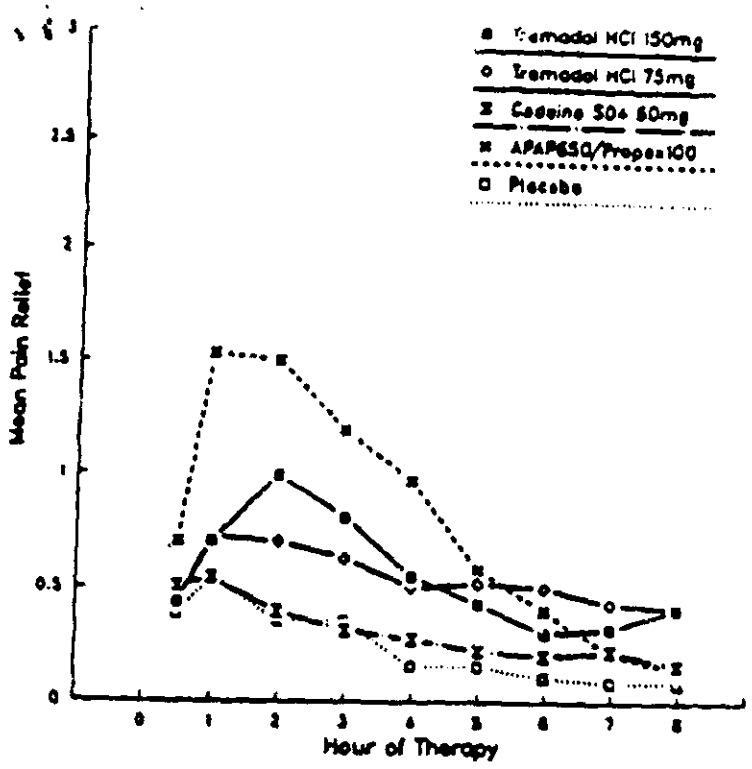
Of the 245 patients enrolled, 228 (93%) completed the study either by finishing the 8-hour protocol or receiving a rescue analgesic, 15 patients (6%) discontinued the study prematurely, and two patients (1%) were lost to follow-up with no post-baseline data recorded. Twenty-one patients were excluded from the analyses of efficacy: 12 patients (one tramadol 150 mg, three tramadol 75 mg, three APAP/propoxyphene, one codeine and four placebo) for not completing one hour (60 minutes) of evaluation, eight patients (one tramadol 150 mg, three APAP/propoxyphene, two codeine and two placebo) because of significant protocol violations and one APAP/propoxyphene patient for sleeping during the half-hour through the 4-hour evaluations. A total of 222 patients were included in the analyses of efficacy.

APAP/propoxyphene was statistically superior to placebo with respect to all efficacy variables except SPID (Sum of Pain Intensity Difference; 0 - 8 hour scores) and time to remedication. Codeine was numerically favored over placebo with respect to all efficacy variables except SPID (0 - 3 hour scores), although this was not statistically significant.

Tramadol 150 mg was numerically favored over placebo with respect to all efficacy variables, but was statistically superior to placebo only with respect to TOTPAR (sum of 0 - 4 hour scores). Tramadol 75 mg was numerically favored over placebo with respect to all efficacy variables, although this was not statistically significant. There was no significant tramadol dose-response for TOTPAR (sum of 0 - 3, 0 - 4, and 0 - 6 hour scores), or for SPID (0 - 3 and 0 - 6 hour scores).

Although this study showed model sensitivity, tramadol 150 mg did not separate from placebo for any efficacy variables except for TOTPAR (sum of 0 - 4 hour scores). APAP/propoxyphene was statistically superior to the other active treatments with respect to TOTPAR (sum of 0 - 3 and 0 - 4 hour scores) and SPID (0 - 3 and 0 - 6 hour scores), and was statistically superior to tramadol 75 mg and codeine 60 mg for TOTPAR (sum of 0 - 6 hour scores). There were no statistically significant differences among tramadol 150 mg, tramadol 75 mg and codeine. There was no significant overall treatment difference with respect to SPID (0 - 8 hour scores) and time to remedication; therefore, no further tests were performed for these two variables.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TI2

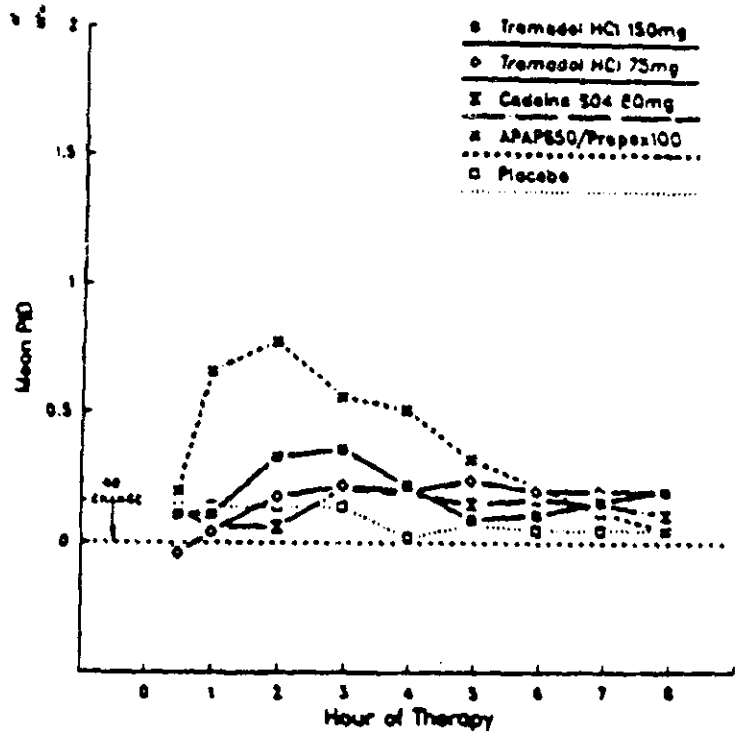


Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 150mg	2.40(3.22) B	3.71(5.88) AB
TR 75mg	1.94(2.96) B	3.50(5.93) B
APAP/PROP	3.83(3.55) A	5.80(6.80) A
CO 60mg	1.26(2.40) B	1.98(4.39) B
Placebo	1.19(2.29) B	1.63(3.95) B
P-VALUE	0.000	0.004
RMS ERROR	2.907	5.462

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 150mg	0.44(0.89) 45	0.71(1.12) 45 B	1.00(1.30) 36 B	0.82(1.27) 21 AB	0.56(1.24) 14 AB	0.44(1.12) 11	0.31(1.02) 7	0.33(1.09) 6	0.42(1.22) 6
TR 75mg	0.44(0.84) 44	0.73(1.19) 45 B	0.71(1.16) 30 BC	0.64(1.13) 15 B	0.51(1.14) 11 AB	0.53(1.14) 10	0.51(1.12) 10	0.44(1.08) 8	0.42(1.08) 7
APAP/PROP	0.71(0.96) 41	1.54(1.34) 40 A	1.51(1.55) 34 A	1.20(1.62) 23 A	0.98(1.62) 15 A	0.59(1.32) 9	0.41(1.09) 7	0.22(0.79) 5	0.15(0.65) 2
CO 60mg	0.51(1.12) 47	0.55(1.04) 46 B	0.40(0.90) 33 C	0.32(0.93) 13 B	0.28(0.90) 6 B	0.23(0.79) 5	0.21(0.72) 5	0.23(0.87) 4	0.17(0.79) 3
Placebo	0.39(0.72) 44	0.55(0.90) 44 B	0.36(0.84) 28 C	0.36(1.01) 14 B	0.16(0.75) 5 B	0.16(0.75) 2	0.11(0.62) 2	0.09(0.60) 1	0.09(0.60) 1
P-VALUE	0.543	0.000	0.000	0.005	0.015	0.231	0.285	0.436	0.224
RMS ERROR	0.918	1.125	1.170	1.206	1.157	1.040	0.934	0.906	0.889

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TI2

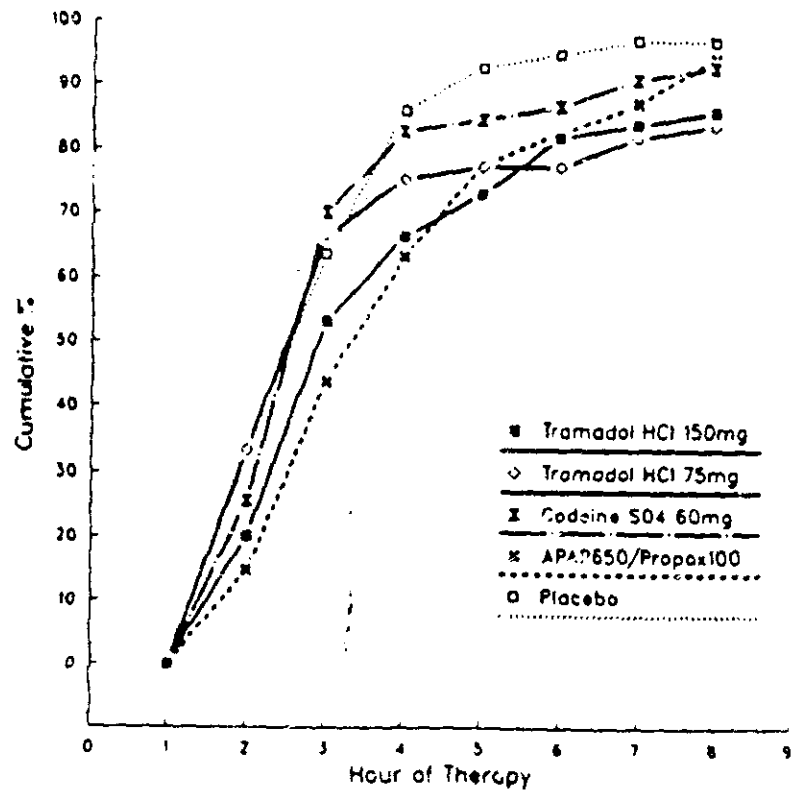


Treatment	SPID (extrapolated) 3-hour		6-hour	
TR 150mg	0.8[illegible](1.99)	B	1.22(3.30)	B
TR 75mg	0.40(1.48)	B	1.04(2.63)	B
APAP/PROP	1.77(2.18)	A	2.82(4.21)	A
CO 60mg	0.37(1.89)	B	0.88(3.35)	B
Placebo	0.39(1.34)	B	0.52(2.11)	B
P-VALUE	0.001		0.013	
RMS ERROR	1.799		3.182	

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 150mg	0.11(0.57) 45	0.11(0.75) 45 B	0.33(0.85) 36 B	0.36(0.74) 21	0.22(0.64) 14 B	0.09(0.63) 11	0.11(0.57) 7	0.16(0.64) 6	0.20(0.69) 6
TR 75mg	-.04(0.52) 44	0.04(0.82) 45 B	0.18(0.65) 30 B	0.22(0.47) 15	0.20(0.55) 11 B	0.24(0.53) 10	0.20(0.55) 10	0.20(0.50) 8	0.20(0.50) 7
APAP/PROP	0.20(0.51) 41	0.66(0.82) 40 A	0.78(1.01) 34 A	0.56(1.03) 23	0.51(1.03) 15 A	0.32(0.82) 9	0.22(0.65) 7	0.12(0.40) 5	0.05(0.22) 2
CO 60mg	0.13(0.71) 47	0.06(0.79) 46 B	0.06(0.76) 33 B	0.21(0.69) 13	0.19(0.65) 6 B	0.15(0.55) 5	0.17(0.56) 5	0.15(0.55) 4	0.11(0.48) 3
Placebo	0.09(0.36) 44	0.14(0.67) 44 B	0.14(0.55) 28 B	0.14(0.55) 14	0.02(0.40) 5 B	0.07(0.33) 2	0.05(0.30) 2	0.05(0.30) 1	0.05(0.30) 1
P-VALUE	0.351	0.001	0.000	0.059	0.024	0.245	0.557	0.672	0.332
RMS ERROR	0.550	0.773	0.779	0.716	0.677	0.590	0.540	0.496	0.474

CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TI2



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	-hour	5-hour	6-hour	7-hour	8-hour
TR 150mg	45(100.0%)	36(80.0%)	21(46.7%)	15(33.3%)	12(26.7%)	8(17.8%)	7(15.6%)	6(13.3%)
TR 75mg	45(100.0%)	30(66.7%)	15(33.3%)	11(24.4%)	10(22.2%)	10(22.2%)	8(17.8%)	7(15.6%)
APAP/PROP	41(100.0%)	35(85.4%)	23(56.1%)	15(36.6%)	9(22.0%)	7(17.1%)	5(12.2%)	2(4.9%)
CO 60mg	47(100.0%)	35(74.5%)	14(29.8%)	8(17.0%)	7(14.9%)	6(12.8%)	4(8.5%)	3(6.4%)
Placebo	44(100.0%)	29(65.9%)	16(36.4%)	6(13.6%)	3(6.8%)	2(4.5%)	1(2.3%)	1(2.3%)

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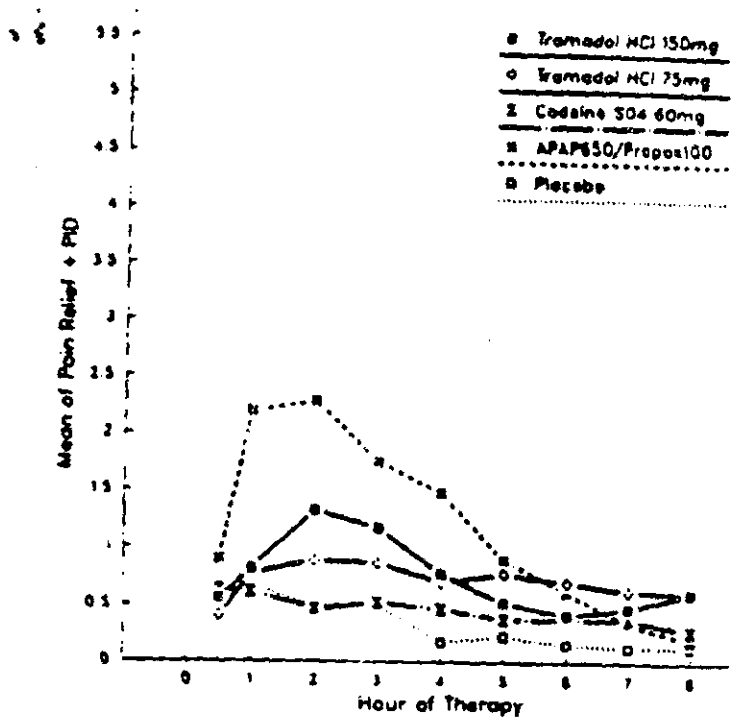
MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TI2



Treatment	SPRID (extrapolated) 3-hour		6-hour	
TR 150mg	3.20(5.03)	B	4.93(8.94)	B
TR 75mg	2.34(4.28)	B	4.54(8.42)	B
APAP/PROP	5.60(5.62)	A	8.62(10.86)	A
CO 60mg	1.63(4.17)	B	2.86(7.68)	B
Placebo	1.58(3.46)	B	2.15(5.93)	B
P-VALUE	0.000		0.006	
RMS ERROR	4.554		8.473	

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 150mg	0.56(1.36) 45	0.82(1.77) 45 B	1.33(2.07) 36 B	1.18(1.93) 21 AB	0.78(1.83) 14 AB	0.53(1.69) 11	0.42(1.56) 7	0.49(1.70) 6	0.62(1.89) 6
TR 75mg	0.40(1.19) 44	0.78(1.93) 45 B	0.89(1.72) 30 BC	0.87(1.56) 15 B	0.71(1.66) 11 B	0.78(1.65) 10	0.71(1.63) 10	0.64(1.57) 8	0.62(1.57) 7
APAP/PROP	0.90(1.37) 41	2.20(2.11) 40 A	2.29(2.51) 34 A	1.76(2.59) 23 A	1.49(2.51) 15 A	0.90(2.12) 9	0.63(1.71) 7	0.34(1.17) 5	0.20(0.87) 2
CO 60mg	0.64(1.76) 47	0.62(1.75) 46 B	0.47(1.57) 33 C	0.53(1.60) 13 B	0.47(1.54) 6 B	0.38(1.33) 5	0.38(1.28) 5	0.38(1.41) 4	0.28(1.17) 3
Placebo	0.48(0.95) 44	0.68(1.43) 44 B	0.50(1.30) 28 C	0.50(1.53) 14 B	0.18(1.11) 5 B	0.23(1.08) 2	0.16(0.91) 2	0.14(0.90) 1	0.14(0.90) 1
P-VALUE	0.490	0.000	0.000	0.012	0.017	0.271	0.405	0.518	0.253
RMS ERROR	1.360	1.808	1.869	1.869	1.801	1.600	1.444	1.386	1.348

PROTOCOL T12

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	54	31	199
TR 75mg	75	40	685
APAP/PROP	33	23	63
CO 60mg	47	26	242
Placebo	63	39	158

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	2:45	2:20	3:35
TR 75mg	2:20	1:55	2:50
APAP/PROP	3:05	2:30	3:55
CO 60mg	2:25	2:05	2:45
Placebo	2:20	1:50	2:55

Tramadol Protocol TI2

Demographic Frequencies and Means

Drug	Sex M	Sex F	Race Wht	Race Blk	Race Oth	Mean Age	Mean Weight	Baseline Pain None	Baseline Pain Slight	Baseline Pain Moderate	Baseline Pain Severe	Surgical Procedure Dental Surgery	Reason for Discontinuation Patient Choice	Reason for Discontinuation Protocol Violation	Reason for Discontinuation Other
Tramadol 150 MG	22	25	45	1	1	23.62	146.57	0	0	32	15	47	0	1	1
Tramadol 75 MG	24	25	41	7	0	22.43	149.08	0	0	29	19	49	0	0	1
Codeine SO4	26	24	44	5	1	23.60	155.84	0	0	24	25	50	0	2	1
APAP/Propoxyhene	23	26	44	2	2	21.12	139.16	0	0	28	18	49	0	3	4
Placebo	24	26	47	2	1	22.02	142.24	0	0	31	17	50	1	2	1

2900 00

This display includes all patients, including those who were not included in the analysis.

Study: TO Inve	Pain Model: Dental Pain Study Design: si, sd, db, r, p* Duration: 8 hours Tx: Tramadol (TR) 200 mg and 100 mg Codeine Sulfate 60 mg (Codeine) Placebo
A single investigator, randomized, double-blind, single-dose, parallel group study of tramadol hydrochloride 200 mg and 100 mg (tramadol), codeine sulfate 60 mg (codeine) and placebo in outpatients with moderate or severe baseline pain following dental surgery.	
TR 200 mg: 52 pts. Codeine: 50 pts. Placebo: 53 pts. TR 100 mg: 51 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* si = single investigator; sd = single-dose; db = double-blind; r = randomized; p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

Of the 206 patients enrolled, 200 (97%) completed the study either by finishing eight hours of evaluations or by receiving a rescue analgesic, and six patients (3%) discontinued the study prematurely. Six patients were excluded from all analyses of efficacy: in three patients (one tramadol 200 mg, one tramadol 100 mg and one codeine) remedication occurred less than 60 minutes postdose, two patients (one tramadol 200 mg and one codeine) used ice during the evaluation period and one codeine patient was unreliable and noncompliant. Partial data were excluded from an additional three placebo patients.

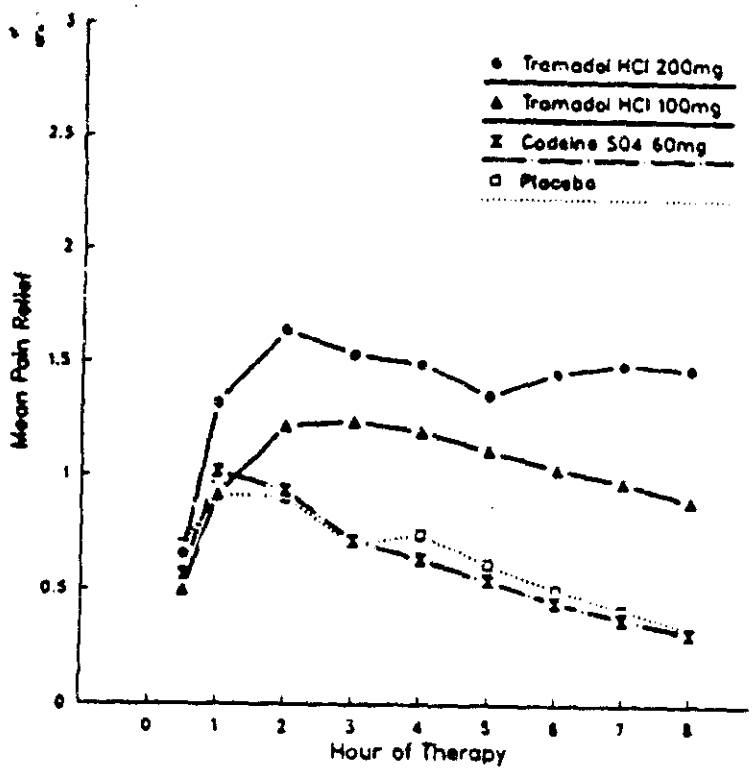
A significant tramadol dose-response was observed for TOTPAR (Total Pain Relief; sum of 0 - 8 hour score) and SPID (Sum of the Pain Intensity Differences; 0 - 3, 0 - 4, 0 - 6, and 0 - 8 hour scores), thus establishing model sensitivity.

Tramadol 200 mg was statistically superior to placebo with respect to all efficacy variables for which model sensitivity was established. Tramadol 100 mg was numerically favored over placebo with respect to all efficacy variables, although this was not statistically significant.

Comparing the three active treatment groups, tramadol 200 mg was statistically superior to codeine for TOTPAR (sum of 0 - 3, 0 - 6, and 0 - 8 hour scores) and SPID (0 - 3, 0 - 4, 0 - 6 and 0 - 8 hour scores). Mean SPID scores during the 0 - 3, 0 - 6, and 0 - 8 hour time periods in the tramadol 200 mg group were also statistically superior to those in the tramadol 100 mg group. Tramadol 200 mg was statistically superior to tramadol 100 mg and codeine with respect to patient global evaluation scores.

This study demonstrated model sensitivity, and tramadol 200 mg provided pain relief statistically superior to that of placebo. In this study, the order of relative efficacy over all variables was tramadol 200 mg > tramadol 100 mg > codeine and placebo.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TO

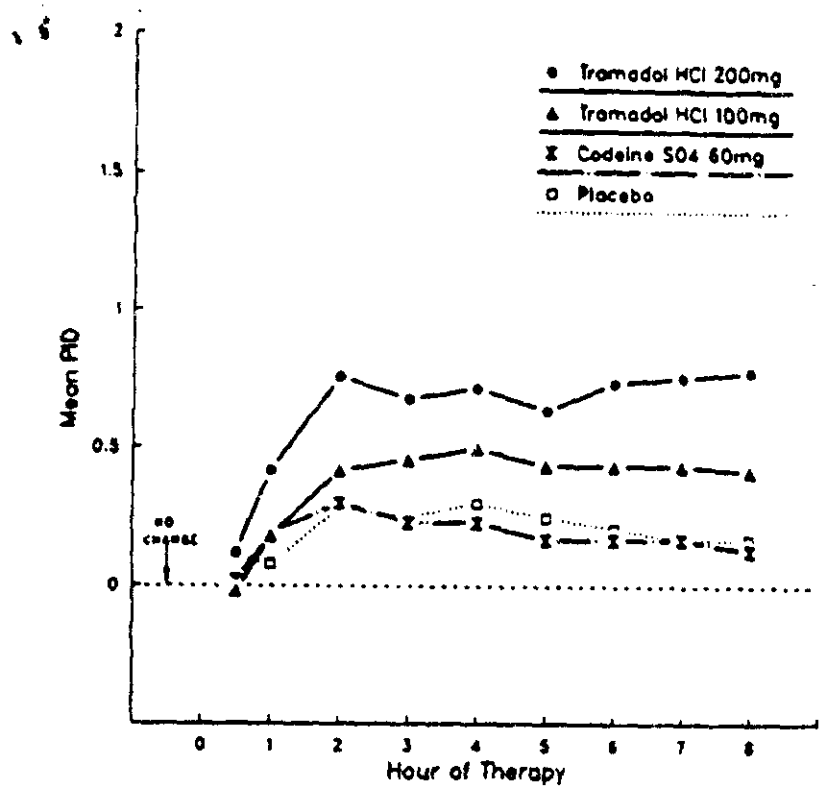


Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 200mg	4.17(3.46) A	8.49(7.75) A
TR 100mg	3.17(3.49) AB	6.53(7.62) AB
CO 60mg	2.46(3.00) B	4.10(5.68) B
Placebo	2.42(2.87) B	4.30(6.07) B
P-VALUE	0.022	0.004
RMS ERROR	3.211	6.850

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 200mg	0.66(0.87) 50	1.32(1.08) 49	1.64(1.51) 36 A	1.54(1.54) 29 A	1.50(1.63) 29 A	1.36(1.60) 25 A	1.46(1.72) 23 A	1.50(1.78) 23 A	1.48(1.81) 22 A
TR 100mg	0.50(0.68) 50	0.92(1.08) 50	1.22(1.49) 30 AB	1.24(1.49) 22 AB	1.20(1.50) 22 AB	1.12(1.55) 20 AB	1.04(1.58) 19 A	0.98(1.57) 16 A	0.90(1.57) 15 B
CO 60mg	0.57(0.83) 46	1.02(1.03) 47	0.94(1.24) 31 B	0.72(1.21) 19 B	0.64(1.17) 13 C	0.55(1.18) 12 C	0.45(1.12) 9 C	0.38(1.01) 7 B	0.32(0.96) 6 C
Placebo	0.70(0.93) 52	0.92(1.05) 53	0.91(1.21) 33 B	0.70(1.22) 21 B	0.75(1.31) 16 BC	0.62(1.20) 14 BC	0.51(1.12) 11 BC	0.42(1.08) 10 B	0.34(1.02) 8 C
P-VALUE	0.632	0.195	0.028	0.005	0.009	0.010	0.001	0.000	0.000
RMS ERROR	0.834	1.062	1.369	1.374	1.416	1.394	1.409	1.399	1.387

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TO

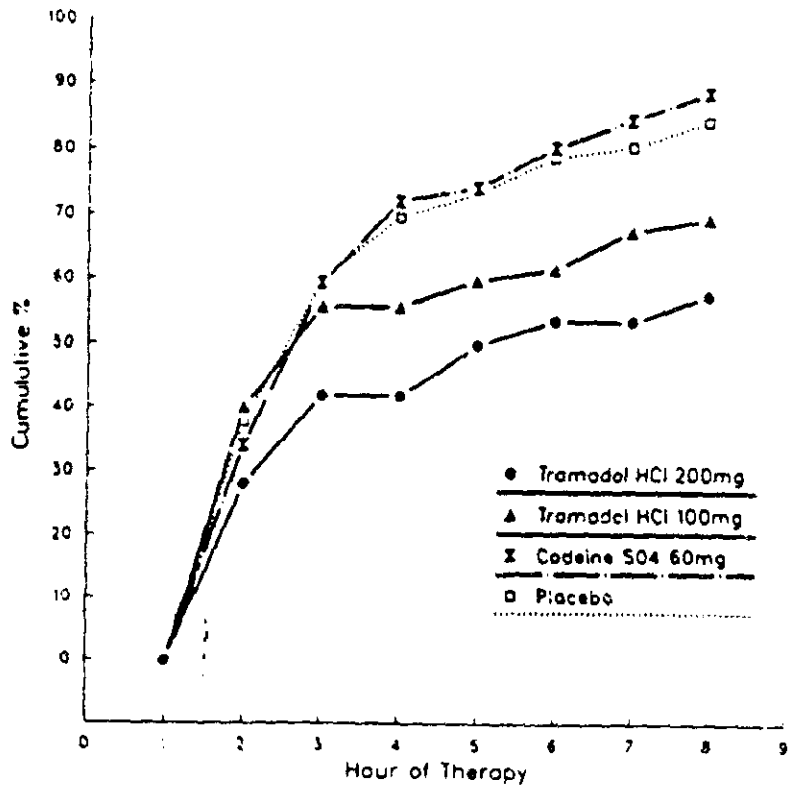


	SPID (extrapolated)	
Treatment	3-hour	6-hour
TR 200mg	1.71(2.10) A	3.81(4.53) A
TR 100mg	0.96(1.74) B	2.34(3.50) B
CO 60mg	0.64(1.77) B	1.21(3.16) B
Placebo	0.62(1.61) B	1.38(2.97) B
P-VALUE	0.009	0.001
RMS ERROR	1.812	3.587

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 200mg	0.12(0.66) 50	0.42(0.84) 49	0.76(0.87) 36 A	0.68(0.87) 29 A	0.72(1.01) 29 A	0.64(0.88) 25 A	0.74(0.96) 23 A	0.76(1.00) 23 A	0.78(1.04) 22 A
TR 100mg	-.02(0.59) 50	0.18(0.77) 50	0.42(0.78) 30 B	0.46(0.61) 22 AB	0.50(0.68) 22 AB	0.44(0.70) 20 AB	0.44(0.79) 19 B	0.44(0.76) 16 B	0.42(0.78) 15 B
CO 60mg	0.02(0.64) 46	0.19(0.95) 47	0.30(0.69) 31 B	0.23(0.67) 19 B	0.23(0.56) 13 B	0.17(0.64) 12 B	0.17(0.60) 9 B	0.17(0.48) 7 B	0.13(0.45) 6 C
Placebo	0.11(0.58) 52	0.08(0.76) 53	0.28(0.66) 33 B	0.25(0.68) 21 B	0.30(0.61) 16 B	0.25(0.52) 14 B	0.21(0.49) 11 B	0.17(0.47) 10 B	0.17(0.47) 8 BC
P-VALUE	0.596	0.200	0.006	0.005	0.005	0.004	0.000	0.000	0.000
RMS ERROR	0.617	0.828	0.756	0.713	0.736	0.694	0.733	0.713	0.727

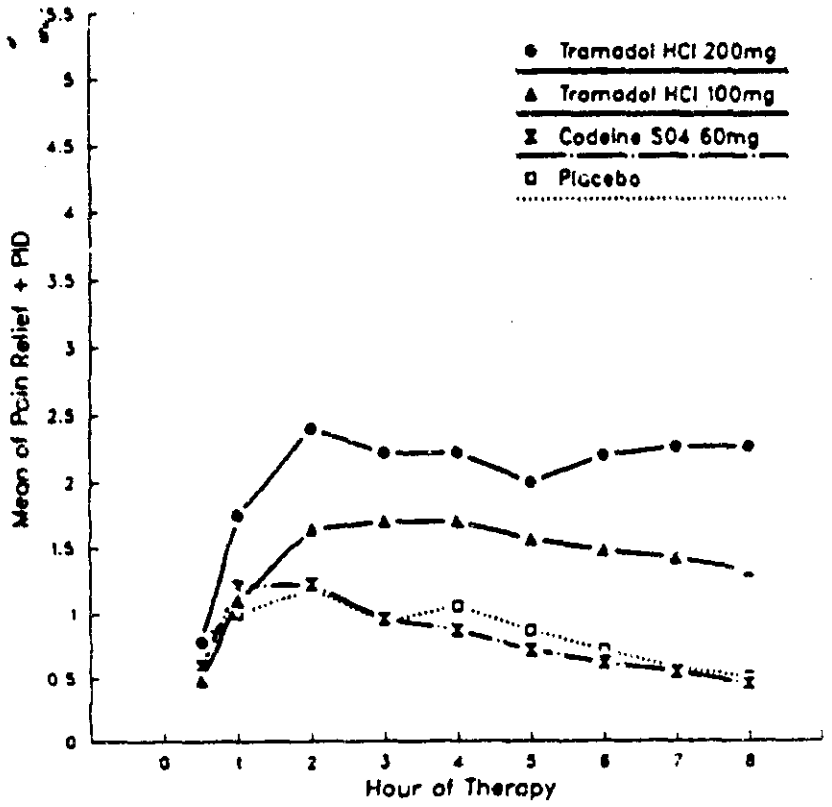
CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TO



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour	7-hour	8-hour
TR 200mg	50(100.0%)	36(72.0%)	29(58.0%)	29(58.0%)	25(50.0%)	23(46.0%)	23(46.0%)	21(42.0%)
TR 100mg	50(100.0%)	30(60.0%)	22(44.0%)	22(44.0%)	20(40.0%)	19(38.0%)	16(32.0%)	15(30.0%)
CO 60mg	47(100.0%)	31(66.0%)	19(40.4%)	13(27.7%)	12(25.5%)	9(19.1%)	7(14.9%)	5(10.6%)
Placebo	53(100.0%)	33(62.3%)	21(39.6%)	16(30.2%)	14(26.4%)	11(20.8%)	10(18.9%)	8(15.1%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TO



Treatment	SPRID (extrapolated) 3-hour	6-hour
TR 200mg	5.88(5.37) A	12.30(12.01) A
TR 100mg	4.13(5.10) AB	8.87(11.00) AB
CO 60mg	3.10(4.54) B	5.31(8.55) B
Placebo	3.04(4.35) B	5.68(8.90) B
P-VALUE	0.012	0.002
RMS ERROR	4.855	10.221

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 200mg	0.78(1.39) 50	1.74(1.80) 49	2.40(2.29) 36 A	2.22(2.35) 29 A	2.22(2.58) 29 A	2.00(2.43) 25 A	2.20(2.64) 23 A	2.26(2.75) 23 A	2.26(2.81) 22 A
TR 100mg	0.48(1.15) 50	1.10(1.73) 50	1.64(2.21) 39 AB	1.70(2.07) 22 AB	1.70(2.15) 22 AB	1.56(2.21) 20 AB	1.48(2.34) 19 AB	1.42(2.31) 18 B	1.32(2.33) 15 B
CO 60mg	0.60(1.31) 46	1.21(1.88) 47	1.23(1.83) 31 B	0.96(1.79) 19 B	0.87(1.68) 13 B	0.72(1.75) 12 C	0.62(1.69) 9 C	0.56(1.49) 7 C	0.45(1.40) 6 C
Placebo	0.81(1.39) 52	1.00(1.71) 53	1.19(1.79) 33 B	0.94(1.83) 21 B	1.06(1.90) 16 B	0.87(1.69) 14 BC	0.72(1.59) 11 BC	0.58(1.54) 10 C	0.51(1.46) 8 BC
P-VALUE	0.541	0.161	0.012	0.003	0.006	0.006	0.001	0.000	0.000
RMS ERROR	1.314	1.779	2.043	2.025	2.106	2.045	2.110	2.090	2.087

PROTOCOL TO

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 200mg	38	26	78
TR 100mg	63	37	193
CO 60mg	50	31	141
Placebo	37	25	70

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 200mg	4:30	2:15	> 8:00
TR 100mg	2:20	1:45	5:20
CO 60mg	2:30	1:55	3:10
Placebo	2:20	1:50	3:05

Tramadol Protocol TO 15:09 Friday, June 3, 1994 1

Demographic Frequencies and Means

Drug	Sex M	Sex F	Race Wht	Race Blk	Race Oth	Mean Age	Mean Weight	Baseline Pain Slight	Baseline Pain Moderate	Baseline Pain Severe	Surgical Procedure Dental Surgery	Reason for Discontinuation Adv Exp	Reason for Discontinuation Patient Choice	Reason for Discontinuation Protocol Violation	Reason for Discontinuation Other
Tramadol 200 MG	26	26	42	2	8	24.79	153.83	0	37	15	52	0	0	1	0
Tramadol 100 MG	27	24	41	4	6	24.98	150.16	0	39	12	51	0	0	0	0
Codeine SO4	25	25	47	2	1	25.42	154.56	0	41	9	50	0	0	0	1
Placebo	26	27	45	2	6	25.19	160.43	0	46	7	53	2	1	0	1

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This display includes all patients, including those who were not included in the analysis.

Study: TQ Investigators:	Pain Model: Dental Study Design: si, sd, db, r, p* Duration: 8 hours Tx: Tramadol (TR) 150 and 75 mg Acetaminophen 650 mg/Propoxyphene Napsylate 100 mg (APAP/propoxyphene) Codeine Sulfate 60 mg (Codeine) Placebo
A single investigator, randomized, double-blind, single-dose, parallel group, inpatient study of tramadol hydrochloride 150 mg and 75 mg, APAP/propoxyphene, codeine and placebo in patients with moderate or severe baseline pain following extraction of third molars.	
TR 150 mg: 50 pts. APAP/propoxyphene: 49 pts. Codeine: 50 pts. Placebo: 51 pts. TR 75 mg: 50 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* si = single investigator; sd = single-dose; db = double-blind; r = randomized; p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

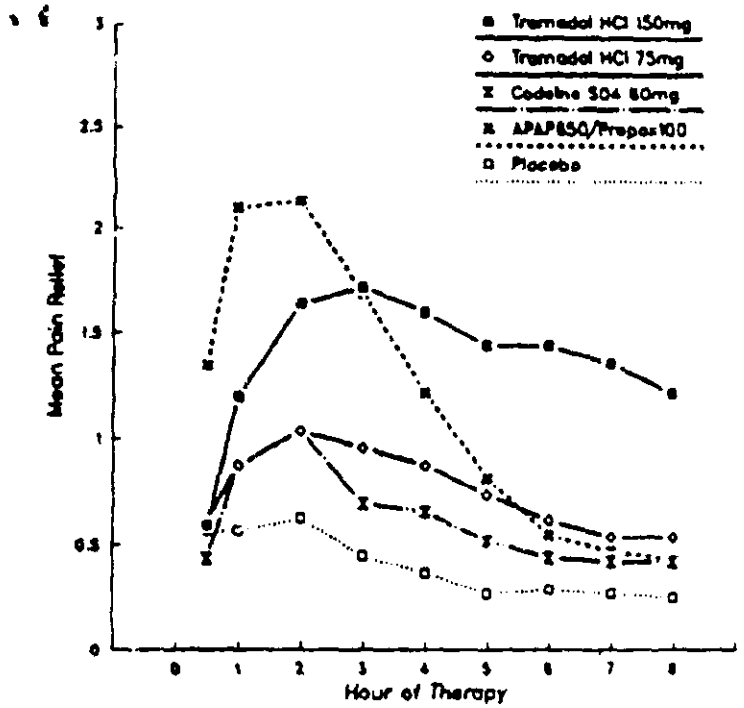
Of the 250 patients enrolled, 245 (98%) completed the study either by finishing eight hours of evaluation or by receiving a rescue analgesic, and five patients (2%) discontinued the study prematurely. All patients (N = 250) were included in the analyses of efficacy.

APAP/propoxyphene was statistically superior to placebo with respect to all efficacy variables. Codeine was numerically favored over placebo with respect to all efficacy variables, but was statistically superior to placebo only with respect to the time to remedication. Tramadol 150 mg was statistically superior to placebo with respect to all efficacy variables. Tramadol 75 mg was numerically favored over placebo with respect to all efficacy variables, but was statistically superior to placebo only with respect to TOTPAR (Total Pain Relief; sum of 0 - 4 hour scores). A significant tramadol dose-response was observed for all of the efficacy variables.

Comparing the four active treatment groups with respect to all efficacy variables, tramadol 150 mg and APAP/propoxyphene were numerically superior to the other treatments. These two treatments were not statistically different with respect to any efficacy variables except TOTPAR (sum of 0 - 3 hour scores) for which APAP/propoxyphene was superior. Tramadol 150 mg and APAP/propoxyphene were statistically superior to tramadol 75 mg and codeine with respect to TOTPAR and SPID (Sum of the Pain Intensity Difference) scores during the 0 - 3, 0 - 4, and 0 - 6 hour time intervals. There were no statistically significant differences between tramadol 75 mg and codeine. During the 0 - 8 hour time interval, tramadol 150 mg was statistically superior to tramadol 75 mg and codeine, and APAP/propoxyphene was statistically superior to codeine with respect to TOTPAR and SPID scores. There were no statistically significant differences between APAP/propoxyphene and tramadol 75 mg or between tramadol 75 mg and codeine during the 0 - 8 hour time interval. APAP/propoxyphene was statistically superior to tramadol 75 mg, but not statistically different from tramadol 150 mg and codeine with respect to time to remedication.

This study showed model sensitivity, and tramadol 150 mg provided pain relief statistically superior to that of placebo. In this study, the relative efficacy over all variables was tramadol 150 mg and APAP/propoxyphene > tramadol 75 mg > codeine > placebo. In comparing tramadol 150 mg and APAP/propoxyphene, APAP/propoxyphene had greater, although not statistically superior, pain relief initially, but this effect decayed and tramadol 150 mg demonstrated a greater pain relief over the entire study consistent with a more prolonged effect.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TQ



Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 150mg	4.26(3.45) B	8.74(7.71) A
TR 75mg	2.75(3.29) C	4.99(6.81) B
APAP/PROP	5.56(3.29) A	8.15(6.27) A
CO 60mg	2.40(2.54) C	4.02(5.25) B
Placebo	1.65(2.60) C	2.59(4.90) B
P-VALUE	0.000	0.000
RMS ERROR	3.055	6.268

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 150mg	0.60(0.81) 50 B	1.20(1.07) 50 B	1.64(1.34) 44 B	1.72(1.59) 30 A	1.60(1.55) 28 A	1.44(1.54) 26 A	1.44(1.57) 25 A	1.36(1.61) 23 A	1.22(1.57) 21 A
TR 75mg	0.62(0.78) 50 B	0.88(1.08) 50 BC	1.04(1.32) 41 C	0.96(1.43) 18 B	0.88(1.39) 16 BC	0.74(1.27) 14 BC	0.62(1.21) 14 B	0.54(1.20) 9 B	0.54(1.23) 9 B
APAP/PROP	1.35(1.23) 49 A	2.10(1.29) 49 A	2.14(1.26) 49 A	1.69(1.46) 39 A	1.22(1.48) 25 AB	0.82(1.25) 18 B	0.55(1.12) 14 B	0.47(1.10) 9 B	0.43(1.04) 8 B
CO 60mg	0.44(0.58) 50 B	0.88(0.96) 50 BC	1.04(1.14) 48 C	0.70(1.07) 22 B	0.66(1.10) 16 C	0.52(1.05) 13 BC	0.44(1.03) 11 B	0.42(0.97) 9 B	0.42(0.97) 9 B
Placebo	0.57(0.78) 51 B	0.57(0.81) 51 C	0.63(1.08) 35 C	0.45(0.99) 12 B	0.37(0.92) 8 C	0.27(0.80) 7 C	0.29(0.92) 6 B	0.27(0.90) 5 B	0.25(0.89) 5 B
P-VALUE	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001
RMS ERROR	0.861	1.053	1.231	1.327	1.308	1.209	1.190	1.182	1.166

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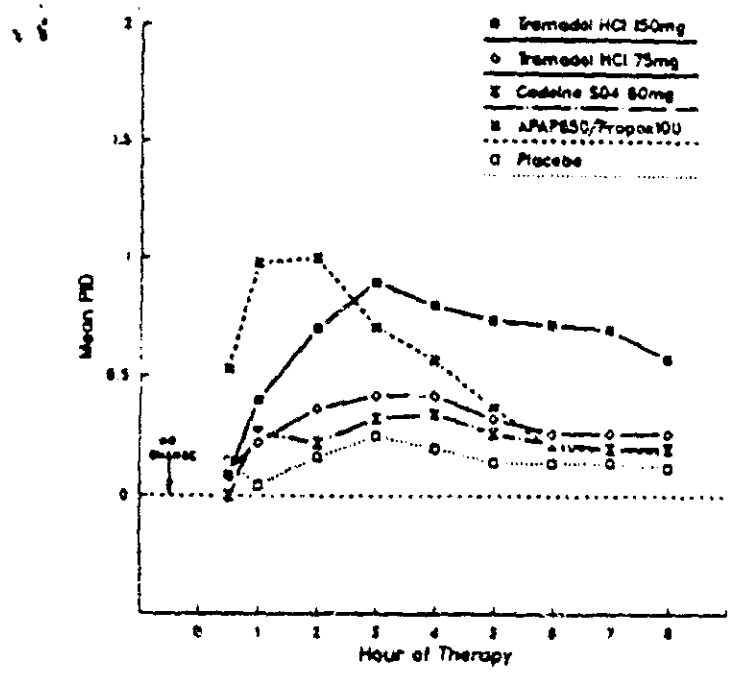
MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TQ

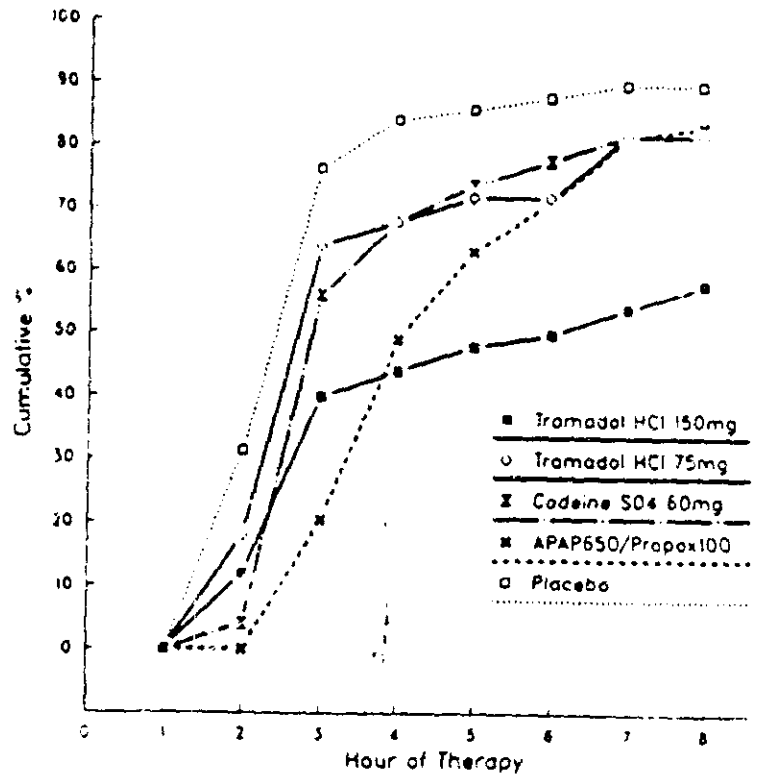


Treatment	SPID (extrapolated) 3-hour	6-hour
TR 150mg	1.84(2.40) A	4.10(4.70) A
TR 75mg	0.94(1.92) B	1.94(3.47) B
APAP/PROP	2.47(2.03) A	3.61(3.26) A
CO 60mg	0.67(1.86) B	1.49(3.06) B
Placebo	0.50(1.85) B	0.97(2.89) B
P-VALUE	0.000	0.000
RMS ERROR	2.021	3.536

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 150mg	0.08(0.63) 50 B	0.40(0.86) 50 B	0.70(0.93) 44 AB	0.90(0.95) 30 A	0.80(0.88) 28 A	0.74(0.85) 26 A	0.72(0.86) 25 A	0.70(0.91) 23 A	0.58(0.86) 21 A
TR 75mg	0.10(0.58) 50 B	0.22(0.79) 50 BC	0.36(0.88) 41 BC	0.42(0.67) 18 BC	0.42(0.67) 16 BC	0.32(0.59) 14 B	0.26(0.63) 14 B	0.26(0.60) 9 B	0.26(0.63) 9 B
APAP/PROP	0.53(0.84) 49 A	0.98(0.88) 49 A	1.00(0.79) 49 A	0.71(0.84) 39 AB	0.57(0.71) 25 AB	0.37(0.60) 18 B	0.20(0.58) 14 B	0.20(0.54) 9 B	0.18(0.49) 8 B
CO 60mg	0.00(0.67) 50 B	0.26(0.78) 50 BC	0.22(0.89) 48 C	0.32(0.65) 22 C	0.34(0.59) 16 BC	0.26(0.53) 13 B	0.22(0.51) 11 B	0.20(0.45) 9 B	0.20(0.45) 9 B
Placebo	0.14(0.66) 51 B	0.04(0.77) 51 C	0.16(0.86) 35 C	0.25(0.59) 12 C	0.20(0.49) 8 C	0.14(0.40) 7 B	0.14(0.45) 6 B	0.14(0.45) 5 B	0.12(0.43) 5 B
P-VALUE	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001
RMS ERROR	0.683	0.816	0.870	0.754	0.680	0.611	0.620	0.613	0.594

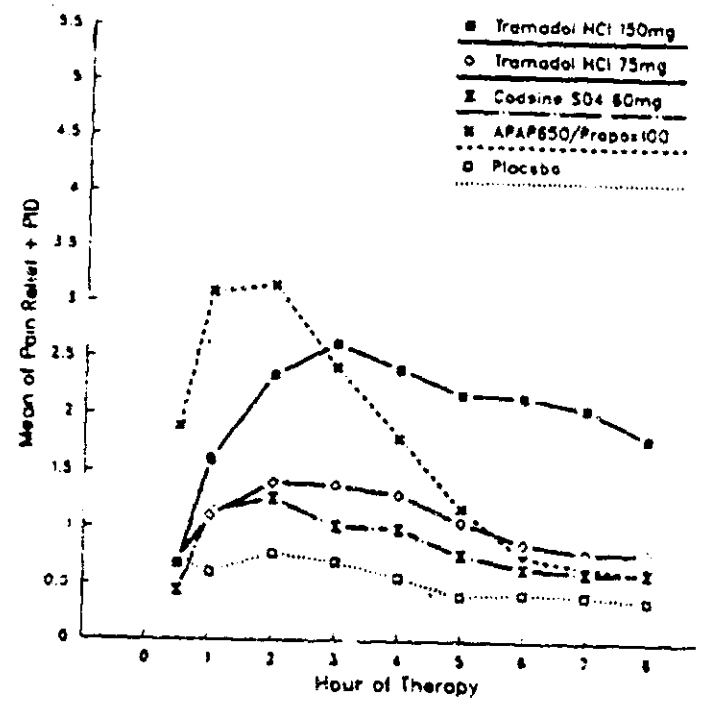
CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TO



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour	7-hour	8-hour
TR 150mg	50(100.0%)	44(88.0%)	30(60.0%)	28(56.0%)	26(52.0%)	25(50.0%)	23(46.0%)	21(42.0%)
TR 75mg	50(100.0%)	41(82.0%)	18(36.0%)	16(32.0%)	14(28.0%)	14(28.0%)	9(18.0%)	9(18.0%)
APAP/PPOP	49(100.0%)	49(100.0%)	39(79.6%)	25(51.0%)	18(36.7%)	14(28.6%)	9(18.4%)	8(16.3%)
CO 60mg	50(100.0%)	48(96.0%)	22(44.0%)	16(32.0%)	13(26.0%)	11(22.0%)	9(18.0%)	9(18.0%)
Placebo	51(100.0%)	35(68.6%)	12(23.5%)	8(15.7%)	7(13.7%)	6(11.8%)	5(9.8%)	5(9.8%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TQ



Treatment	SPRID (extrapolated) 3-hour	6-hour
TR 150mg	6.10(5.71) A	12.84(12.17) A
TR 75mg	3.69(5.08) B	6.93(10.14) B
APAP/PROP	8.03(5.13) A	11.77(9.27) A
CO 60mg	3.07(4.26) B	5.51(8.13) B
Placebo	2.15(4.35) B	3.56(7.68) B
P-VALUE	0.000	0.000
RMS ERROR	4.932	9.605

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 150mg	0.68(1.33) 50 B	1.60(1.84) 50 B	2.34(2.19) 44 B	2.62(2.49) 30 A	2.40(2.37) 28 A	2.18(2.34) 26 A	2.16(2.38) 25 A	2.06(2.49) 23 A	1.80(2.39) 21 A
TR 75mg	0.72(1.25) 50 B	1.10(1.78) 50 BC	1.40(2.11) 41 C	1.38(2.08) 18 B	1.30(2.04) 16 BC	1.06(1.83) 14 BC	0 88(1.81) 14 B	0.80(1.78) 9 B	0.80(1.85) 9 B
APAP/PROP	1.88(2.01) 49 A	3.08(2.09) 49 A	3.14(1.96) 49 A	2.41(2.24) 39 A	1.80(2.14) 25 AB	1.18(1.81) 18 B	0.76(1.65) 14 B	0.67(1.61) 9 B	0.61(1.50) 8 B
CO 60mg	0.44(1.15) 50 B	1.14(1.65) 50 BC	1.26(1.95) 48 C	1.02(1.67) 22 B	1.00(1.65) 16 C	0.78(1.56) 13 BC	0.66(1.52) 11 B	0.62(1.40) 9 B	0.52(1.40) 9 B
Placebo	0.71(1.35) 51 B	0.61(1.50) 51 C	0.78(1.86) 35 C	0.71(1.55) 12 B	0.57(1.39) 8 C	0.41(1.19) 7 C	0.43(1.36) 6 B	0.41(1.33) 5 B	0.37(1.31) 5 B
P-VALUE	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001
RMS ERROR	1.444	1.780	2.016	2.033	1.949	1.785	1.781	1.770	1.735

PROTOCOL TQ

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	44	28	99
TR 75mg	42	28	82
APAP/PROP	16	12	23
CO 60mg	68	39	259
Placebo	43	28	91

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	4:30	2:40	> 8:00
TR 75mg	2:35	2:15	2:55
APAP/PROP	3:55	3:20	4:50
CO 60mg	2:45	2:30	3:20
Placebo	2:20	2:00	2:40

Tramadol Protocol TQ 07:53 Monday, June 27, 1994 1

Demographic Frequencies and Means

	Sex		Race					Baseline Pain			Surgical Procedure	Reason for Discontinuation			
Drug	M	F	Wht	Blk	Oth	Mean Age	Mean Weight	Slight	Moderate	Severe	Odontectomy	Adv Exp	Patient Choice	Protocol Violation	Other
Tramadol 150 MG	24	26	37	3	10	23.82	141.52	0	34	16	50	2	0	0	0
Tramadol 75 MG	27	23	37	5	8	24.28	151.92	0	34	16	50	1	0	0	0
Codeine SO4	23	27	41	4	5	24.98	146.46	0	34	16	50	0	0	0	0
APAP/Propoxyhene	25	24	35	4	10	24.20	155.61	0	33	16	49	1	0	0	1
Placebo	26	25	42	3	6	26.16	162.41	0	34	17	51	0	0	0	0

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This display includes all patients, including those who were not included in the analysis.

Study: TT2	Pain/Model: Dental Study Design: si, md, db, r, p* Duration: 6 hours Tx: Tramadol (TR) 100, 75, and 50 mg Placebo
A single investigator, randomized, double-blind, multiple-dose, parallel group, outpatient study of tramadol hydrochloride and placebo in patients with moderate or severe baseline pain following dental surgery: single bony impaction(s), difficult extraction(s), tissue impaction(s), alveolectomy(s) multiple extractions, or apicoectomy(s).	
TR 100 mg: 100 pts. TR 75 mg: 100 pts. TR 50 mg: 100 pts.	Placebo: 100 pts.
Time-observation points: 1, 2, 3, 4, 5 and 6 hours after the first dose Remedication allowed: every four to six hours; preferably not until at least one hour after each study drug dose. Rescue medication: One or two ibuprofen (200 mg) tablets	

* *si = single investigator*; *md = multiple-dose*; *db = double-blind*;
r = randomized; p = parallel

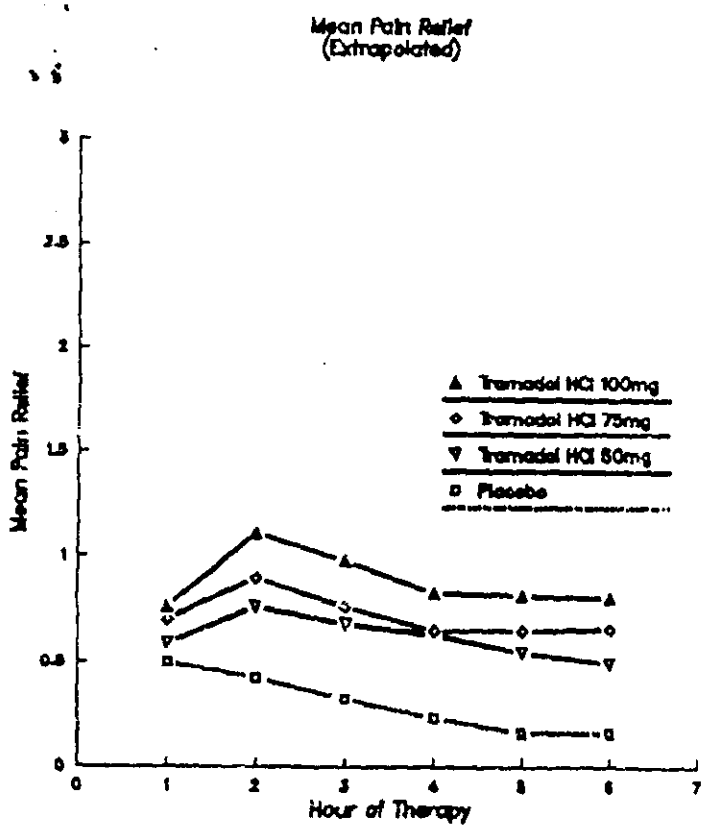
NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report. Information is limited to the six hours after the first dose of this multiple-dose study.

Of the 400 patients enrolled, 378 (94.5%) completed the study and 22 (5.5%) discontinued the study prematurely. All patients were included in the analyses of efficacy.

Each tramadol dosage was statistically superior to placebo with respect to all efficacy variables except TOTPAR (Total Pain Relief; sum of 0 - 3 hour scores) for tramadol 50 mg, which was numerically superior to placebo. A statistically significant linear dose response was observed for all the efficacy variables.

This study showed model sensitivity, and tramadol 100, 75 and 50 mg provided statically superior pain relief to that of placebo. In this study, the relative order of efficacy over all variables was tramadol 100 mg > tramadol 75 mg > tramadol 50 mg > placebo.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TT2

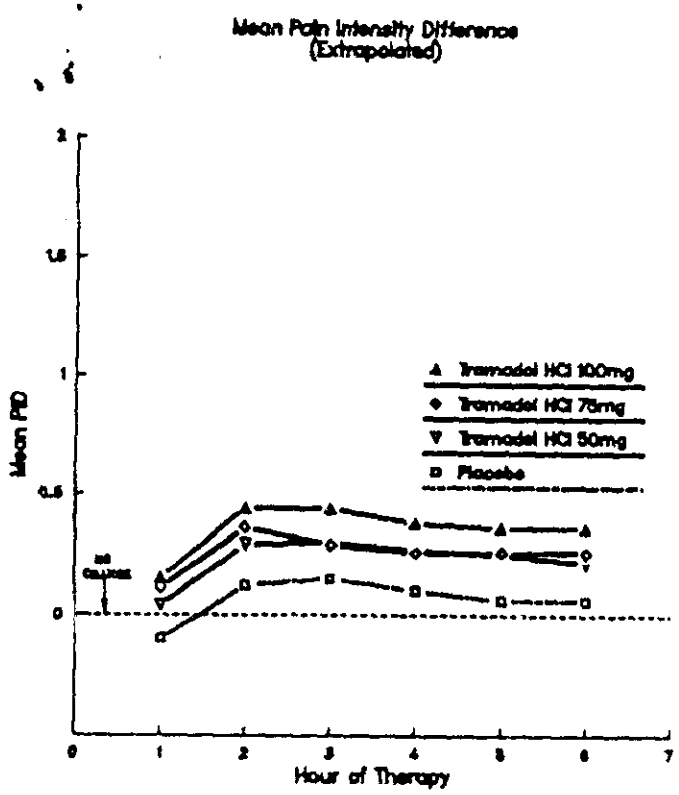


Treatment	TOTPAR (extrapolated) 3-hour		6-hour	
TR 100mg	2.85(3.24)	A	5.31(6.75)	A
TR 75mg	2.36(3.18)	AB	4.32(6.48)	A
TR 50mg	2.03(2.82)	BC	3.71(6.01)	A
Placebo	1.24(2.19)	C	1.79(3.65)	B
P-VALUE	0.001		0.000	
RMS ERROR	2.886		5.853	

MEAN SCORES OF PAIN RELIEF (Extrapolated)

Treatment	Assessment Time-Points (in hours) 1	2	3	4	5	6
TR 100mg	0.76(1.04)	1.11(1.27)	0.98(1.38)	0.83(1.34)	0.82(1.38)	0.81(1.40)
	100	58 A	39 A	31 A	29 A	27 A
TR 75mg	0.70(0.97)	0.90(1.23)	0.76(1.27)	0.65(1.18)	0.65(1.27)	0.66(1.28)
	100	49 AB	31 A	29 A	25 A	24 A
TR 50mg	0.59(0.81)	0.76(1.15)	0.68(1.21)	0.63(1.24)	0.55(1.19)	0.50(1.17)
	100	45 B	27 A	24 A	20 A	18 A
Placebo	0.50(0.82)	0.42(0.87)	0.32(0.83)	0.23(0.71)	0.16(0.65)	0.16(0.65)
	100	36 C	17 B	11 B	7 B	6 B
P-VALUE	0.189	0.000	0.001	0.002	0.001	0.001
RMS ERROR	0.913	1.139	1.191	1.141	1.159	1.159

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TT2



Treatment	SPID (extrapolated) 3-hour		6-hour	
TR 100mg	1.03(1.79)	A	2.13(3.47)	A
TR 75mg	0.76(1.56)	A	1.54(2.83)	A
TR 50mg	0.63(1.58)	A	1.37(3.02)	A
Placebo	0.17(1.34)	B	0.39(1.93)	B
P-VALUE	0.002		0.000	
RMS ERROR	1.577		2.867	

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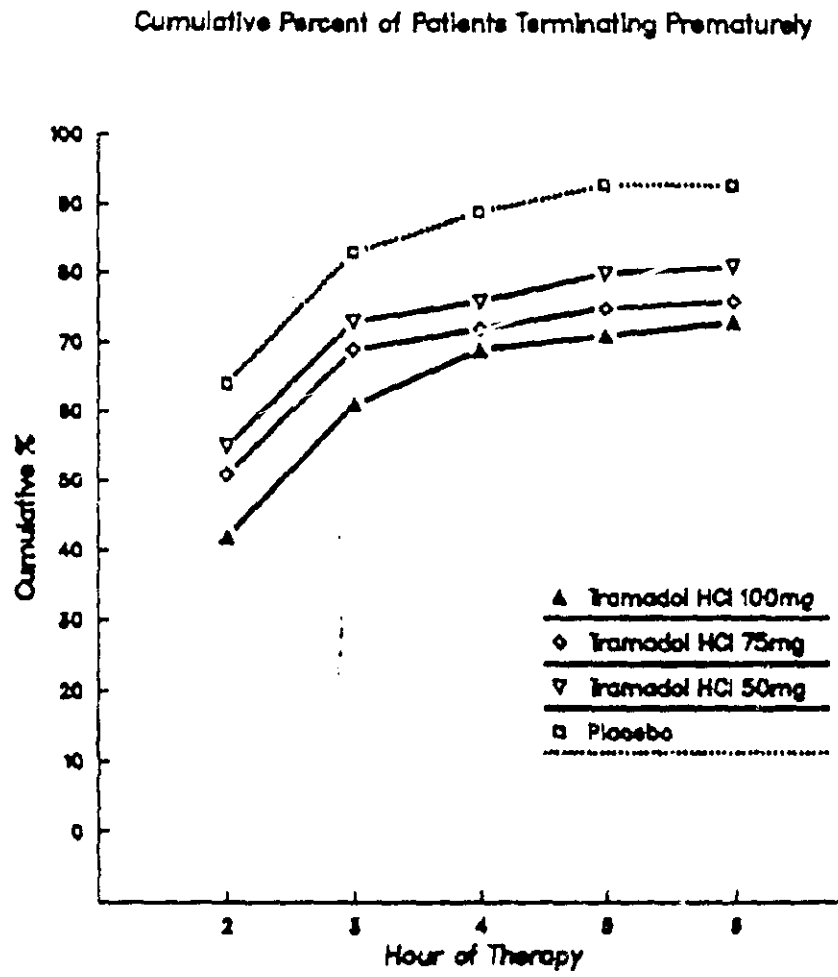
MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated)

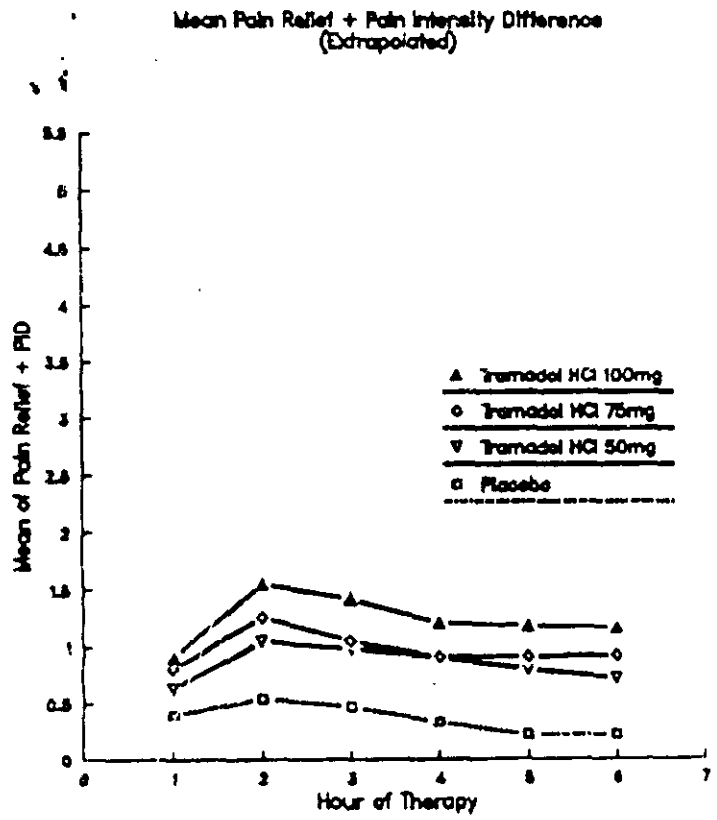
Treatment	Assessment Time-Points (in hours) 1		2		3		4		5		6	
TR 100mg	0.15(0.70)		0.44(0.69)		0.44(0.67)		0.38(0.65)		0.36(0.67)		0.36(0.67)	
	100	A	58	A	39	A	31	A	29	A	27	A
TR 75mg	0.11(0.69)		0.36(0.59)		0.29(0.50)		0.26(0.48)		0.26(0.54)		0.26(0.54)	
	100	A	49	A	31	A	28	A	25	A	24	A
TR 50mg	0.04(0.65)		0.29(0.59)		0.30(0.59)		0.27(0.58)		0.25(0.59)		0.22(0.58)	
	100	AB	45	A	27	AB	24	A	20	A	18	A
Placebo	-.10(0.69)		0.12(0.50)		0.15(0.44)		0.10(0.33)		0.06(0.24)		0.06(0.28)	
	100	B	36	B	17	B	11	A	7	B	6	B
P-VALUE	0.053		0.002		0.004		0.003		0.001		0.001	
RMS ERROR	0.684		0.596		0.557		0.526		0.538		0.539	

CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TT2



	Number of Patients in Study at Time-Observation Point					
Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour
TR 100mg	100(100.0%)	99(99.0%)	99(99.0%)	99(99.0%)	99 (99.0%)	90 (90.0%)
TR 75mg	100(100.0%)	100(100.0%)	100(100.0%)	100(100.0%)	100 (100.0%)	86 (86.0%)
TR 50mg	100(100.0%)	100(100.0%)	100(100.0%)	99(99.0%)	99 (99.0%)	92 (92.0%)
Placebo	100(100.0%)	100(100.0%)	100(100.0%)	100(100.0%)	100 (100.0%)	97 (97.0%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TT2



	SPRID (extrapolated)			
Treatment	3-hour		6-hour	
TR 100mg	3.88(4.92)	A	7.44(10.07)	A
TR 75mg	3.12(4.65)	AB	5.86(9.24)	A
TR 50mg	2.66(4.30)	B	5.08(8.91)	A
Placebo	1.41(3.44)	BC	2.18(5.48)	B
P-VALUE	0.001		0.000	
RMS ERROR	4.365		8.605	

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MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated)

	Assessment Time-Points (in hours)					
Treatment	1	2	3	4	5	6
TR 100mg	0.91(1.64)	1.55(1.90)	1.42(2.02)	1.21(1.96)	1.18(2.02)	.17(2.04)
	100	58 A	39 A	31 A	29 A	27 A
TR 75mg	0.81(1.57)	1.26(1.77)	1.05(1.76)	0.91(1.65)	0.91(1.80)	0.92(1.81)
	100	49 AB	31 A	28 A	25 A	24 A
TR 50mg	0.63(1.36)	1.05(1.70)	0.98(1.78)	0.90(1.80)	0.80(1.76)	0.72(1.72)
	100	45 B	27 A	24 A	20 A	19 A
Placebo	0.40(1.41)	0.54(1.31)	0.47(1.24)	0.33(1.03)	0.22(0.88)	0.22(0.91)
	100	36 C	17 B	11 B	7 B	6 B
P-VALUE	0.085	0.000	0.002	0.002	0.001	0.001
RMS ERROR	1.502	1.681	1.723	1.645	1.676	1.676

00 0104

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	66	48	103
TR 75mg	74	53	121
TR 50mg	95	67	168
Placebo	150	88	512

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	2:15	1:50	2:50
TR 75mg	1:55	1:40	2:20
TR 50mg	1:50	1:40	2:10
Placebo	1:45	1:35	1:50

Tramadol Protocol TT2 15:08 Monday, June 6, 1994 1

Demographic Frequencies and Means

Drug	Sex M	Sex F	Race Wht	Race Blk	Race Oth	Mean Age	Mean Weight	Baseline Pain Moderate	Baseline Pain Severe	Surgical Procedure Dental	Surgery	Reason for Discontinuation Adv Exp	Patient Choice	Protocol Violation	Drug Ineffective	Other
Tramadol 100 MG	48	52	81	7	12	27.17	155.79	77	23	100		6	1	2	0	0
Tramadol 75 MG	57	43	73	6	19	25.67	153.44	77	23	100		7	0	3	0	0
Tramadol 50 MG	44	56	81	8	11	26.20	153.80	77	23	100		1	0	0	1	0
Placebo	46	54	77	6	17	25.73	155.99	76	24	100		0	1	0	0	0

8900 00

This display includes all patients, including those who were not included in the analysis.

Tramadol Protocol TT2 15:08 Monday, June 6, 1994 2

Frequencies of Diagnosis

Drug	Diagnosis					
	Multiple Extraction	Single Bony Impaction	Apicoectomy	Other	Difficult Extraction	Tissue Impaction
Tramadol 100 MG	82	11	3	1	2	1
Tramadol 75 MG	82	11	3	1	3	0
Tramadol 50 MG	84	9	4	1	2	0
Placebo	87	4	4	3	1	1

6900 00

This display includes all patients, including those who were not included in the analysis.

Study: TA Investigator:	Pain Model: Post-Surgical Study Design: si, sd, db, r, p* Duration: 8 hours Tx: Tramadol (TR) 100 and 50 mg Codeine Sulfate 60 mg (Codeine) Placebo
This was a single investigator, randomized, double-blind, single-dose, parallel group study of tramadol hydrochloride 100 mg and 50 mg (tramadol), codeine sulfate 60 mg (codeine) and placebo in outpatients with moderate or severe baseline pain following surgery.	
TR 100 mg: 64 pts. TR 50 mg: 56 pts. Codeine: 29 pts. Placebo: 35 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

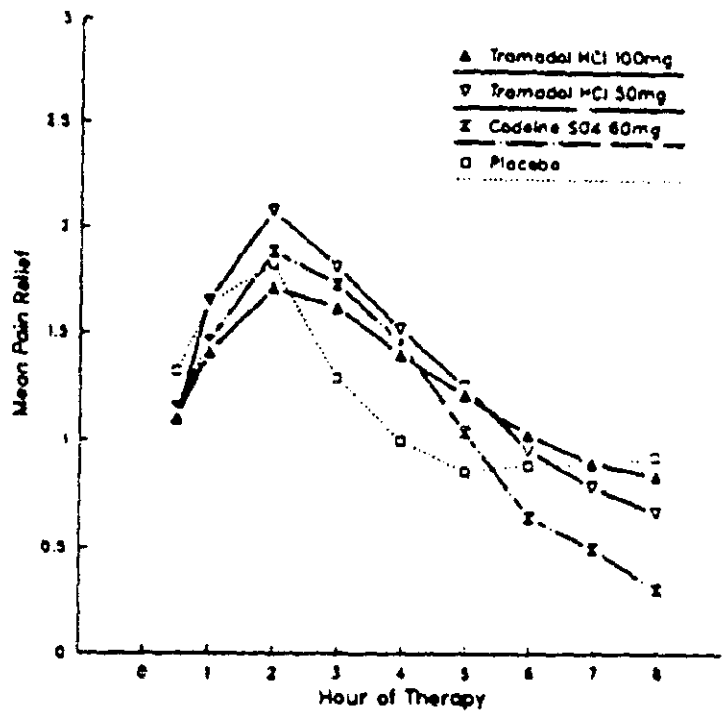
* si = single investigator; sd = single-dose; db = double-blind; r = randomized; p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

One hundred eighty-four patients were enrolled in the study (64 tramadol 100 mg, 56 tramadol 50 mg, 29 codeine and 35 placebo). A total of 177 patients were included in the analyses of demographic characteristics. Of the 184 patients enrolled, 155 (84%) completed the study either by finishing eight hours of evaluations or by receiving a rescue analgesic, 22 patients (12%) discontinued the study prematurely, and 7 patients (4%) were lost to follow-up.

In this study, there were no statistically significant overall treatment effects for any of the efficacy variables: TOTPAR (Total Pain Relief; sum of 0 - 3, 0 - 4, 0 - 6, and 0 - 8 hour scores), SPID (Sum of the Pain Intensity Differences; 0 - 3, 0 - 4, 0 - 6, and 0 - 8 hour scores) and time to remedication. This study is considered to be a model failure, and no further efficacy analyses were conducted.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TA

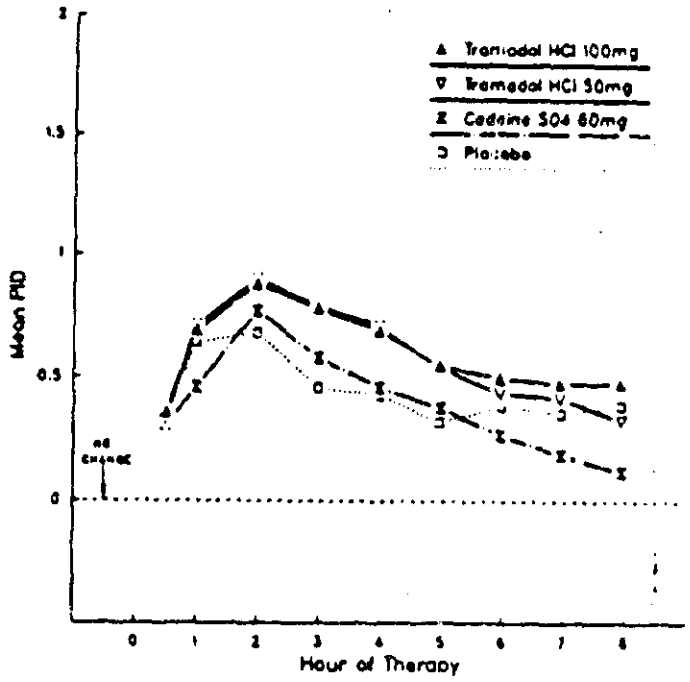


Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 100mg	4.57(3.39)	8.26(6.89)
TR 50mg	5.26(2.90)	8.99(6.04)
CO 60mg	4.92(2.62)	8.08(4.64)
Placebo	4.59(2.82)	7.34(6.10)
P-VALUE	0.644	0.715
RMS ERROR	3.031	6.181

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 100mg	1.10(1.04) 58	1.41(1.14) 58	1.71(1.38) 55	1.62(1.39) 49	1.40(1.46) 43	1.21(1.39) 36	1.03(1.35) 32	0.90(1.29) 26	0.84(1.27) 26
TR 50mg	1.10(1.01) 52	1.65(1.03) 52	2.08(1.17) 51	1.81(1.25) 49	1.52(1.31) 44	1.25(1.43) 37	0.96(1.30) 30	0.79(1.24) 25	0.67(1.18) 19
CO 60mg	1.15(1.05) 26	1.46(1.03) 26	1.88(1.11) 26	1.73(1.04) 26	1.46(1.24) 25	1.04(1.11) 19	0.65(1.02) 16	0.50(0.86) 11	0.31(0.68) 8
Placebo	1.32(1.16) 28	1.64(1.06) 28	1.82(1.19) 29	1.29(1.15) 26	1.00(1.25) 18	0.86(1.27) 15	0.89(1.47) 12	0.89(1.55) 12	0.93(1.54) 12
P-VALUE	0.804	0.621	0.479	0.351	0.410	0.597	0.665	0.585	0.220
RMS ERROR	1.053	1.075	1.241	1.256	1.345	1.341	1.310	1.268	1.221

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TA



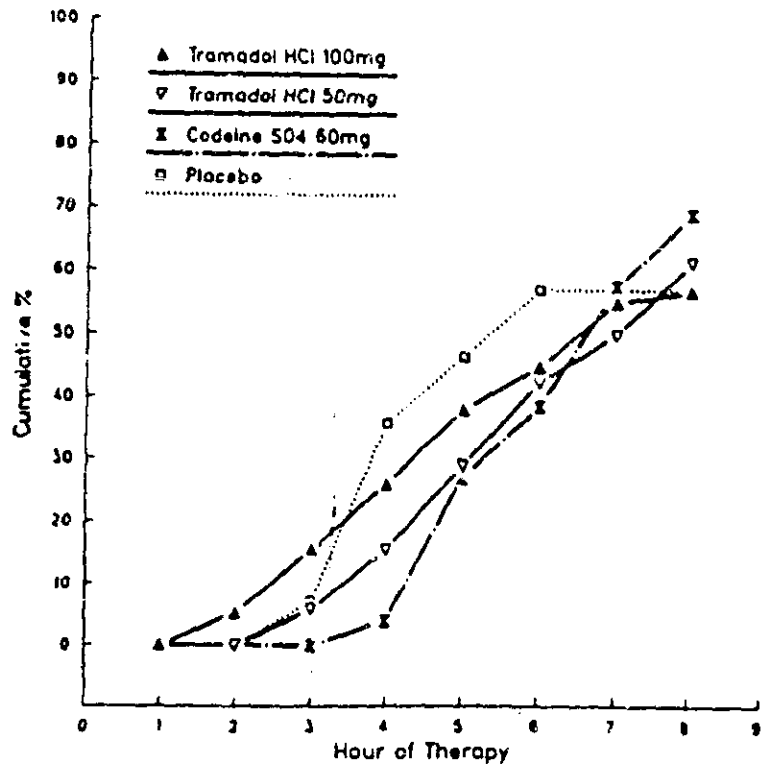
Treatment	SPID (extrapolated) 3-hour	6-hour
TR 100mg	2.17(2.12)	3.93(4.18)
TR 50mg	2.21(2.02)	3.90(3.99)
CO 60mg	1.73(1.42)	2.85(2.59)
Placebo	1.64(1.78)	2.79(3.31)
P-VALUE	0.476	0.378
RMS ERROR	1.937	3.769

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	
TR 100mg	0.36(0.52) 58	0.69(0.73) 58	0.88(0.84) 55	0.78(0.92) 49	0.69(0.94) 43	0.55(0.82) 36	0.50(0.78) 32	0.48(0.75) 26	0.48(0.75) 26
TR 50mg	0.33(0.58) 52	0.71(0.64) 52	0.90(0.82) 52	0.79(0.85) 49	0.71(0.82) 44	0.54(0.92) 37	0.44(0.75) 30	0.42(0.80) 26	0.33(0.73) 20
CO 60mg	0.31(0.47) 26	0.46(0.51) 26	0.77(0.65) 26	0.58(0.70) 26	0.46(0.76) 25	0.38(0.64) 19	0.27(0.45) 16	0.19(0.40) 11	0.12(0.33) 8
Placebo	0.36(0.62) 28	0.64(0.83) 28	0.68(0.77) 28	0.46(0.69) 26	0.43(0.69) 18	0.32(0.61) 15	0.39(0.79) 12	0.36(0.87) 12	0.39(0.88) 12
P-VALUE	0.971	0.468	0.610	0.276	0.337	0.527	0.598	0.418	0.189
RMS ERROR	0.552	0.689	0.796	0.829	0.838	0.797	0.729	0.749	0.721

CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TA

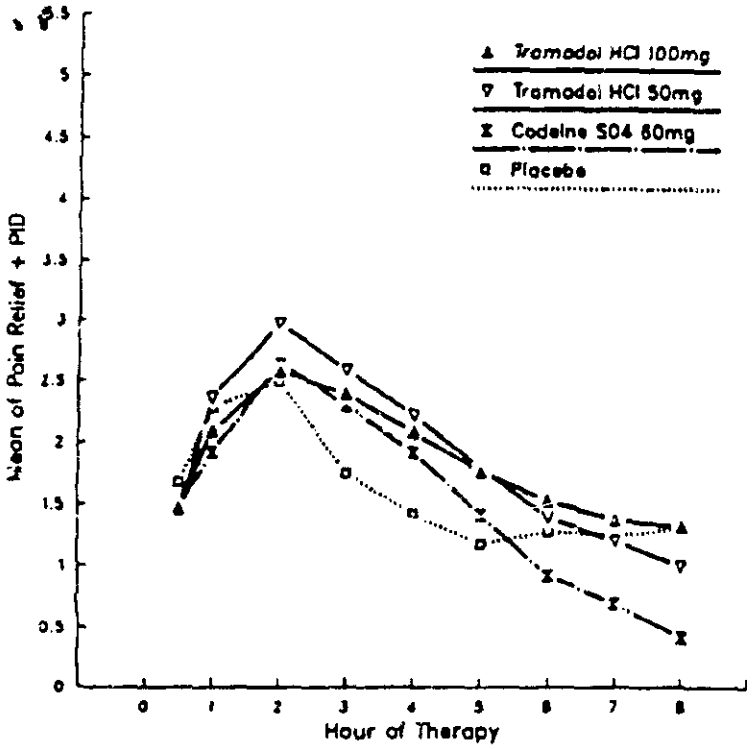
Cumulative Percent of Patients Terminating Prematurely



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour	7-hour	8-hour
TR 100mg	58(100.0%)	55(94.8%)	49(84.5%)	43(74.1%)	36(62.1%)	32(55.2%)	26(44.8%)	25(43.1%)
TR 50mg	52(100.0%)	52(100.0%)	49(94.2%)	44(84.6%)	37(71.2%)	30(57.7%)	26(50.0%)	20(38.5%)
CO 60mg	26(100.0%)	26(100.0%)	26(100.0%)	25(96.2%)	19(73.1%)	16(61.5%)	11(42.3%)	8(30.8%)
Placebo	28(100.0%)	28(100.0%)	26(92.9%)	18(64.3%)	15(53.6%)	12(42.9%)	12(42.9%)	12(42.9%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TA



	SPRID (extrapolated)	
Treatment	3-hour	6-hour
TR 100mg	6.74(5.27)	12.19(10.71)
TR 50mg	7.47(4.68)	12.83(9.56)
CO 60mg	6.65(3.70)	10.92(6.74)
Placebo	6.23(4.19)	10.13(8.97)
P-VALUE	0.689	0.602
RMS ERROR	4.686	9.524

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 100mg	1.47(1.43) 58	2.10(1.73) 58	2.59(2.11) 55	2.40(2.22) 49	2.09(2.33) 43	1.76(2.14) 36	1.53(2.05) 32	1.38(1.98) 26	1.33(1.96) 26
TR 50mg	1.42(1.50) 52	2.37(1.53) 52	2.98(1.87) 51	2.60(1.97) 49	2.23(2.01) 44	1.79(2.25) 37	1.40(1.96) 30	1.21(1.94) 25	1.00(1.81) 19
CO 60mg	1.46(1.39) 26	1.92(1.41) 26	2.65(1.62) 26	2.31(1.59) 26	1.92(1.87) 25	1.42(1.60) 19	0.92(1.41) 16	0.69(1.23) 11	0.42(0.95) 8
Placebo	1.68(1.68) 28	2.29(1.70) 28	2.50(1.80) 28	1.75(1.71) 26	1.43(1.85) 18	1.18(1.83) 15	1.29(2.21) 12	1.25(2.37) 12	1.32(2.36) 12
P-VALUE	0.901	0.664	0.650	0.332	0.414	0.544	0.615	0.517	0.192
RMS ERROR	1.491	1.618	1.914	1.970	2.083	2.052	1.966	1.945	1.870

PROTOCOL TA

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	21	17	29
TR 50mg	21	16	30
CO 60mg	21	15	33
Placebo	18	13	29

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	6:05	4:35	> 8:00
TR 50mg	6:25	5:10	7:50
CO 60mg	6:10	4:45	7:25
Placebo	4:40	3:30	> 8:00

Tramadol Protocol TA

11:31 Thursday, June 2, 1994 1

Demographic Frequencies and Means

Drug	Sex M	Sex F	Race White	Race Black	Race Other	Mean Age	Mean Weight	Baseline Pain Moderate	Baseline Pain Severe	Arthroscopic Knee Surgery	Reason for Discontinuation: Adverse Experience	Patient Choice	Protocol Violation	Other
Tramadol 100 MG	43	21	60	1	3	36.34	185.80	39	23	64	0	5	3	3
Tramadol 50 MG	33	23	55	0	1	36.41	178.09	41	12	56	0	3	1	5
Codeine SO4 60 MG	18	11	27	2	0	35.96	184.86	24	4	29	0	0	1	1
Placebo	23	12	33	2	0	40.18	173.06	23	10	35	1	1	2	3

This display includes all patients, including those who were not included in the analysis.

Study: TC Investigators:	Pain Model: Post-Surgical Study Design: si, sd, db, r, p* Duration: 6 hours Tx: Tramadol (TR) 100 and 50 mg Aspirin 650 mg/Codeine Phosphate 60 mg (ASA/Codeine) Codeine Sulfate 60 mg (Codeine) Placebo
A single investigator, randomized, double-blind, single-dose, parallel group study of tramadol hydrochloride 100 mg and 50 mg (tramadol), aspirin 650 mg with codeine phosphate 60 mg (ASA/codeine), codeine sulfate 60 mg (codeine) and placebo in hospitalized patients with moderate or severe baseline pain following general surgery.	
TR 100 mg: 39 pts. ASA /Codeine: 41 pts. Codeine: 40 pts. Placebo: 40 pts. TR 50 mg: 40 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5 and 6 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* si = single investigator; sd = single-dose; db = double-blind; r = randomized; p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

Of the 200 patients enrolled, 196 (98%) completed the study either by finishing the 6-hour protocol or receiving a rescue analgesic, and four patients (2%) discontinued the study prematurely. Two patients were excluded from the analyses of efficacy: one ASA/codeine patient because no baseline pain was recorded and one codeine patient for a significant protocol violation.

ASA/codeine was statistically superior to placebo with respect to TOTPAR (Total Pain Relief; sum of 0 - 3 and 0 - 6 hour scores), SPID (Sum of Pain Intensity Differences; 0 - 3 and 0 - 6 hour scores), time to remedication and patient global evaluation scores. Codeine was numerically favored over placebo with respect to all efficacy variables, although this was not statistically significant. Tramadol 100 mg was numerically favored over placebo with respect to all efficacy variables, although not statistically significant. Tramadol 50 mg was numerically favored over placebo with respect to all efficacy variables, although this was not statistically significant.

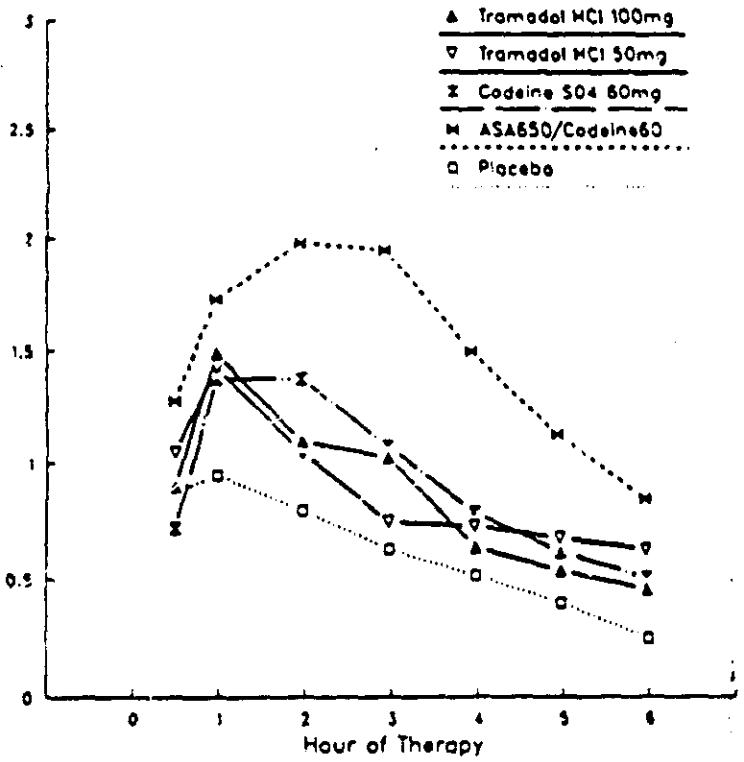
Although this study showed model sensitivity, tramadol 100 mg did not separate from placebo for any efficacy variables. Because the pairwise testing procedure used for time to remedication is not as sensitive as that used for TOTPAR and SPID, subsequent pairwise comparisons were conducted for this variable despite a lack of separation of tramadol from placebo. Thus, pairwise comparisons among the active treatments were conducted for time to remedication and patient global evaluation.

ASA/codeine was statistically superior to tramadol 100 mg, but was not statistically different from tramadol 50 mg and codeine with respect to time to remedication. There were no statistically significant differences among tramadol 100 mg, tramadol 50 mg and codeine.

ASA/codeine was statistically superior to tramadol 50 mg and codeine, but was not statistically different from tramadol 100 mg with respect to patient global evaluation scores. There were no statistically significant differences among tramadol 100 mg, tramadol 50 mg and codeine.

This study showed model sensitivity. Tramadol 100 mg provided pain relief numerically, although not statistically, superior to that of placebo.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TC

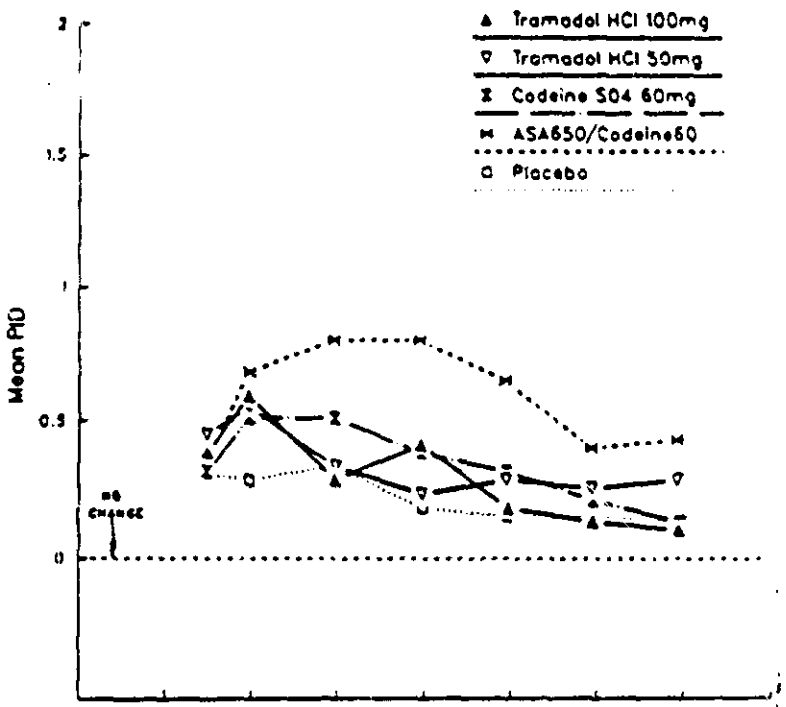


Treatment	TOTPAR (extrapolated) 3-hour		6-hour	
TR 100mg	3.32(3.25)	B	4.96(5.95)	B
TR 50mg	3.04(3.32)	B	5.06(6.71)	B
ASA/COD	5.43(3.40)	A	8.90(6.73)	A
CO 60mg	3.51(2.94)	B	5.44(5.50)	B
Placebo	2.34(2.66)	B	3.51(4.73)	B
P-VALUE	0.000		0.002	
RMS ERROR	3.129		5.974	

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	0.90(0.91) 39	1.49(1.21) 39	1.10(1.27) 28 BC	1.03(1.37) 19 B	0.64(1.06) 13 B	0.54(1.12) 10	0.46(1.05) 8
TR 50mg	1.05(1.08) 40	1.43(1.36) 40	1.05(1.22) 32 BC	0.75(1.24) 20 B	0.73(1.22) 13 B	0.68(1.27) 12	0.63(1.21) 11
ASA/COD	1.28(1.22) 40	1.73(1.13) 40	1.98(1.25) 34 A	1.95(1.38) 30 A	1.50(1.47) 27 A	1.13(1.49) 22	0.85(1.37) 15
CO 60mg	0.72(0.89) 39	1.38(1.14) 39	1.38(1.23) 31 B	1.08(1.22) 24 B	0.79(1.20) 15 B	0.62(1.07) 11	0.51(0.97) 11
Placebo	0.88(1.04) 40	0.95(1.04) 40	0.80(1.02) 29 C	0.63(1.00) 17 B	0.52(0.99) 12 B	0.40(0.93) 10	0.25(0.90) 7
P-VALUE	0.168	0.063	0.000	0.000	0.003	0.081	0.185
RMS ERROR	1.037	1.180	1.200	1.248	1.199	1.191	1.114

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TC



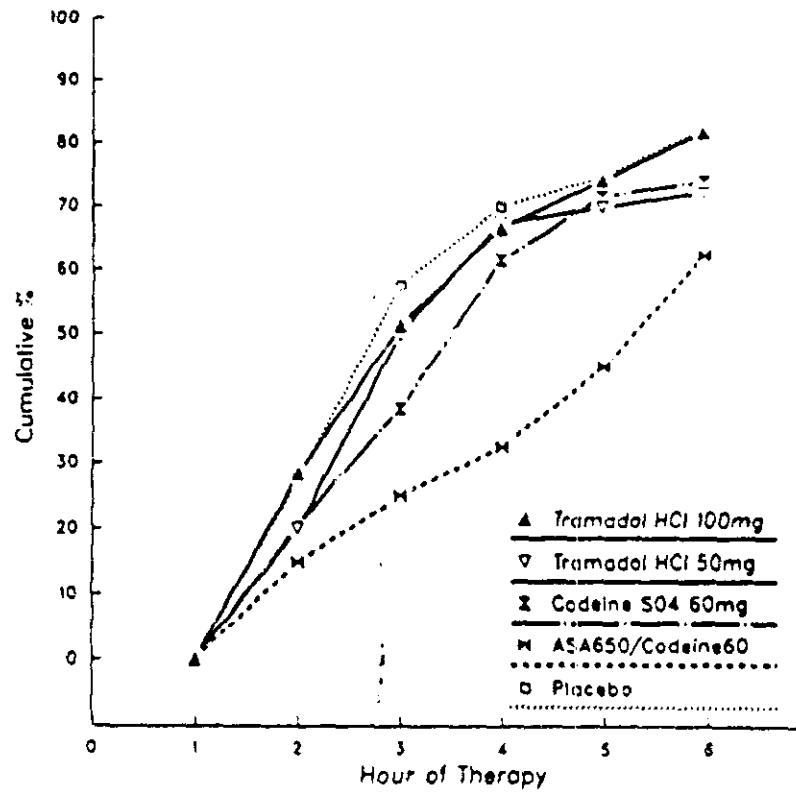
Treatment	SPID (extrapolated) 3-hour		6-hour	
TR 100mg	1.18(1.60)	B	1.59(2.31)	B
TR 50mg	1.05(1.69)	B	1.85(3.18)	B
ASA/COD	2.11(1.91)	A	3.59(3.48)	A
CO 60mg	1.31(1.69)	B	1.95(2.61)	B
Placebo	0.79(1.35)	B	1.21(2.54)	B
P-VALUE	0.037		0.003	
RMS ERROR	1.657		2.858	

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	0.38(0.67) 39	0.59(0.64) 39	0.28(0.69) 28 B	0.41(0.64) 19 B	0.18(0.39) 13 B	0.13(0.41) 10	0.10(0.31) 8 B
TR 50mg	0.45(0.68) 40	0.55(0.81) 40	0.33(0.69) 32 B	0.23(0.66) 20 B	0.28(0.55) 13 B	0.25(0.54) 12	0.28(0.60) 11 AB
ASA/COD	0.35(0.70) 40	0.68(0.73) 40	0.80(0.76) 34 A	0.80(0.72) 30 A	0.65(0.80) 27 A	0.40(0.84) 22	0.43(0.71) 15 A
CO 60mg	0.31(0.52) 39	0.51(0.68) 39	0.51(0.79) 31 AB	0.38(0.67) 24 B	0.31(0.61) 15 B	0.21(0.47) 11	0.13(0.34) 11 B
Placebo	0.30(0.56) 40	0.28(0.75) 40	0.33(0.69) 29 B	0.18(0.50) 17 B	0.15(0.53) 12 B	0.15(0.58) 10	0.13(0.46) 7 B
P-VALUE	0.825	0.151	0.009	0.000	0.002	0.258	0.023
RMS ERROR	0.631	0.726	0.726	0.643	0.595	0.589	0.509

CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TC

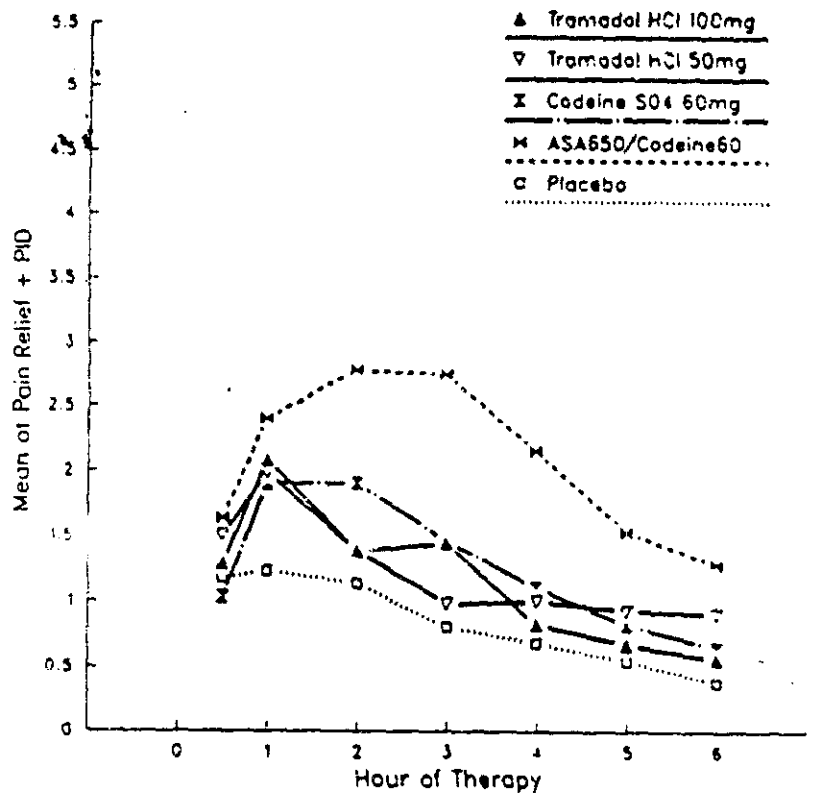
Cumulative Percent of Patients Terminating Prematurely



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour
TR 100mg	39(100.0%)	28(71.8%)	19(48.7%)	13(33.3%)	10(25.6%)	7(17.9%)
TR 50mg	40(100.0%)	32(80.0%)	20(50.0%)	13(32.5%)	12(30.0%)	11(27.5%)
ASA/COD	40(100.0%)	34(85.0%)	30(75.0%)	27(67.5%)	22(55.0%)	15(37.5%)
CO 60mg	39(100.0%)	31(79.5%)	24(61.5%)	15(38.5%)	11(28.2%)	10(25.6%)
Placebo	40(100.0%)	29(72.5%)	17(42.5%)	12(30.0%)	10(25.0%)	7(17.5%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TC



Treatment	SPRID (extrapolated) 3-hour		6-hour	
TR 100mg	4.50(4.72)	B	6.55(8.09)	B
TR 50mg	4.09(4.94)	B	6.91(9.81)	B
ASA/COD	7.54(5.09)	A	12.49(9.98)	A
CO 60mg	4.82(4.48)	B	7.38(7.92,	B
Placebo	3.13(3.83)	B	4.73(7.03)	B
P-VALUE	0.001		0.002	
RMS ERROR	4.633		8.649	

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	1.28(1.47) 39	1.08(1.72) 39	1.38(1.89) 28 B	1.44(1.97) 19 B	0.82(1.39) 13 B	0.67(1.47) 10	0.56(1.31) 8
TR 50mg	1.50(1.69) 40	1.98(2.09) 40	1.38(1.84) 32 B	0.98(1.83) 20 B	1.00(1.74) 13 B	0.93(1.79) 12	0.90(1.77) 11
ASA/COD	1.63(1.81) 40	2.40(1.75) 40	2.78(1.87) 34 A	2.75(2.03) 30 A	2.15(2.20) 27 A	1.53(2.25) 22	1.28(2.05) 15
CO 60mg	1.03(1.33) 39	1.90(1.73) 39	1.90(1.94) 31 B	1.46(1.82) 24 B	1.10(1.73) 15 B	0.82(1.48) 11	0.64(1.27) 11
Placebo	1.17(1.53) 40	1.23(1.69) 40	1.13(1.51) 29 B	0.80(1.42) 17 B	0.68(1.44) 12 B	0.55(1.43) 10	0.38(1.35) 7
P-VALUE	0.445	0.063	0.001	0.000	0.002	0.105	0.107
RMS ERROR	1.577	1.804	1.815	1.827	1.726	1.717	1.583

PROTOCOL TC

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	23	17	37
TR 50mg	20	15	31
ASA/COD	18	14	28
CO 60mg	29	21	50
Placebo	26	18	43

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	2:45	2:00	3:45
TR 50mg	2:50	2:15	3:40
ASA/COD	5:00	3:30	5:55
CO 60mg	3:15	2:30	4:05
Placebo	2:35	2:00	3:20

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Demographic Frequencies and Means

Drug	Sex M	Sex F	Race Wht	Race Blk	Race Oth	Mean Age	Mean Weight	Baseline Pain Moderate	Baseline Pain Severe	Surgical Procedure Orthopedic Surgery	Reason for Discontinuation Adv Exp	Reason for Discontinuation Patient Choice	Reason for Discontinuation Protocol Violation	Reason for Discontinuation Other
Tramadol 100 MG	26	13	28	8	3	41.23	175.92	32	7	39	0	1	0	0
Tramadol 50 MG	27	13	27	6	7	41.73	172.29	31	9	39	0	0	0	0
Codeine SO4	16	24	29	6	5	47.80	165.18	32	8	40	0	0	0	1
ASA / Codeine	25	16	30	5	6	44.59	177.50	32	8	41	0	0	0	1
Placebo	20	20	30	6	4	44.03	168.10	31	9	40	0	0	0	0

00 0053

This display includes all patients, including those who were not included in the analysis.

Study: TJ	Pain Model: Post-Surgical Pain Study Design: si, sd, db, r, p* Duration: 6 hours Tx: Tramadol (TR) 100 and 50 mg IM injection Morphine sulphate (morphine) 10 and 5 mg
A single investigator, randomized, double-blind, single-dose, parallel group study of orally administered tramadol hydrochloride 100 mg and 50 mg (tramadol) and an intramuscular injection of morphine sulfate 10 mg and 5 mg (morphine) in hospitalized patients with moderate or severe baseline pain following surgery.	
TR 100 mg: 38 pts. Morphine 10 mg: 40 pts. Morphine 5 mg: 39 pts. TR 50 mg: 43 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, and 6 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* si = single investigator; sd = single-dose; db = double-blind; r = randomized; p = parallel

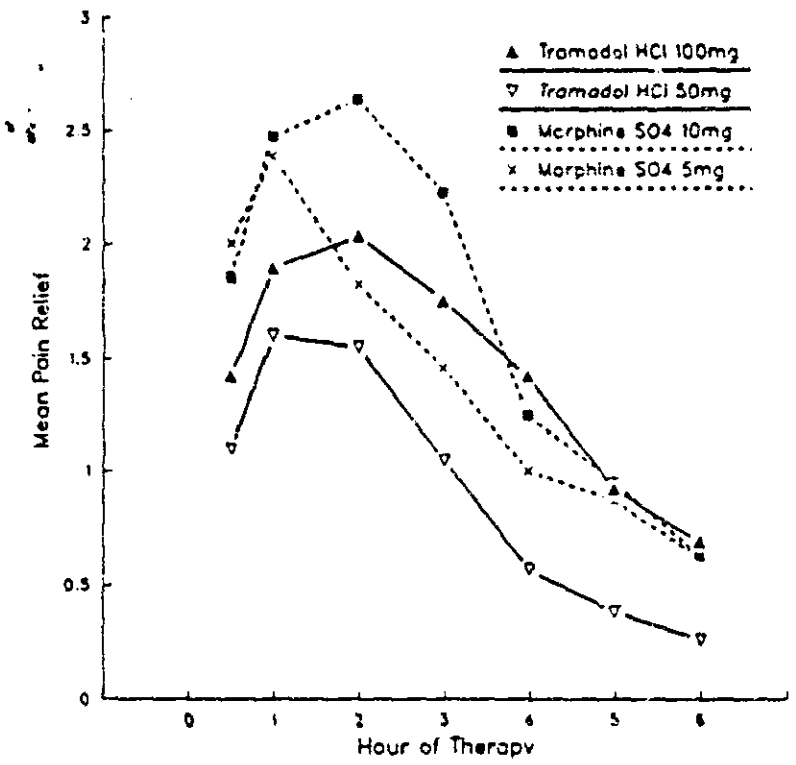
NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

Of the 160 patients enrolled, 159 (99%) completed the study either by finishing the six hours of evaluations or receiving a rescue analgesic, and one patient (1%) discontinued the study prematurely. Three patients were excluded from the analyses of efficacy: two tramadol 100 mg patients and one tramadol 50 mg patient for not completing 60 minutes of evaluation.

The relative potency of morphine to tramadol is defined as the ratio of morphine dose to equieffective tramadol dose. A relative potency of 0.050 means, therefore, that 5 mg of morphine is estimated to be equieffective to 100 mg of tramadol. The estimation of relative potency requires a significant common linear regression and the lack of significant deviations from parallelism. Linear regression was significant for the efficacy variables of TOTPAR (Total Pain Relief) and SPID (Sum of Pain Intensity Differences). In addition, there was a significant effect of preparation for the TOTPAR (sum of 0 - 3 hour scores) and SPID (0 - 3 hour scores). No significant interactions between dose and treatment (i.e., deviation from parallelism) were observed for any efficacy variable. The relative potency of morphine to tramadol across all efficacy variables ranged from 0.0394 to 0.0783.

The higher dose of tramadol and morphine were statistically superior to the lower dose of the respective drug in this study. The relative analgesic efficacy of intramuscular morphine to oral tramadol ranged from 0.0394 to 0.0783 in this study. This translates into a 100 mg dose of tramadol being equivalent to 3.9 to 7.8 mg morphine.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TJ

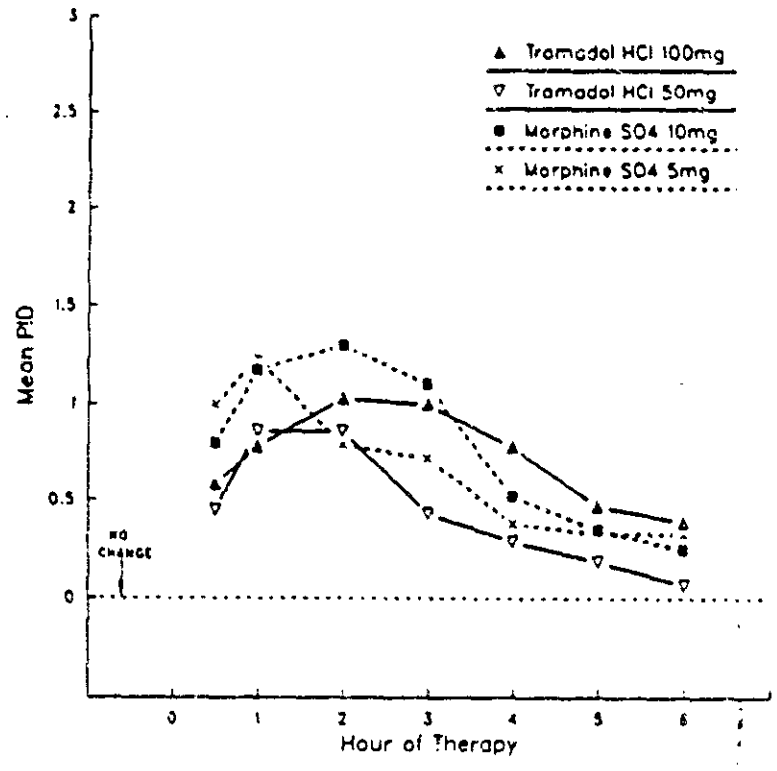


Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 100mg	5.43(3.26) B	8.46(6.11) A
TR 50mg	3.94(2.62) C	5.15(4.28) B
MO 10mg	7.01(2.82) A	9.84(5.44) A
MO 5mg	5.47(3.42) B	7.96(6.32) A
P-VALUE	0.000	0.002
RMS ERROR	3.032	5.559

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	1.42(1.16) 36 BC	1.89(1.14) 36 BC	2.03(1.30) 32 B	1.75(1.48) 27 AB	1.42(1.44) 24 A	0.92(1.32) 15	0.69(1.28) 11
TR 50mg	1.10(0.96) 42 C	1.60(1.11) 42 C	1.55(1.25) 34 B	1.05(1.31) 26 C	0.57(1.02) 15 B	0.38(0.82) 9	0.26(0.70) 7
MO 10mg	1.85(1.03) 40 AB	2.47(1.11) 40 A	2.63(1.15) 40 A	2.22(1.33) 37 A	1.25(1.35) 32 A	0.95(1.38) 17	0.63(1.10) 12
MO 5mg	2.00(1.26) 39 A	2.38(1.09) 39 AB	1.82(1.47) 35 B	1.46(1.52) 26 BC	1.00(1.34) 20 AB	0.87(1.47) 14	0.62(1.27) 11
P-VALUE	0.001	0.001	0.002	0.002	0.024	0.142	0.289
RMS ERROR	1.101	1.111	1.295	1.408	1.290	1.265	1.104

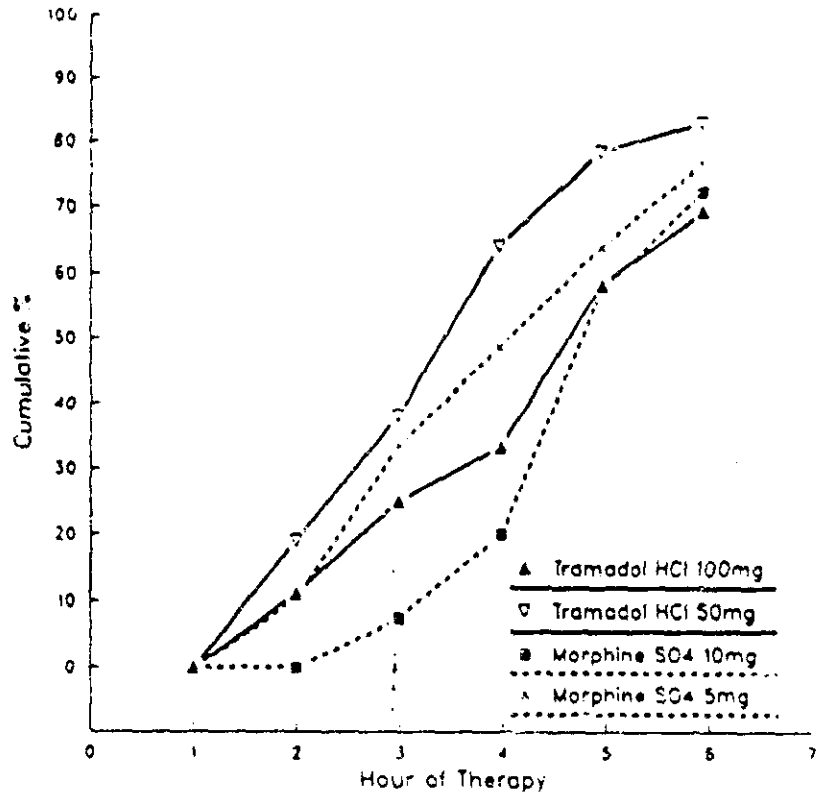
MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TJ



Treatment	SPID (extrapolated) 3-hour	6-hour
TR 100mg	2.71(2.26) AB	4.35(4.05) A
TR 50mg	1.94(1.54) B	2.49(2.34) B
MO 10mg	3.39(2.15) A	4.51(3.46) A
MO 5mg	2.63(2.12) AB	3.68(3.59) AB
P-VALUE	0.017	0.033
RMS ERROR	2.024	3.389

Treatment	Assessment Time-Points (in hours) 1/2	1	2	3	4	5	6
TR 100mg	0.58(0.69) 36 BC	0.78(0.90) 36 C	1.03(0.97) 32	1.00(1.01) 27 A	0.78(0.90) 24 A	0.47(0.77) 15	0.39(0.77) 11
TR 50mg	0.45(0.67) 42 C	0.86(0.68) 42 BC	0.86(0.84) 34	0.43(0.70) 26 B	0.29(0.55) 15 B	0.19(0.45) 9	0.07(0.26) 7
MO 10mg	0.80(0.69) 40 AB	1.17(0.75) 40 AB	1.30(0.94) 40	1.10(0.96) 37 A	0.52(0.82) 32 AB	0.35(0.74) 17	0.25(0.59) 12
MO 5mg	1.00(0.89) 39 A	1.23(0.87) 39 A	0.79(0.89) 35	0.72(0.94) 26 AB	0.38(0.63) 20 B	0.33(0.77) 14	0.33(0.74) 11
P-VALUE	0.006	0.029	0.065	0.005	0.024	0.356	0.111
RMS ERROR	0.739	0.801	0.911	0.907	0.732	0.692	0.613

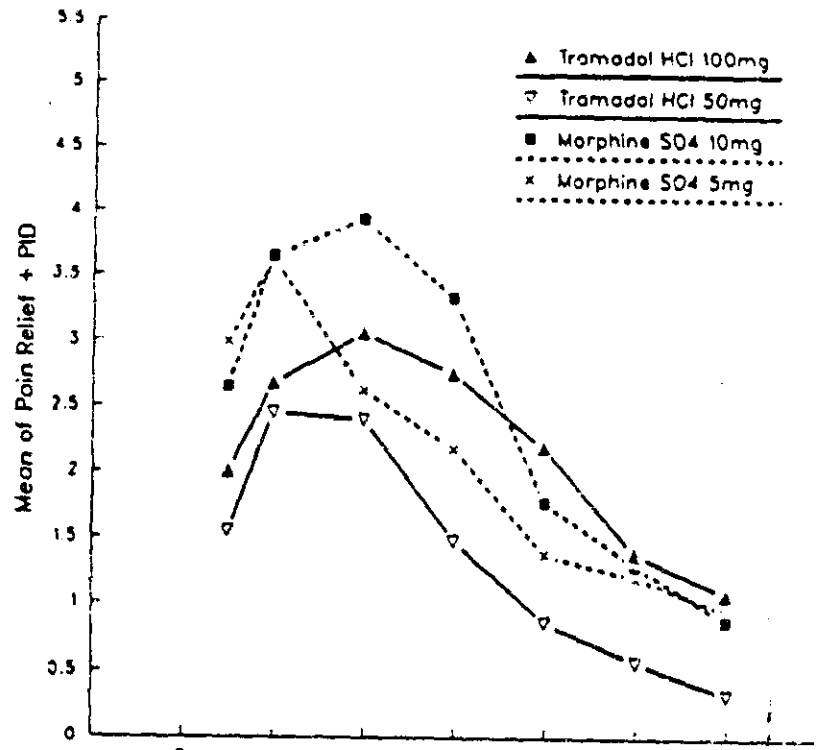
CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TJ



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour
TR 100mg	36(100.0%)	32(88.9%)	27(75.0%)	24(66.7%)	15(41.7%)	11(30.6%)
TR 50mg	42(100.0%)	34(81.0%)	26(61.9%)	15(35.7%)	9(21.4%)	7(16.7%)
MO 10mg	40(100.0%)	40(100.0%)	37(92.5%)	32(80.0%)	17(42.5%)	11(27.5%)
MO 5mg	39(100.0%)	35(89.7%)	26(66.7%)	20(51.3%)	14(35.9%)	9(23.1%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TJ



Treatment	SPRID (extrapolated) 3-hour		6-hour	
TR 100mg	8.14(5.23)	B	12.81(9.76)	A
TR 50mg	5.68(3.99)	C	7.64(6.39)	B
MO 10mg	10.40(4.63)	A	14.35(8.50)	A
MO 5mg	7.10(5.37)	B	11.64(9.75)	A
P-VALUE	0.001		0.005	
RMS ERROR	4.810		8.647	

Treatment	Assessment Time-Points (in hours) 1/2	1	2	3	4	5	6
TR 100mg	2.00(1.69) 36 BC	2.67(1.90) 36 B	3.06(2.11) 32 AB	2.75(2.41) 27 AB	2.19(2.27) 24 A	1.39(2.03) 15	1.08(1.99) 11
TR 50mg	1.55(1.45) 42 C	2.45(1.66) 42 B	2.40(2.04) 34 B	1.48(1.94) 26 C	0.86(1.52) 15 B	0.57(1.19) 9	0.33(0.93) 7
MO 10mg	2.65(1.58) 40 AB	3.65(1.70) 40 A	3.93(1.95) 40 A	3.33(2.15) 37 A	1.78(2.08) 32 A	1.30(2.02) 17	0.88(1.60) 12
MO 5mg	3.00(2.08) 39 A	3.62(1.84) 39 A	2.62(2.27) 35 B	2.18(2.42) 26 BC	1.38(1.91) 20 AB	1.21(2.20) 14	0.95(1.97) 11
P-VALUE	0.001	0.003	0.007	0.002	0.021	0.200	0.195
RMS ERROR	1.710	1.773	2.093	2.228	1.952	1.888	1.661

PROTOCOL TJ

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	15	12	21
TR 50mg	19	15	27
MO 10mg	11	10	14
MO 5mg	10	8	13

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	4:25	3:20	5:20
TR 50mg	3:15	2:30	3:50
MO 10mg	4:40	4:10	5:15
MO 5mg	3:45	2:50	4:55

Tramadol Protocol TJ 14:46 Friday, June 3, 1994

Demographic Frequencies and Means

	Sex		___Race___					____Baseline Pain_____			____Surgical Procedure____			_Reason for Discontinuat		
Drug	M	F	Wht	Blk	Oth	Mean Age	Mean Weight	Slight	Moderate	Severe	Orthopedic	Abdominal	Other	Adv Exp	Patient Choice	Protocol Violation
Tramadol 100 MG	11	27	36	2	0	49.74	175.74	0	15	23	20	15	3	0	1	0
Tramadol 50 MG	13	30	39	4	0	46.21	176.65	0	12	31	30	9	4	0	0	0
Morphine SO4 10 MG	19	21	37	3	0	47.45	184.03	0	19	21	27	11	2	0	0	0
Morphine SO4 5 MG	16	23	36	3	0	48.87	1.2.21	0	22	17	20	14	5	1	0	0

This display includes all patients, including those who were not included in the analysis.

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Demographic Frequencies and Means

Diagnosis

Drug	Acrimo-plasty	Abdomino-plasty	Vein Ligation Stripping	Excision Herniat Nucleus Pulpos	Herino graphy	Mammo-plasty	Total Hip Replac	Lamine -ctomy	Append ectomy	Cholecys tecomy	Cholecys tecomy Gram	Repair Cystocel Retrocel	Genito Urinary Surgery	Trans vesic Ureth oplex
Tramadol 100 MG	0	0	0	1	0	0	0	0	0	1	6	0	0	1
Tramadol 50 MG	1	1	0	0	0	1	0	0	0	1	2	0	1	0
Morphine SO4 10 MG	0	0	0	1	0	0	0	2	0	2	3	1	0	0
Morphine SO4 5 MG	0	0	1	0	1	1	1	2	1	0	2	0	0	0

Diagnosis

Prost atec tomy	Ooph orec tomy	Hyster ectomy Salpingo	Gyneco logical Surgery	Lobec tomy	Back Surg	Arthro plasty	Ortho pedic Surgy	Hyster ectomy	Recon strc Surgy	Abdom ino plasty /Lypo sucton	Knee Surgy	Hemorr hoid ectomy Fistul ectomy	Hip Surgy	Ureter oneo cysto tomy	Lapar otomy Ooph orec tomy	Abdom Surgy	Foot Surgy	Ventral Hernia Repair
0	1	1	3	0	0	0	11	2	4	1	4	0	0	0	0	1	0	1
1	0	0	3	0	1	2	22	2	1	0	1	0	1	1	0	0	1	0
0	0	0	3	1	1	1	15	2	5	0	1	0	0	0	0	0	1	0
2	1	0	5	0	2	0	13	3	2	1	0	1	0	0	0	0	0	0

This display includes all patients, inc..ii. those who were not included in the analysis.

Study: TW Investigator:	Pain Model: Post-Surgical Study Design: si, sd, db, r, p Duration: 6 hours Tx: Tramadol (TR) 100 and 50 mg Acetaminophen 650 mg/Propoxyphene Napsylate 100 mg (APAP/propoxyphene) Codeine Sulfate 60 mg (Codeine) Placebo
A single investigator, randomized, double-blind, single-dose, parallel group study of tramadol hydrochloride 100 and 50 mg (tramadol), acetaminophen 650 mg with propoxyphene napsylate 100 mg (APAP/propoxyphene), codeine sulfate 60 mg (codeine) and placebo in patients with moderate or severe baseline pain following surgery.	
TR 100 mg: 40 pts. APAP/propoxyphene: 39 pts. Codeine: 41 pts. Placebo: 40 pts. TR 50 mg: 40 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, and 6 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

si = single investigator; sd = single-dose; db = double-blind; r = randomized; p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

Of the 200 patients enrolled, 195 patients (98%) completed the study either by finishing the 6-hour protocol or by taking rescue analgesic, and five patients (3%) discontinued the study prematurely. Two codeine patients who discontinued the study prematurely were excluded from the analyses of efficacy because they discontinued prior to the 60 minute efficacy evaluation.

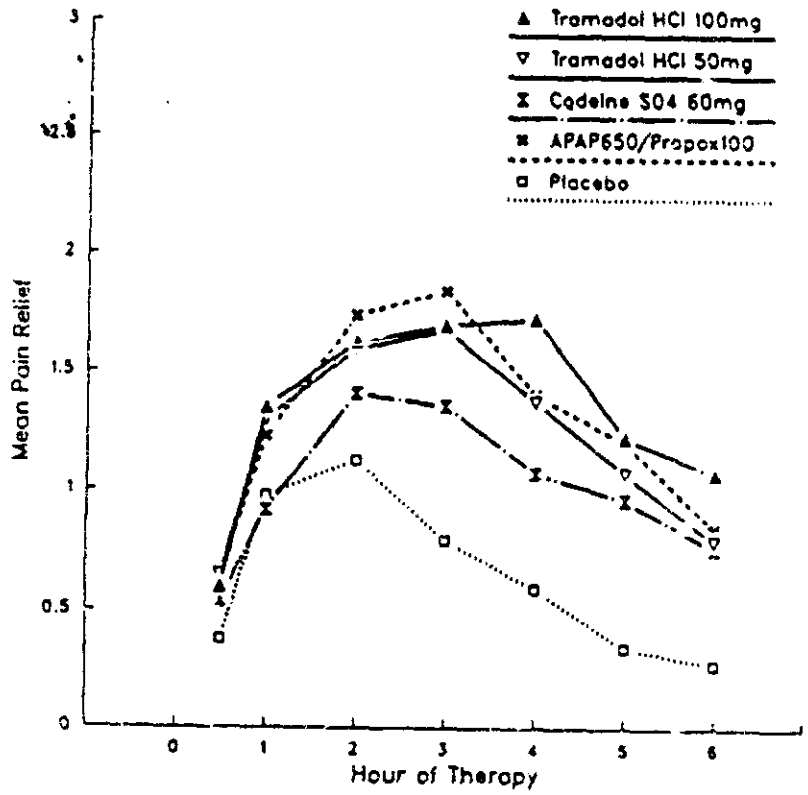
APAP/propoxyphene was statistically superior compared to placebo for all efficacy variables. Codeine was numerically favored over placebo with respect to all efficacy variables, and was statistically superior to placebo only for SPID (Sum of the Pain Intensity Differences; 0 - 6 hour interval scores). There was no statistically significant treatment effect for SPID (0 - 3 hour interval scores); therefore no pairwise statistical analyses were conducted for this interval.

Tramadol 100 mg and 50 mg were statistically superior compared to placebo with respect to all efficacy variables. There was no tramadol dose-response.

Comparing the four active treatment groups, tramadol 100 mg and APAP/propoxyphene were favored numerically over the other treatments with respect to most efficacy variables. Means for tramadol 50 mg were numerically greater for TOTPAR (total pain relief 0 - 3 and 0 - 6 hour interval scores) compared to those for codeine. There were no statistical differences among the tramadol 100 mg, tramadol 50 mg, APAP/propoxyphene and codeine treatment groups or any efficacy variable.

This study showed model sensitivity and demonstrated pain relief for tramadol 100 and 50 mg statistically superior to that of placebo. There were no statistical differences among the active treatments in producing overall analgesia over the entire study.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TW

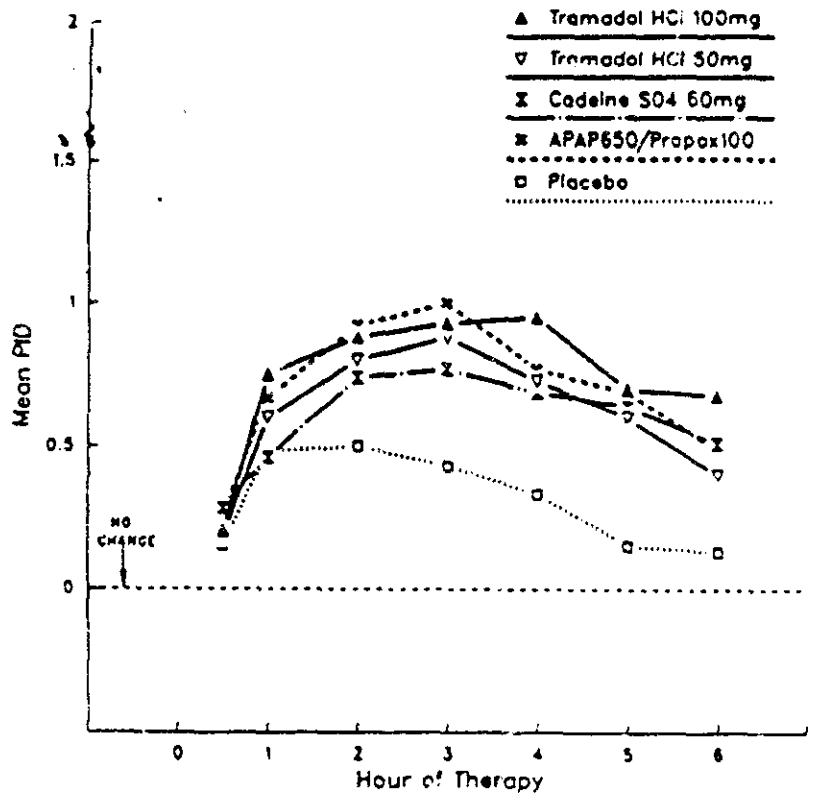


Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 100mg	4.30(3.30) A	8.33(6.78) A
TR 50mg	4.25(3.30) A	7.50(6.66) A
APAP/PROP	4.53(3.20) A	7.99(6.76) A
CO 60mg	3.50(3.49) AB	6.32(7.20) AB
Placebo	2.60(2.83) B	3.83(4.95) B
P-VALUE	0.053	0.016
RMS ERROR	3.229	6.513

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	0.60(0.67) 40	1.35(1.19) 40	1.63(1.23) 35	1.70(1.38) 28 A	1.73(1.48) 26 A	1.23(1.31) 26 A	1.08(1.42) 25
TR 50mg	0.65(0.74) 40	1.30(1.11) 40	1.60(1.30) 36	1.68(1.40) 30 A	1.38(1.46) 26 AB	1.08(1.46) 22 A	0.80(1.36) 18
APAP/PROP	0.64(0.78) 39	1.23(1.04) 39	1.74(1.21) 35	1.85(1.41) 29 A	1.41(1.41) 26 AB	1.21(1.49) 23 A	0.85(1.41) 17
CO 60mg	0.54(0.88) 39	0.92(1.11) 39	1.41(1.33) 37	1.36(1.46) 30 AB	1.08(1.44) 23 BC	0.97(1.51) 16 A	0.77(1.37) 15
Placebo	0.38(0.67) 40	0.98(1.03) 40	1.13(1.11) 36	0.80(1.09) 23 B	0.60(1.01) 17 C	0.35(0.86) 9 B	0.28(0.75) 8
P-VALUE	0.464	0.294	0.200	0.006	0.005	0.026	0.086
RMS ERROR	0.751	1.097	1.239	1.354	1.372	1.347	1.286

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TW



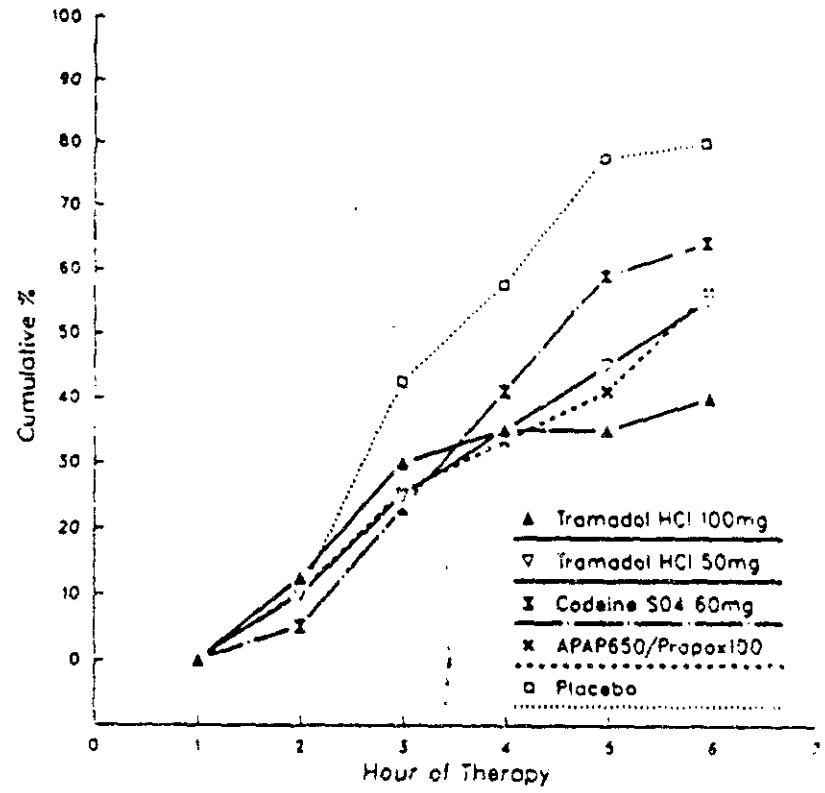
Treatment	SPID (extrapolated) 3-hour	6-hour	
TR 100mg	2.28(2.06)	4.60(4.73)	A
TR 50mg	2.06(1.75)	3.79(4.09)	A
APAP/PROP	2.38(2.18)	4.33(4.58)	A
CO 60mg	1.88(2.42)	3.73(5.14)	AB
Placebo	1.24(1.77)	1.84(3.18)	B
P-VALUE	0.106	0.050	
RMS ERROR	2.049	390	

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	0.20(0.46) 40	0.75(0.78) 40	0.88(0.76) 35	0.93(0.89) 28 A	0.95(0.96) 26 A	0.70(0.97) 26 A	0.68(1.02) 25
TR 50mg	0.18(0.38) 40	0.60(0.71) 40	0.80(0.72) 36	0.88(0.76) 30 A	0.73(0.93) 26 A	0.60(0.93) 22 A	0.40(0.90) 18
APAP/PROP	0.26(0.59) 39	0.67(0.77) 39	0.92(0.87) 35	1.00(0.89) 29 A	0.77(0.87) 26 A	0.69(0.95) 23 A	0.49(0.94) 17
CO 60mg	0.28(0.60) 39	0.46(0.79) 39	0.74(0.94) 37	0.77(1.04) 30 AB	0.69(0.98) 23 AB	0.64(1.04) 16 A	0.51(1.00) 15
Placebo	0.15(0.43) 40	0.48(0.64) 40	0.50(0.75) 36	0.43(0.68) 23 B	0.33(0.66) 17 B	0.15(0.53) 9 B	0.13(0.52) 8
P-VALUE	0.751	0.352	0.164	0.030	0.035	0.036	0.090
RMS ERROR	0.502	0.739	0.811	0.857	0.887	0.900	0.894

CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TW

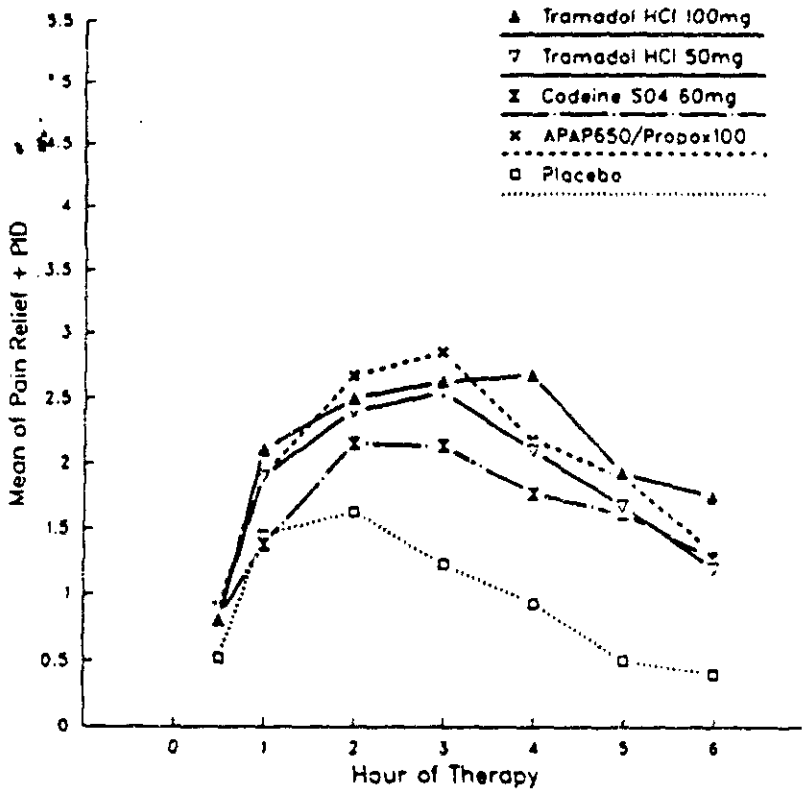
Cumulative Percent of Patients Terminating Prematurely



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour
TR 100mg	40(100.0%)	35(87.5%)	28(70.0%)	26(65.0%)	26(65.0%)	24(60.0%)
TR 50mg	40(100.0%)	36(90.0%)	30(75.0%)	26(65.0%)	22(55.0%)	18(45.0%)
APAP/PROP	39(100.0%)	35(89.7%)	29(74.4%)	26(66.7%)	23(59.0%)	17(43.6%)
CO 60mg	39(100.0%)	37(94.9%)	30(76.9%)	23(59.0%)	16(41.0%)	14(35.9%)
Placebo	40(100.0%)	36(90.0%)	23(57.5%)	17(42.5%)	9(22.5%)	8(20.0%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TW



Treatment	SPRID (extrapolated) 3-hour	6-hour
TR 100mg	6.58(5.15)	12.93(11.23) A
TR 50mg	6.31(4.88)	11.29(10.51) A
APAP/PROP	6.91(5.20)	12.32(11.06) A
CO 60mg	5.38(5.78)	10.05(12.16) AB
Placebo	3.84(4.45)	5.66(7.90) B
P-VALUE	0.057	0.022
RMS ERROR	5.107	10.660

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	0.60(1.04) 40	2.10(1.89) 40	2.50(1.89) 35	2.63(2.19) 28 A	2.68(2.39) 26 A	1.93(2.22) 26 A	1.75(2.42) 25
TR 50mg	0.83(1.06) 40	1.90(1.75) 40	2.40(1.93) 36	2.55(2.09) 30 A	2.10(2.35) 26 A	1.68(2.36) 22 A	1.20(2.23) 18
APAP/PROP	0.90(1.29) 39	1.90(1.74) 39	2.67(1.89) 35	2.85(2.23) 29 A	2.18(2.20) 26 A	1.90(2.39) 23 A	1.33(2.32) 17
CO 60mg	0.82(1.43) 39	1.38(1.84) 39	2.15(2.21) 37	2.13(2.43) 30 AB	1.77(2.38) 23 AB	1.62(2.52) 16 A	1.28(2.34) 15
Placebo	0.52(1.04) 40	1.45(1.58) 40	1.63(1.79) 36	1.23(1.72) 23 B	0.93(1.62) 17 B	0.50(1.36) 9 B	0.40(1.24) 8
P-VALUE	0.671	0.296	0.155	0.008	0.010	0.026	0.084
RMS ERROR	1.182	1.766	1.967	2.142	2.207	2.207	2.152

PROTOCOL TW

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	38	27	64
TR 50mg	35	26	61
APAP/PROP	33	23	62
CO 60mg	37	23	83
Placebo	57	35	152

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	> 6:00	2:55	> 6:00
TR 50mg	5:00	3:25	> 6:00
APAP/PROP	5:15	3:30	> 6:00
CO 60mg	4:15	3:20	5:45
Placebo	3:10	2:35	4:10

Tramadol Protocol TW 11:29 Tuesday, June 7, 1994 1

Demographic Frequencies and Means

	Sex		_____Race_____					_Baseline Pain_		_____Surgical Procedure_____					_Reason for Discontinuat	
Drug	M	F	Wht	Blk	Oth	Orien	Mean Age	Mean Weight	Moderate	Severe	Cesarean Section	Hysterectomy or Other Gynecological	Orthopedic	Adv Exp	Fat Choice	Proto Viola	Other
Tramadol 100 MG	13	27	2	35	2	1	29.48	187.69	24	16	20	5	15	0	0	0	0
Tramadol 50 MG	13	27	7	33	0	0	28.43	176.40	24	16	20	4	16	0	2	0	0
Codeine SO4	11	30	2	37	2	0	32.05	167.71	25	16	21	2	13	2	0	0	0
APAP/Propoxyhene	10	29	4	35	0	0	30.38	175.11	24	15	20	3	16	0	0	0	1
Placebo	14	26	6	33	1	0	29.33	167.72	24	16	24	1	15	0	0	0	0

This display includes all patients, including those who were not included in the analysis.

Tramadol Protocol TW 11:29 Tuesday, June 7, 1994 2

Demographic Frequencies and Means

Diagnosis								
Lamin ectomy	Tubal Liga tion	Arthro plasty	Ortho pedic Surgery	Cesarean Section	Hyster ectomy	Foot Surgery	Cesarean Section /Tubal Ligation	Cesarean Section /Hyster ectomy
0	0	0	16	19	4	0	1	0
0	0	0	16	18	3	1	2	0
0	0	2	16	20	2	0	1	0
1	1	0	15	17	2	0	3	0
0	0	0	15	20	1	0	3	1

00 0072

This display includes all patients, including those who were *not* included in the analysis.

Study: TX inves	Pain Model: Post-Surgical Pain Study Design: si, sd, db, r, p* *Duration: 8 hours* Tx: Tramadol (TR) 150 mg and 75 mg Acetaminophen 650 mg/propoxyphene napsylate 100 mg (APAP/propoxyphene) Codeine sulfate 60 mg (Codeine) Placebo
A single investigator, randomized, double-blind, single-dose, parallel group study of tramadol hydrochloride 150 mg and 75 mg (tramadol), acetaminophen 650 mg with propoxyphene napsylate 100 mg (APAP/propoxyphene), codeine sulfate 60 mg (codeine) and placebo in hospitalized patients and outpatients with moderate or severe baseline pain following surgery.	
TR 150 mg: 40 pts. APAP/propoxyphene: 37 pts. Codeine: 33 pts. Placebo: 36 pts. TR 75 mg: 36 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours Remedication allowed: None before 60 minutes after study drug administration. *Rescue medication*: Not specified	

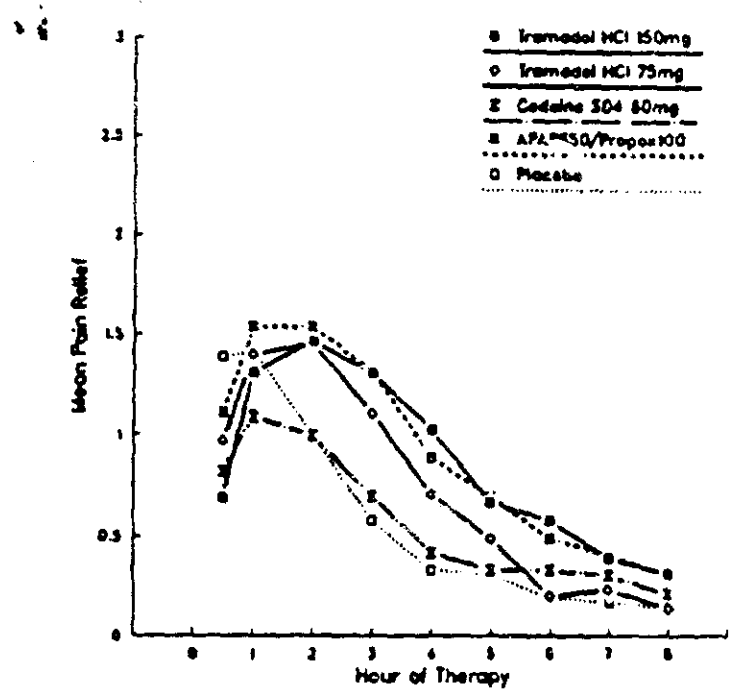
* si = single investigator; sd = single-dose; db = double-blind; r = randomized; p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

Of the 182 patients enrolled, 173 (95%) completed the study either by finishing eight hours of evaluations or by receiving a rescue analgesic, and nine patients (5%) discontinued the study prematurely. Five patients were excluded from the analyses of efficacy: four tramadol 150 mg patients for not completing one hour (60 minutes) of evaluation and one tramadol 75 mg patient for a significant protocol violation. A total of 177 patients was included in the analyses of efficacy.

In this study, there were no statistically significant overall treatment effects for any of the efficacy variables: TOTPAR (Total Pain Relief; sum of 0 - 3, 0 - 4, 0 - 6, and 0 - 8 hour scores), SPID (Sum of the Pain Intensity Differences; 0 - 3, 0 - 4, 0 - 6, and 0 - 8 hour scores) and time to remedication. This study is considered to be a model failure, and no further efficacy analyses were conducted.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TX

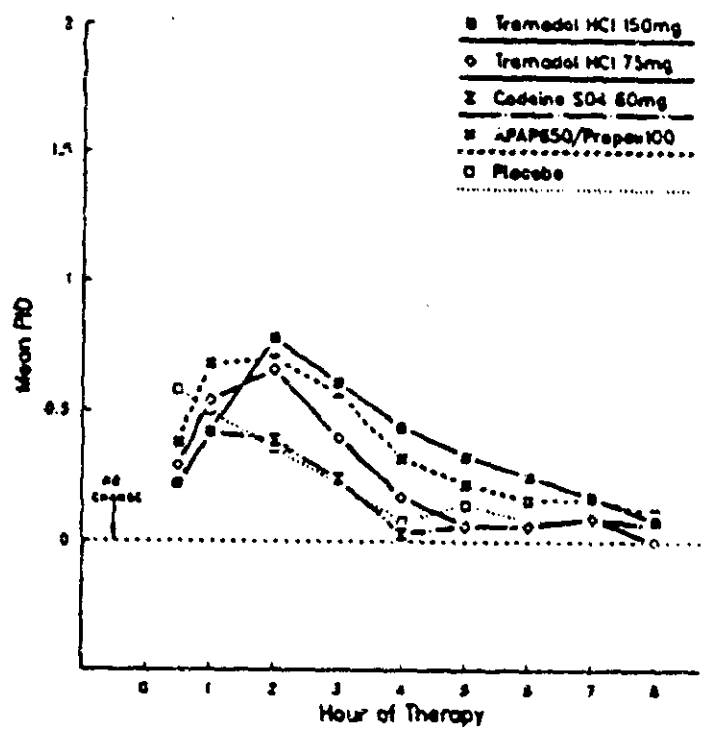


Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 150mg	3.78(3.83)	6.06(7.04)
TR 75mg	3.76(3.56)	5.16(5.28)
APAP/PROP	4.19(3.52)	6.27(6.66)
CO 60mg	2.65(2.32)	3.74(3.90)
Placebo	2.99(3.47)	3.82(4.89)
P-VALUE	0.307	0.188
RMS ERROR	3.395	5.707

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 150mg	0.69(0.79) 36 B	1.31(1.26) 36	1.47(1.59) 23	1.31(1.56) 20	1.03(1.46) 18	0.67(1.20) 14	0.58(1.18) 10	0.39(0.99) 7	0.31(0.82) 6
TR 75mg	0.97(1.10) 35 AB	1.40(1.31) 35	1.46(1.52) 21	1.11(1.30) 19	0.71(1.07) 16	0.49(0.89) 11	0.20(0.72) 7	0.23(0.77) 5	0.14(0.60) 4
APAP/PROP	1.11(0.91) 37 AB	1.54(1.32) 37	1.54(1.50) 25	1.32(1.51) 23	0.89(1.39) 16	0.70(1.29) 12	0.49(1.22) 9	0.41(1.12) 7	0.30(1.02) 4
CO 60mg	0.82(0.95) 33 B	1.09(1.01) 33	1.00(1.00) 24	0.70(1.02) 19	0.42(0.79) 13	0.33(0.82) 7	0.33(0.85) 5	0.30(0.92) 4	0.21(0.74) 3
Placebo	1.39(1.27) 36 A	1.42(1.36) 36	1.00(1.47) 22	0.58(1.20) 15	0.33(0.86) 9	0.31(0.95) 5	0.19(0.82) 3	0.17(0.70) 3	0.14(0.59) 3
P-VALUE	0.044	0.659	0.296	0.055	0.056	0.363	0.354	0.770	0.818
RMS ERROR	1.016	1.264	1.440	1.340	1.156	1.049	0.984	0.914	0.776

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TX

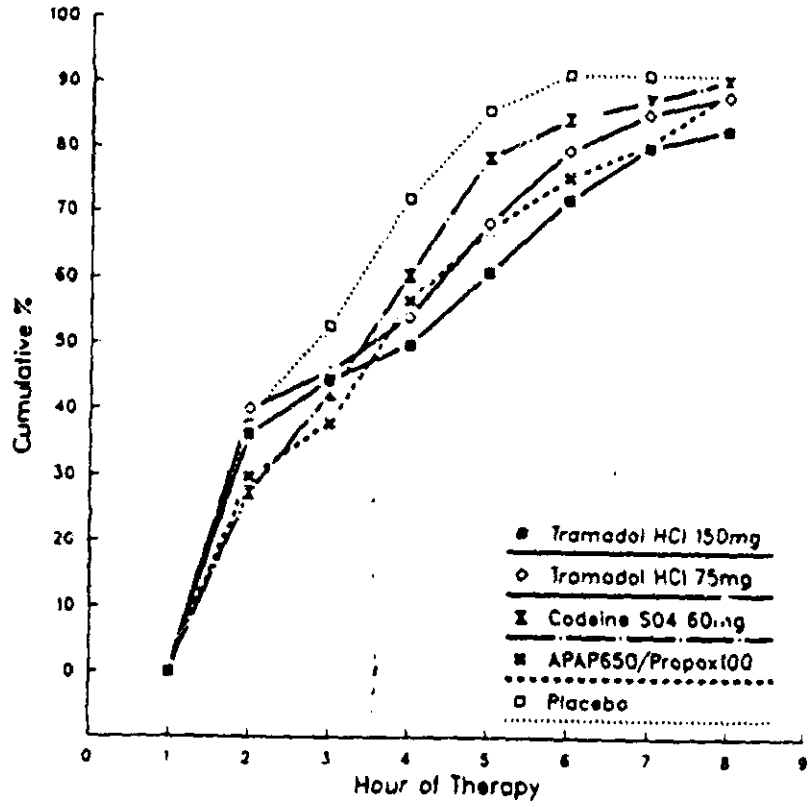


Treatment	SPID (extrapolated) 3-hour	6-hour	
TR 150mg	1.71(2.05)	2.74(3.53)	A
TR 75mg	1.47(1.63)	1.76(2.03)	ABC
APAP/PROP	1.80(1.91)	2.50(3.06)	AB
CO 60mg	0.95(1.28)	1.11(1.85)	C
Placebo	1.13(1.91)	1.43(2.46)	BC
P-VALUE	0.216	0.055	
RMS ERROR	1.785	2.677	

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 150mg	0.22(0.54) 36	0.42(0.91) 36	0.78(0.87) 23	0.61(0.84) 20	0.44(0.73) 18 A	0.33(0.59) 14	0.25(0.60) 10	0.17(0.45) 7	0.08(0.28) 6
TR 75mg	0.29(0.62) 35	0.54(0.66) 35	0.66(0.80) 21	0.40(0.55) 19	0.17(0.45) 16 BC	0.06(0.34) 11	0.06(0.42) 7	0.09(0.37) 5	0.00(0.24) 4
APAP/PROP	0.38(0.64) 37	0.68(0.78) 37	0.70(0.85) 25	0.57(0.83) 23	0.32(0.58) 16 AB	0.22(0.53) 12	0.16(0.60) 9	0.16(0.50) 7	0.11(0.46) 4
CO 60mg	0.21(0.55) 33	0.42(0.56) 33	0.39(0.66) 24	0.24(0.50) 19	0.03(0.47) 13 C	0.06(0.35) 7	0.06(0.24) 5	0.09(0.38) 4	0.06(0.24) 3
Placebo	0.58(0.65) 36	0.50(0.70) 36	0.36(0.87) 22	0.22(0.76) 16	0.08(0.44) 9 BC	0.14(0.42) 5	0.08(0.37) 3	0.08(0.37) 3	0.06(0.23) 3
P-VALUE	0.061	0.561	0.113	0.068	0.010	0.065	0.361	0.829	0.650
RMS ERROR	0.602	0.734	0.814	0.717	0.548	0.460	0.472	0.419	0.306

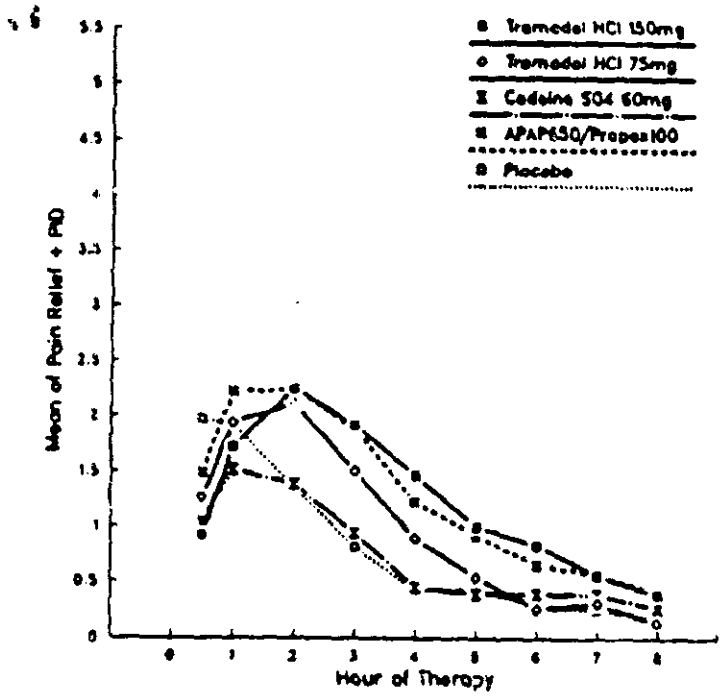
CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TX



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour	7-hour	8-hour
TR 150mg	36(100.0%)	23(63.9%)	20(55.6%)	18(50.0%)	14(38.9%)	10(27.8%)	7(19.4%)	6(16.7%)
TR 75mg	35(100.0%)	21(60.0%)	19(54.3%)	16(45.7%)	11(31.4%)	7(20.0%)	5(14.3%)	4(11.4%)
APAP/PROP	37(100.0%)	26(70.3%)	23(62.2%)	16(43.2%)	12(32.4%)	9(24.3%)	7(18.9%)	4(10.8%)
CO 60mg	33(100.0%)	24(72.7%)	19(57.6%)	13(39.4%)	7(21.2%)	5(15.2%)	4(12.1%)	3(9.1%)
Placebo	36(100.0%)	22(61.1%)	17(47.2%)	10(27.8%)	5(13.9%)	3(8.3%)	3(8.3%)	3(8.3%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TX



Treatment	SPRID (extrapolated) 3-hour	6-hour
TR 150mg	5.49(5.78)	8.79(10.43)
TR 75mg	5.23(5.09)	6.91(7.15)
APAP/PROP	5.99(5.31)	8.77(9.59)
CO 60mg	3.61(3.38)	4.85(5.46)
Placebo	4.11(5.28)	5.25(7.24)
P-VALUE	0.256	0.126
RMS ERROR	5.058	8.228

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6	7	8
TR 150mg	0.92(1.16)	1.72(2.06)	2.25(2.42)	1.92(2.36)	1.47(2.16)	1.00(1.76)	0.83(1.73)	0.56(1.40)	0.39(1.05)
	36 B	36	23	20 A	18 A	14	10	7	6
TR 75mg	1.26(1.63)	1.94(1.89)	2.11(2.26)	1.51(1.82)	0.89(1.43)	0.54(1.15)	0.26(1.09)	0.31(1.11)	0.14(0.77)
	35 B	35	21	19 AB	16 ABC	11	7	5	4
APAP/PROP	1.49(1.39)	2.22(2.06)	2.24(2.29)	1.89(2.28)	1.22(1.95)	0.92(1.77)	0.65(1.78)	0.57(1.61)	0.41(1.44)
	37 AB	37	25	23 A	16 AB	12	9	7	4
CO 60mg	1.03(1.42)	1.52(1.48)	1.39(1.54)	0.94(1.46)	0.45(1.12)	0.39(1.12)	0.39(1.06)	0.39(1.27)	0.27(0.98)
	33 B	33	24	19 B	13 BC	7	5	4	3
Placebo	1.97(1.86)	1.92(1.98)	1.36(2.27)	0.81(1.91)	0.42(1.23)	0.44(1.36)	0.28(1.19)	0.25(1.05)	0.19(0.82)
	36 A	36	22	16 B	9 C	5	3	3	3
P-VALUE	0.030	0.622	0.197	0.051	0.026	0.275	0.349	0.[illegible]9	0.778
RMS ERROR	1.511	1.914	2.188	2.004	1.638	1.467	1.417	1.[illegible]18	1.045

PROTOCOL TX

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	33	23	56
TR 75mg	24	17	43
APAP/PROP	20	15	29
CO 60mg	29	20	56
Placebo	15	12	22

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	3:00	1:45	5:00
TR 75mg	3:00	1:40	4:35
APAP/PROP	3:25	1:55	4:35
CO 60mg	3:05	2:00	4:10
Placebo	2:20	1:40	3:25

Tramadol Protocol TX 09:32 Monday, June 6, 1994 1

Demographic Frequencies and Means

	Sex		___Race___					_Baseline Pain_		_____Surgical Procedure_____				_Reason for Discontinuation_			
Drug	M	F	Wht	Blk	Oth	Mean Age	Mean Weight	Moderate	Severe	Orthopedic Surgery	Cholecys tectomy	Hernio rrhaphy	Other	Adv Exp	Patient Choice	Protocol Violation	Other
Tramadol 150 MG	13	27	35	1	4	38.95	169.15	30	10	29	5	3	3	2	0	0	0
Tramadol 75 MG	9	27	30	0	6	41.44	162.28	29	6	26	4	1	5	1	0	1	1
Codeine SO4	14	19	31	1	1	43.06	171.55	25	8	24	4	2	3	0	0	0	1
APAP/Propoxyhene	12	25	33	0	4	43.14	165.24	31	6	24	6	2	5	2	0	0	1
Placebo	11	25	32	1	3	44.53	177.00	27	9	28	4	2	2	0	0	0	0

This display includes all patients, including those who were not included in the analysis.

Study: TY Investigator:	Pain Model: Post-Surgical Pain Study Design. si, sd, db, r, p* Duration: 6 hours Tx: Tramadol (TR)150 mg and 75 mg Acetaminophen 650 mg/propoxyphene napsylate100 mg (APAP/propoxyphene) Codeine sulfate 60 mg (Codeine) Placebo
A single investigator, randomized, double-blind, single-dose, parallel group study of tramadol hydrochloride 150 mg and 75 mg (tramadol), acetaminophen 650 mg with propoxyphene napsylate 100 mg (APAP/propoxyphene), codeine sulfate 60 mg (codeine) and placebo in hospitalized patients with moderate or severe baseline pain following surgery.	
TR 150 mg: 30 pts. APAP/propoxyphene: 31 pts. Codeine: 30 pts. Placebo: 30 pts. TR 75 mg: 31 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5 and 6 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

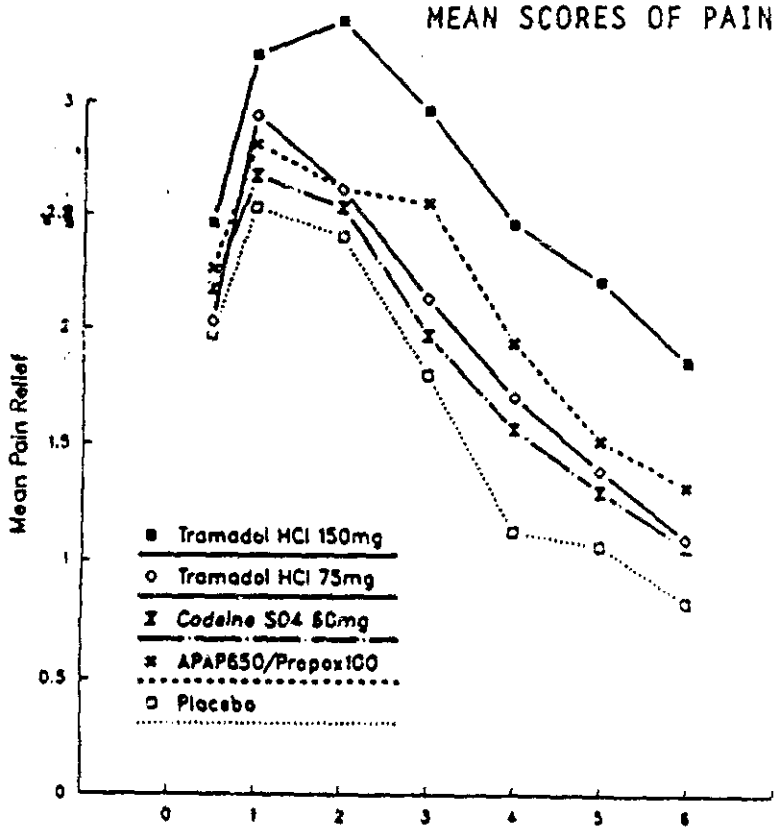
* si = single investigator; sd = single-dose; db = double-blind; r = randomized; p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

Of the 152 patients enrolled, 150 (99%) completed the study either by finishing six hours of evaluation or by receiving a rescue analgesic, and two patients (1%) discontinued the study prematurely. Two tramadol 150 mg patients were excluded from the analyses of efficacy for not completing one hour (60 minutes) of evaluation. A total of 150 patients was included in the analyses of efficacy. All patients (N = 152) were included in the analyses of safety.

In this study, there were no statistically significant overall treatment effects for TOTPAR (Total Pain Relief; sum of 0 - 3 hour scores), SPID (Sum of the Pain Intensity Differences; 0 - 3 and 0 - 6 hour scores) and time to remedication. Moreover, there was no statistically significant separation between the standard analgesics and placebo for TOTPAR (sum of 0 - 6 hour scores). Therefore, this study is considered to be a model failure, and no further efficacy analyses were conducted.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TY

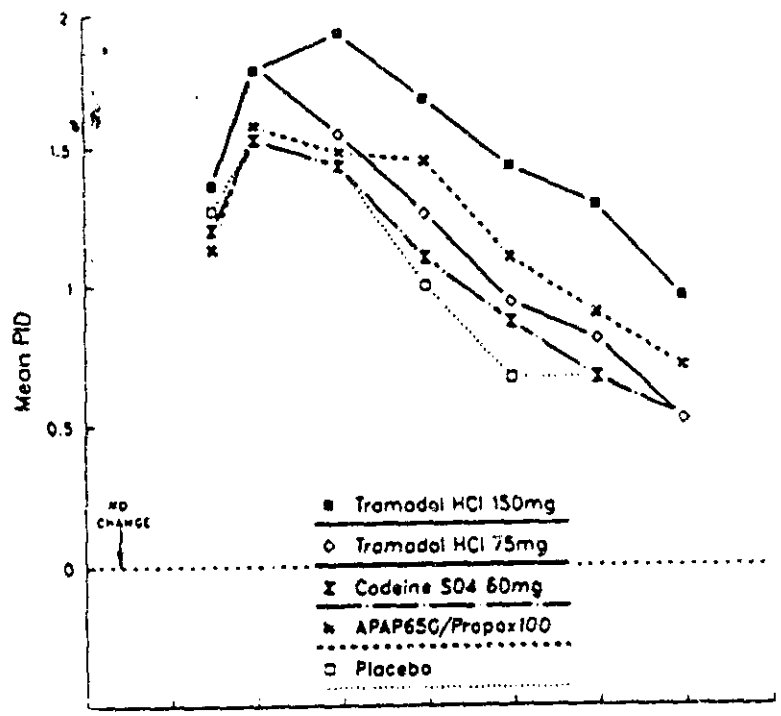


Treatment	TOTPAR (extrapolated) 3-hour	6-hour	
TR 150mg	9.16(2.71)	15.70(7.09)	A
TR 75mg	7.23(3.70)	11.42(8.12)	B
APAP/PROP	7.69(4.07)	12.47(8.43)	AB
CO 60mg	6.92(4.30)	10.85(8.23)	B
Placebo	6.45(3.69)	9.48(7.22)	B
P-VALUE	0.072	0.042	
RMS ERROR	3.749	7.853	

MEAN SCORES OF PAIN RELIEF (Extrapolated)

Treatment	Assessment Time-Points (in hours) 1/2	1	2	3	4	5	6
TR 150mg	2.46(1.17) 28	3.21(0.92) 28	3.36(1.03) 27	2.96(1.29) 27 A	2.46(1.71) 22	2.21(1.79) 19	1.86(1.69) 18
TR 75mg	2.03(1.35) 31	2.94(1.21) 31	2.61(1.50) 27	2.13(1.78) 23 B	1.71(1.92) 17	1.39(1.82) 15	1.10(1.70) 12
APAP/PROP	2.26(1.12) 31	2.81(1.38) 31	2.61(1.56) 27	2.55(1.63) 23 AB	1.94(1.79) 21	1.52(1.84) 16	1.32(1.85) 12
CO 60mg	2.17(1.44) 30	2.67(1.45) 30	2.53(1.63) 26	1.97(1.71) 23 B	1.57(1.76) 16	1.30(1.68) 13	1.07(1.55) 11
Placebo	1.97(1.30) 30	2.53(1.53) 30	2.40(1.50) 27	1.80(1.52) 23 B	1.13(1.50) 16	1.07(1.68) 10	0.83(1.51) 8
P-VALUE	0.606	0.339	0.119	0.043	0.062	0.148	0.188
RMS ERROR	1.284	1.317	1.466	1.601	1.742	1.766	1.667

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TY

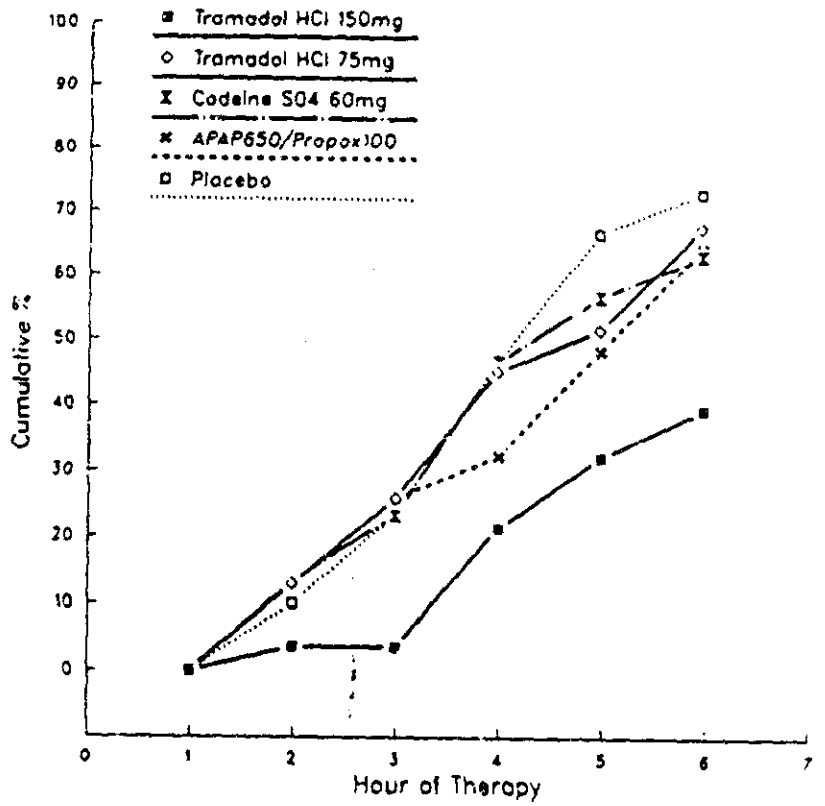


Treatment	SPID (extrapolated) 3-hour	6-hour
TR 150mg	5.18(2.39)	8.86(5.17)
TR 75mg	4.39(2.17)	6.65(4.51)
APAP/PROP	4.29(2.60)	7.00(4.74)
CO 60mg	3.90(2.70)	5.97(4.90)
Placebo	3.83(2.61)	5.70(5.14)
P-VALUE	0.262	.122
RMS ERROR	2.499	4.892

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 150mg	1.36(0.78) 28	1.79(0.96) 28	1.93(0.81) 27	1.68(1.02) 27	1.43(1.10) 22	1.29(1.18) 19	0.96(1.04) 18
TR 75mg	1.35(0.80) 31	1.81(0.79) 31	1.55(0.96) 27	1.26(1.03) 23	0.94(1.18) 17	0.81(1.01) 15	0.52(0.89) 12
APAP/PROP	1.13(0.81) 31	1.58(0.92) 31	1.48(1.09) 27	1.45(0.99) 23	1.10(1.04) 21	0.90(1.04) 16	0.71(1.04) 12
CO 60mg	1.20(0.89) 30	1.53(0.94) 30	1.43(1.01) 26	1.10(1.06) 23	0.87(1.04) 16	0.67(0.96) 13	0.53(0.94) 11
Placebo	1.27(0.87) 30	1.53(1.07) 30	1.43(1.07) 27	1.00(1.02) 23	0.67(1.03) 16	0.67(1.12) 10	0.53(1.07) 8
P-VALUE	0.786	0.639	0.294	0.089	0.096	0.166	0.374
RMS ERROR	0.829	0.940	0.997	1.025	1.081	1.065	0.997

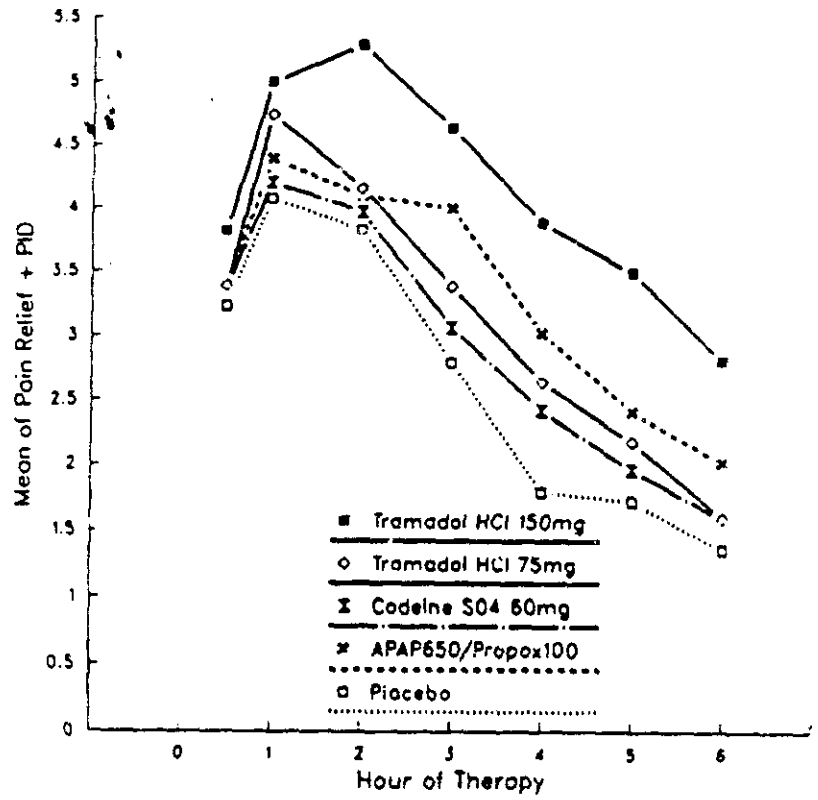
CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TY



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour
TR 150mg	28(100.0%)	27(96.4%)	27(96.4%)	22(78.6%)	19(67.9%)	17(60.7%)
TR 75mg	31(100.0%)	27(87.1%)	23(74.2%)	17(54.8%)	15(48.4%)	10(32.3%)
APAP/PROP	31(100.0%)	27(87.1%)	23(74.2%)	21(67.7%)	16(51.6%)	11(35.5%)
CC 60mg	30(100.0%)	26(86.7%)	23(76.7%)	16(53.3%)	13(43.3%)	11(36.7%)
Placebo	30(100.0%)	27(90.0%)	23(76.7%)	16(53.3%)	10(33.3%)	8(26.7%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TY



	SPRID (extrapolated)	
Treatment	3-hour	6-hour
TR 150mg	14.34(4.85)	24.55(11.75) A
TR 75mg	11.61(5.64)	18.06(12.35) B
APAP/PROP	11.98(6.44)	19.47(12.89) AB
CO 60mg	10.82(6.77)	16.82(12.77) B
Placebo	10.28(6.12)	15.18(12.16) B
P-VALUE	0.107	0.054
RMS ERROR	6.016	12.402

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 150mg	3.82(1.83) 28	5.00(1.76) 28	5.29(1.74) 27	4.64(2.21) 27 A	3.89(2.73) 22	3.50(2.89) 19	2.82(2.64) 18
TR 75mg	3.39(2.06) 31	4.74(1.88) 31	4.16(2.38) 27	3.39(2.75) 23 AB	2.65(3.06) 17	2.19(2.80) 15	1.61(2.55) 12
APAP/PROP	3.39(1.76) 31	4.39(2.19) 31	4.10(2.57) 27	4.00(2.57) 23 AB	3.03(2.77) 21	2.42(2.85) 16	2.03(2.87) 12
CO 60mg	3.37(2.25) 30	4.20(2.31) 30	3.97(2.57) 26	3.07(2.69) 23 B	2.43(2.74) 16	1.97(2.59) 13	1.60(2.43) 11
Placebo	3.23(2.06) 30	4.07(2.53) 30	3.83(2.49) 27	2.80(2.46) 23 B	1.80(2.48) 16	1.73(2.78) 10	1.37(2.57) 8
P-VALUE	0.841	0.446	0.152	0.047	0.064	0.145	0.241
RMS ERROR	2.002	2.159	2.381	2.549	2.765	2.782	2.616

PROTOCOL TY

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	8	7	10
TR 75mg	9	7	11
APAP/PROP	9	7	11
CO 60mg	9	7	12
Placebo	9	8	12

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	> 6:00	4:15	> 6:00
TR 75mg	4:00	3:00	5:45
APAP/PROP	4:45	3:10	5:55
CO 60mg	3:50	3:05	5:55
Placebo	3:50	3:05	4:45

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Tramadol Protocol TY

Demographic Frequencies and Means

	Sex		___Race____					_Baseline Pain_		_____Surgical Procedure_____					_Reason for Discontinuatio		
Drug	M	F	Wht	Blk	Oth	Mean Age	Mean Weight	Moderate	Severe	Hysterectomy/ Laparotomy/ Oophorectomy	Abdominal Soft Tissue	Other Soft Tissue	Bony	Adv Exp	Patient Choice	Prot Viol	Other
Tramadol 150 MG	11	19	28	2	0	46.23	160.72	15	15	3	7	15	5	0	0	0	0
Tramadol 75 MG	14	17	25	5	1	47.23	167.89	14	17	5	6	13	7	0	0	0	0
Codeine SO4	14	16	19	9	2	46.67	164.13	15	15	5	6	6	7	0	0	0	0
APAP/Propoxyhene	12	19	28	3	0	46.39	160.85	15	16	7	10	9	7	1	0	0	0
Placebo	14	16	27	3	0	49.50	177.41	14	16	9	6	12	6	1			
										6	6						

This display includes all patients, including those who were not included in the analysis.

00 0075

Study: TW2 Investigator:	Pain Model: Post-Surgical Pain Study Design: ti, ts, sd, db ,r ,p* Duration: 6 hours Tx: Tramadol (TR) 150 and 75 mg Acetaminophen 650 mg/propoxyphene napsylate 100 mg(APAP/propoxyphene) Codeine Sulfate 60 mg (Codeine) Placebo
A two investigator, two-site, randomized, double-blind, single-dose, parallel group study of tramadol hydrochloride 150 mg and 75 mg (tramadol), acetaminophen 650 mg with propoxyphene napsylate 100 mg (APAP/propoxyphene), codeine sulfate 60 mg (codeine) and placebo in patients with moderate or severe post-surgical pain secondary to gynecologic surgery or cesarean section.	
TR 150 mg: 40 pts. APAP/propoxyphene: 39 pts. Codeine: 41 pts. Placebo: 40 pts. TR 75 mg: 41pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, and 6 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* ti =two investigator; ts= two-site; sd = single-dose; db = double-blind; r = randomized; p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

Of the 201 patients enrolled, 198 patients (99%) completed the study either by finishing the 6-hour protocol or by taking a rescue analgesic, and three patients (1%) discontinued the study prematurely.

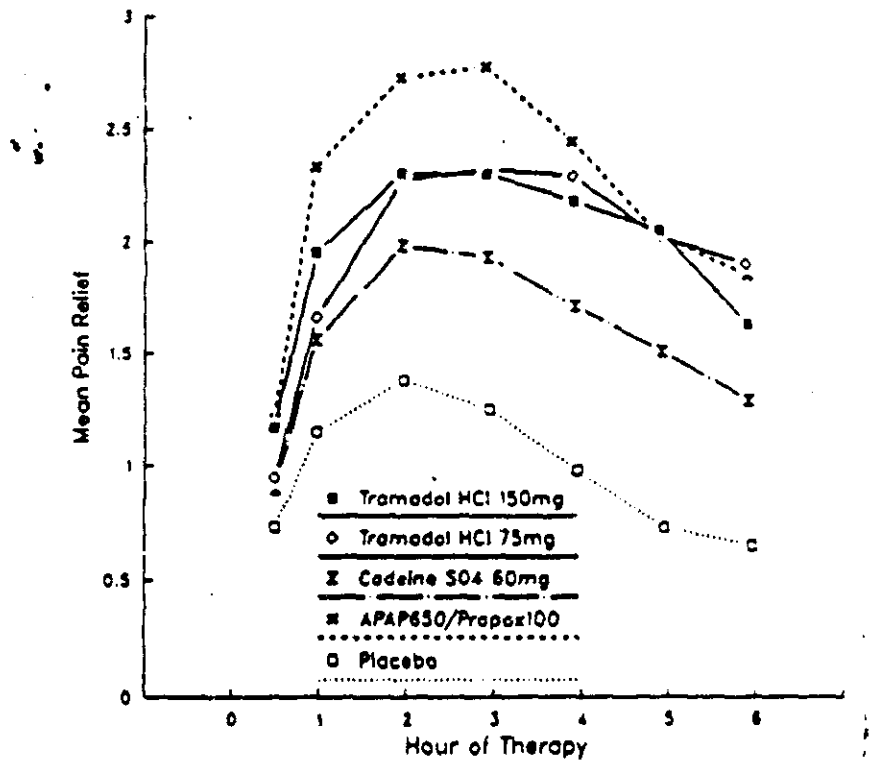
APAP/propoxyphene was statistically superior compared to placebo for all efficacy variables. Codeine was numerically favored over placebo with respect to all efficacy variables, and was statistically superior to placebo for TOTPAR (Total Pain Relief 0 - 3 and 0 - 6 hour interval scores) and SPID (Sum of the Pain Intensity Differences; 0 - 3 and 0 - 6 hour interval scores).

Tramadol 150 mg was statistically superior compared to placebo with respect to all efficacy variables except for time to remedication. Tramadol 75 mg was statistically superior compared to placebo for all efficacy variables. There was no tramadol dose-response.

Comparing the four active treatment groups, APAP/propoxyphene was favored numerically over tramadol 150 mg, tramadol 75 mg and codeine with respect to all efficacy variables. There were no statistical differences among the tramadol 150 mg, tramadol 75 mg and APAP/propoxyphene groups for any efficacy variable. Codeine was not statistically different from the other active treatments for SPID (0 - 6 hour interval scores) and time to remedication.

This study showed model sensitivity and demonstrated pain relief for tramadol 150 mg and 75 mg statistically superior to that of placebo. There were no statistical differences among tramadol 150 mg, tramadol 75 mg and APAP/propoxyphene in producing overall analgesia over the entire study.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TW2

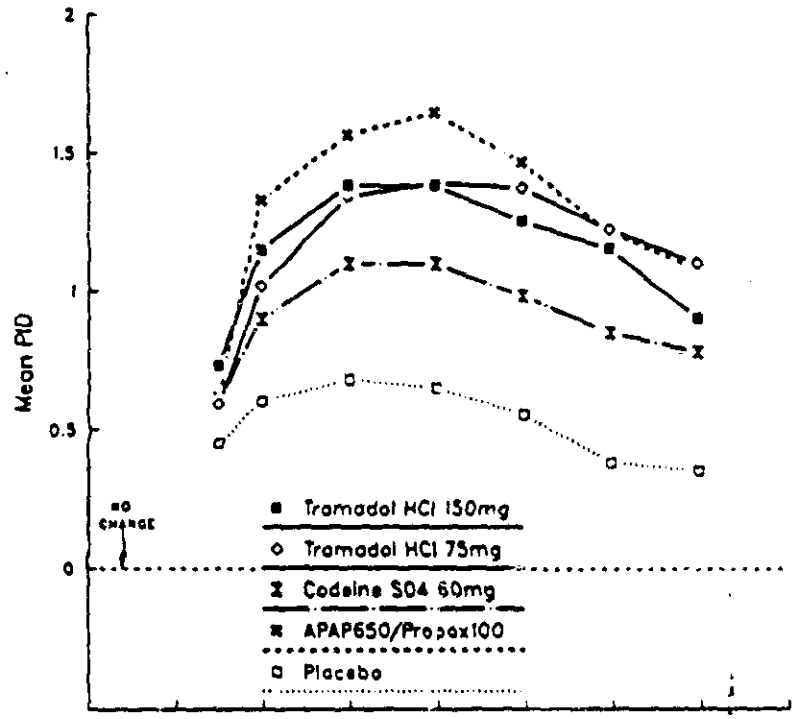


	TOTPAR (extrapolated)	
Treatment	3-hour	6-hour
TR 150mg	6.16(4.11) AB	12.01(8.20) AB
TR 75mg	5.89(3.44) AB	12.11(7.42) AB
APAP/PROP	7.26(2.31) A	13.56(6.13) A
CO 60mg	5.13(3.40) B	9.65(7.27) B
Placebo	3.56(3.19) C	5.91(5.93) C
P-VALUE	0.000	0.000
RMS ERROR	3.346	7.047

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 150mg	1.17(1.20) 40	1.95(1.50) 40 AB	2.30(1.56) 40 AB	2.30(1.49) 36 AB	2.18(1.57) 31 AB	2.05(1.57) 30 A	1.63(1.56) 27 A
TR 75mg	0.95(1.00) 41	1.66(1.20) 41 BC	2.27(1.30) 41 AB	2.32(1.44) 39 AB	2.29(1.52) 33 AB	2.02(1.60) 32 A	1.90(1.53) 30 A
APAP/PROP	1.21(0.98) 39	2.33(0.93) 39 A	2.72(0.94) 39 A	2.77(1.04) 39 A	2.44(1.52) 37 A	2.03(1.51) 35 A	1.85(1.50) 29 A
CO 60mg	0.90(0.74) 41	1.56(1.14) 41 BC	1.98(1.37) 41 B	1.93(1.46) 38 B	1.71(1.47) 28 B	1.51(1.47) 27 A	1.29(1.40) 24 A
Placebo	0.73(0.82) 40	1.15(1.10) 40 C	1.38(1.27) 40 C	1.25(1.39) 34 C	0.98(1.27) 28 C	0.73(1.11) 20 B	0.65(1.12) 15 B
P-VALUE	0.144	0.000	0.000	0.000	0.000	0.000	0.001
RMS ERROR	0.957	1.189	1.307	1.375	1.473	1.464	1.432

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TW2

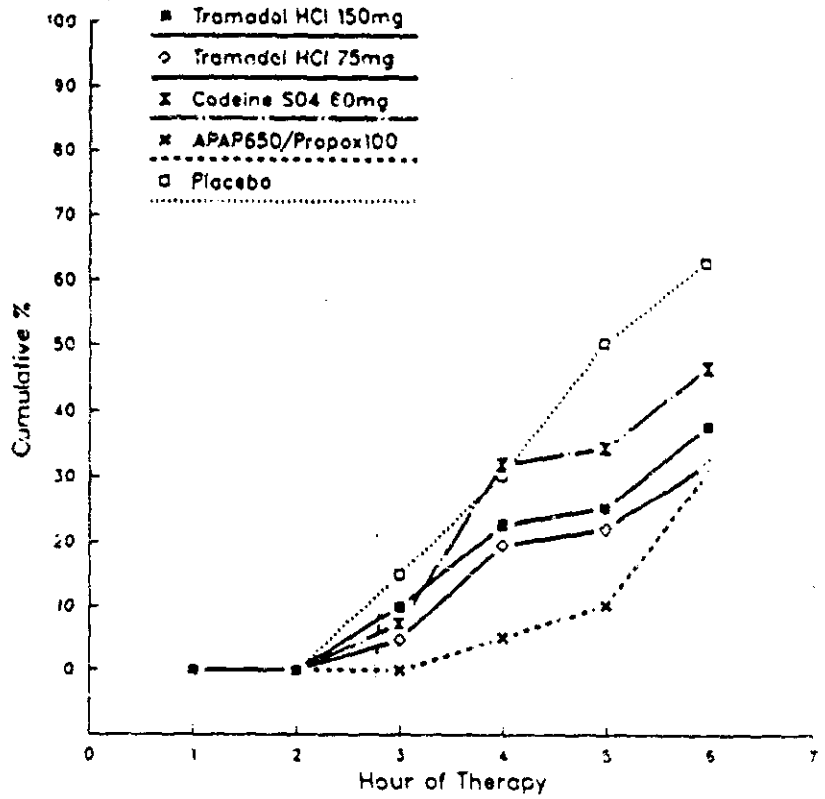


Treatment	SPID (extrapolated) 3-hour	6-hour
TR 150mg	3.69(2.92) AB	6.99(5.72) AB
TR 75mg	3.54(2.42) AB	7.22(5.16) AB
APAP/PROP	4.18(1.70) A	7.92(3.98) A
CO 60mg	2.95(2.51) B	5.56(5.10) B
Placebo	1.85(2.13) C	3.13(3.73) C
P-VALUE	0.000	0.000
RMS ERROR	2.377	4.805

Treatment	Assessment Time-Points (in hours) 1/2	1	2	3	4	5	6
TR 150mg	0.73(0.82) 40	1.15(1.10) 40 AB	1.38(1.13) 40 AB	1.38(1.08) 36 AB	1.25(1.10) 31 AB	1.15(1.08) 30 A	0.90(1.03) 27 A
TR 75mg	0.59(0.74) 41	1.02(0.82) 41 AB	1.34(0.94) 41 AB	1.39(1.02) 39 AB	1.37(1.07) 33 AB	1.22(1.08) 32 A	1.10(1.02) 30 A
APAP/PROP	0.62(0.59) 39	1.33(0.70) 39 A	1.56(0.75) 39 A	1.64(0.78) 39 A	1.46(1.00) 37 A	1.21(0.95) 35 A	1.08(0.90) 29 A
CO 60mg	0.61(0.54) 41	0.90(0.80) 41 BC	1.10(1.02) 41 BC	1.10(1.07) 38 B	0.98(1.01) 28 BC	0.85(1.01) 27 A	0.78(0.94) 24 A
Placebo	0.45(0.60) 40	0.60(0.78) 40 C	0.68(0.94) 40 C	0.65(0.89) 34 C	0.55(0.81) 28 C	0.38(0.70) 20 B	0.35(0.70) 15 B
P-VALUE	0.482	0.003	0.001	0.000	0.000	0.000	0.002
RMS ERROR	0.665	0.851	0.965	0.976	1.004	0.977	0.926

CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TW2

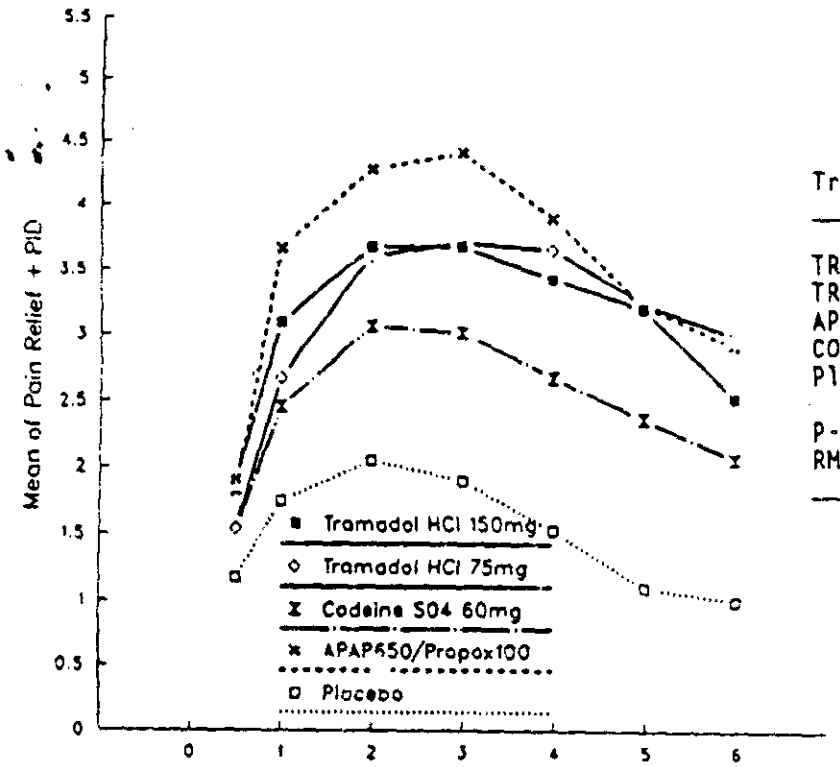
Cumulative Percent of Patients Terminating Prematurely



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour
TR 150mg	40(100.0%)	40(100.0%)	36(90.0%)	31(77.5%)	30(75.0%)	25(62.5%)
TR 75mg	41(100.0%)	41(100.0%)	39(95.1%)	33(80.5%)	32(78.0%)	28(68.3%)
APAP/PROP	39(100.0%)	39(100.0%)	39(100.0%)	37(94.9%)	35(89.7%)	27(69.2%)
CO 60mg	41(100.0%)	41(100.0%)	38(92.7%)	28(68.3%)	27(65.9%)	22(53.7%)
Placebo	40(100.0%)	40(100.0%)	34(85.0%)	28(70.0%)	20(50.0%)	15(37.5%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TW2



Treatment	SPRID (extrapolated) 3-hour	6-hour
TR 150mg	9.85(6.91) AB	19.00(13.66) AB
TR 75mg	9.43(5.69) AB	19.33(12.28) AB
APAP/PROP	11.44(3.77) A	21.49(9.75) A
CO 60mg	8.09(5.77) B	15.21(12.14) B
Placebo	5.41(5.10) C	9.04(9.34) C
P-VALUE	0.000	0.000
RMS ERROR	5.552	11.564

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 150mg	1.90(1.96) 40	3.10(2.54) 40 AB	3.68(2.63) 40 AB	3.68(2.52) 36 AB	3.43(2.62) 31 AB	3.20(2.58) 30 A	2.53(2.54) 27 A
TR 75mg	1.54(1.66) 41	2.68(1.97) 41 B	3.61(2.18) 41 AB	3.71(2.39) 39 AB	3.66(2.54) 33 AB	3.24(2.63) 32 A	3.00(2.50) 30 A
APAP/PROP	1.82(1.43) 39	3.67(1.54) 39 A	4.28(1.62) 39 A	4.41(1.73) 39 A	3.90(2.47) 37 A	3.23(2.41) 35 A	2.92(2.34) 29 A
CO 60mg	1.51(1.21) 41	2.46(1.86) 41 BC	3.07(2.33) 41 B	3.02(2.47) 38 B	2.68(2.43) 28 B	2.37(2.44) 27 A	2.07(2.30) 24 A
Placebo	1.17(1.34) 40	1.75(1.78) 40 C	2.05(2.12) 40 C	1.90(2.22) 34 C	1.53(2.01) 28 C	1.10(1.77) 20 B	1.00(1.78) 15 B
P-VALUE	0.240	0.001	0.000	0.000	0.000	0.000	0.001
RMS ERROR	1.541	1.968	2.205	2.287	2.424	2.388	2.310

PROTOCOL TW2

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	16	12	23
TR 75mg	20	15	29
APAP/PROP	16	13	22
CO 60mg	20	16	26
Placebo	26	19	40

Approximated Duration of Pain Relief *
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	> 6:00	5:20	> 6:00
TR 75mg	> 6:00	5:50	> 6:00
APAP/PROP	> 6:00	5:55	> 6:00
CO 60mg	> 6:00	3:55	> 6:00
Placebo	4:45	3:55	5:55

* More than 50% of the patients in each group except placebo were active in the trial throughout the study. Therefore a mean Duration and Lower Confidence Limit could not be calculated for all groups.

Tramadol Protocol TW2 09:25 Monday, June 6, 1994 1

Demographic Frequencies and Means

	Sex		___Race___					_Baseline Pain_		Surgical Procedure			_Reason for Discontinuation_			
Drug	M	F	Wht	Blk	Oth	Mean Age	Mean Weight	Moderate	Severe	Cesarean Section	Abdominal Hysterectomy	Other	Adv Exp	Patient Choice	Proto Viola	Other
Tramadol 150 MG	0	40	32	8	0	35.65	156.13	12	28	16	21	3	0	0	0	0
Tramadol 75 MG	0	41	35	6	0	29.54	145.24	10	31	27	12	2	0	0	0	0
Codeine SO4	0	41	29	11	0	28.78	141.57	11	30	29	11	1	0	0	0	1
APAP/Propoxyhene	0	39	25	14	0	32.38	152.59	10	29	22	11	6	0	0	0	0
Placebo	0	40	29	11	0	32.80	145.58	13	27	24	13	3	2	0	0	0

This display includes all patients, including those who were not included in the analysis.

Study: TZA Investigator: 8)	Pain Model: Post-Surgical Pain Study Design: si, ts, sd, db ,r ,p* Duration: 6 hours Tx: Tramadol (TR) 150 and 75 mg Acetaminophen 650 mg/propoxyphene napsylate 100mg (APAP/propoxyphene) Codeine Sulfate 60 mg (Codeine) Placebo
A single investigator, two-site, randomized, double-blind, single-dose, parallel group study of tramadol hydrochloride 150 mg and 75 mg (tramadol), acetaminophen 650 mg with propoxyphene napsylate 100 mg (APAP/propoxyphene), codeine sulfate 60 mg (codeine) and placebo in hospitalized patients with moderate or severe baseline pain following gynecologic surgery.	
TR 150 mg: 40 pts. APA/propoxyphene: 39 pts. Codeine: 40 pts. Placebo: 42 pts. TR 75 mg: 40pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, and 6 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* si=single-investigator; ts=two-site; sd=single-dose; db=double-blind; r=randomized; p =parallel

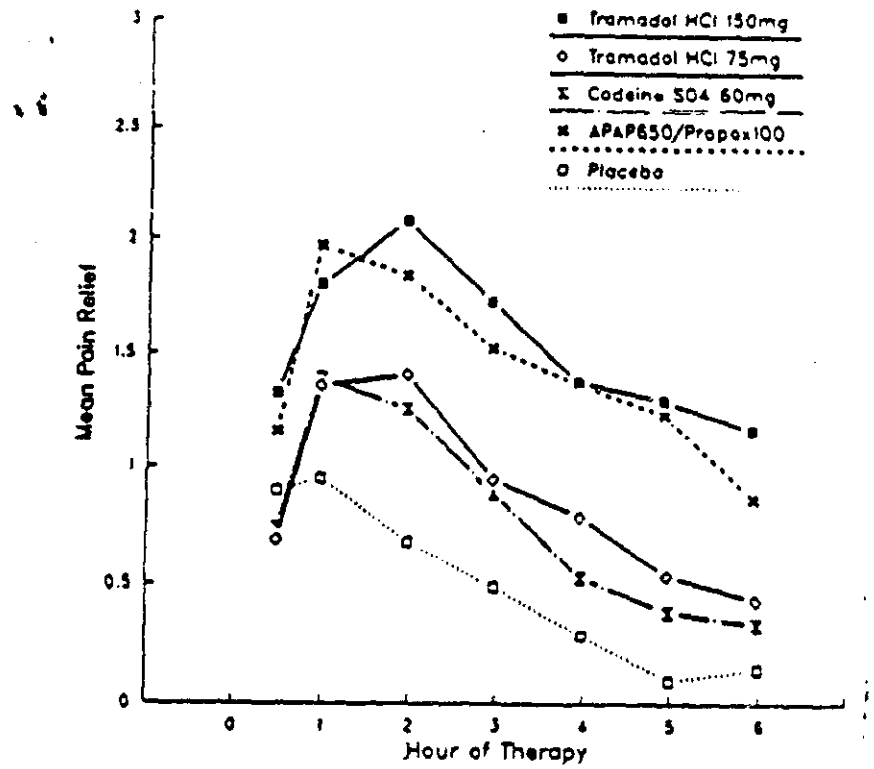
NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

Of the 201 patients enrolled, 199 (99%) completed the study either by finishing six hours of evaluations or by receiving a rescue analgesic, and two patients (1%) discontinued the study prematurely. Five patients were excluded from the analyses of efficacy: four patients (one tramadol 75 mg, one APAP/propoxyphene, one codeine, one placebo) because no baseline pain was recorded and one codeine patient because of no one hour or subsequent evaluations.

APAP/propoxyphene was statistically superior to placebo with respect to all efficacy variables. Codeine was numerically favored over placebo with respect to all efficacy variables, although this was not statistically significant. Tramadol 150 mg was statistically superior to placebo with respect to all efficacy variables. Tramadol 75 mg was numerically favored over placebo with respect to all efficacy variables, but was statistically superior to placebo only with respect to time to remedication. A significant tramadol dose-response was observed for TOTPAR (Total Pain Relief; sum of 0 - 3 and 0 - 6 hour scores), SPID (Sum of the Pain Intensity Difference; 0 - 3 and 0 - 6 hour scores) and time to remedication. Comparing the four active treatment groups with respect to all efficacy variables, tramadol 150 mg and APAP/propoxyphene were numerically superior to the other treatments. These two treatments were not statistically different with respect to any efficacy variables. Mean TOTPAR and SPID scores numerically favored tramadol 150 mg over APAP/ propoxyphene during both time periods. Mean TOTPAR scores numerically favored tramadol 75 mg over codeine during both time periods, although this was not statistically significant. Mean SPID scores numerically favored codeine over tramadol 75 mg during the 0 - 3 hour time period, while tramadol 75 mg was favored over codeine during the 0 - 6 hour time period. These two treatments were not statistically different with respect to SPID scores.

This study showed model sensitivity, and tramadol 150 mg provided pain relief statistically superior to that of placebo. In this study, the order of relative efficacy over all variables was tramadol 150 mg and APAP/propoxyphene > tramadol 75 mg and codeine > placebo.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TZA

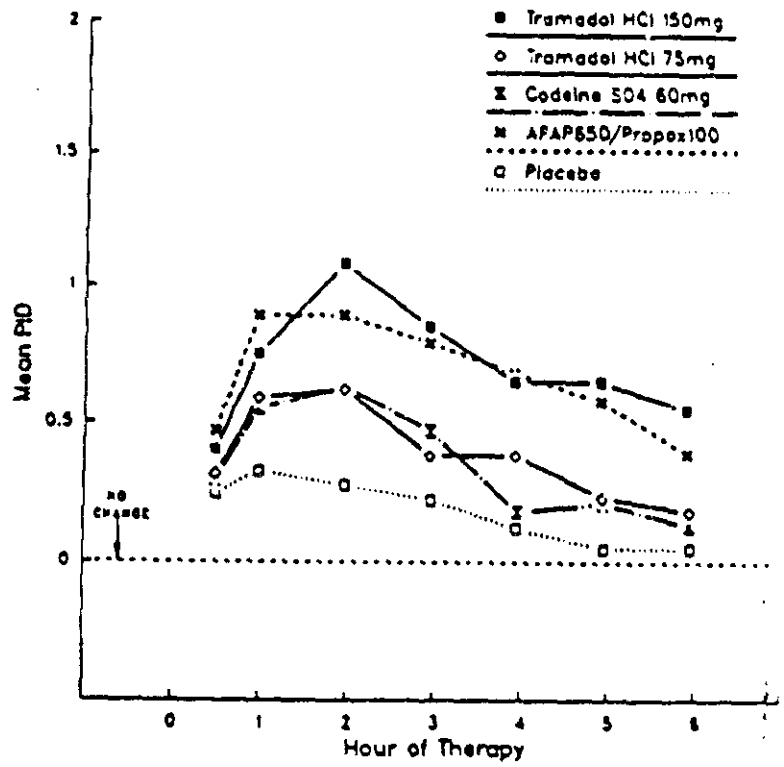


Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 150mg	5.36(4.42) A	9.21(8.49) A
TR 75mg	3.38(3.77) BC	5.15(6.86) B
APAP/PROP	4.93(3.53) AB	8.41(7.52) A
CO 60mg	3.22(3.51) C	4.49(5.80) B
Placebo	2.10(2.59) C	2.63(3.93) B
P-VALUE	0.000	0.000
RMS ERROR	3.607	6.694

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 150mg	1.33(1.21) 40 A	1.80(1.54) 40 AB	2.08(1.80) 30 A	1.73(1.78) 25 A	1.38(1.72) 21 A	1.30(1.71) 16 A	1.17(1.60) 17 A
TR 75mg	0.69(0.89) 39 C	1.36(1.37) 39 BC	1.41(1.60) 26 AB	0.95(1.52) 19 BC	0.79(1.44) 11 AB	0.54(1.17) 10 B	0.44(1.05) 8 BC
APAP/PROP	1.16(1.05) 38 AB	1.97(1.24) 38 A	1.84(1.57) 32 AB	1.53(1.67) 25 AB	1.37(1.67) 20 A	1.24(1.67) 16 A	0.87(1.44) 15 AB
CO 60mg	0.74(0.89) 38 BC	1.39(1.28) 37 BC	1.26(1.54) 24 BC	0.89(1.52) 16 BC	0.53(1.11) 12 B	0.39(1.00) 6 B	0.34(0.97) 5 BC
Placebo	0.90(0.92) 41 ABC	0.95(1.00) 41 C	0.68(1.15) 20 C	0.49(1.14) 10 C	0.29(0.93) 7 B	0.10(0.49) 4 B	0.15(0.65) 2 C
P-VALUE	0.023	0.005	0.001	0.003	0.001	0.000	0.001
RMS ERROR	1.000	1.297	1.544	1.540	1.404	1.286	1.188

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TZA

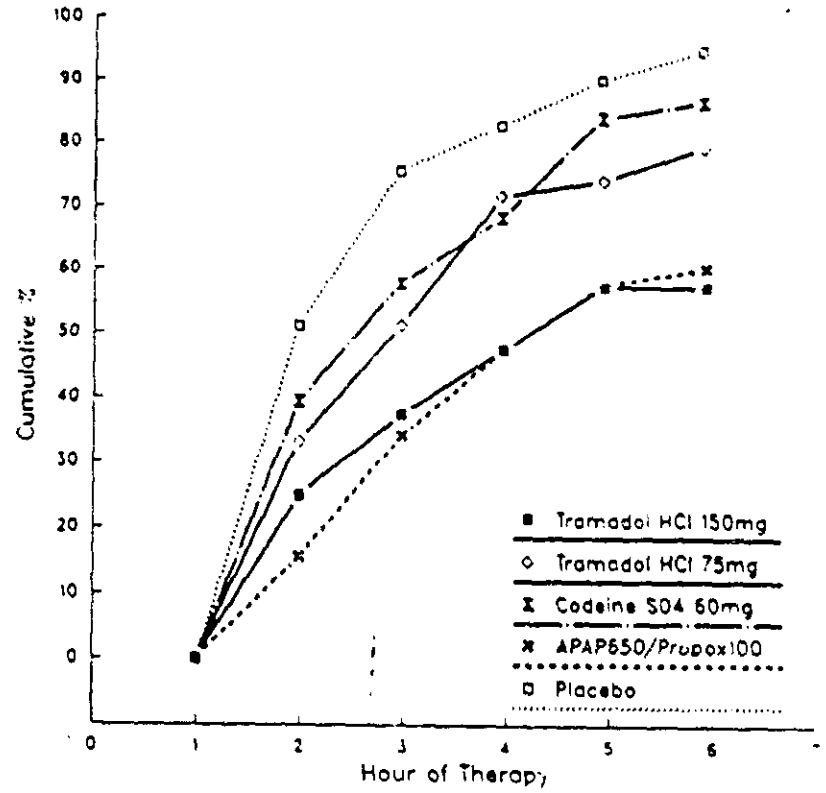


Treatment	SPID (extrapolated) 3-hour	6-hour
TR 150mg	2.50(2.44) A	4.35(4.69) A
TR 75mg	1.45(1.96) C	2.24(3.57) B
APAP/PROP	2.37(1.89) AB	4.03(3.59) A
CO 60mg	1.53(1.91) BC	2.05(2.66) B
Placebo	0.77(1.24) C	0.99(1.72) B
P-VALUE	0.000	0.000
RMS ERROR	1.924	3.425

Treatment	Assessment Time-Points (in hours) 1/2	1	2	3	4	5	6
TR 150mg	0.40(0.67) 40	0.75(0.98) 40 AB	1.08(0.94) 30 A	0.95(0.95) 25 A	0.65(0.98) 21 A	0.65(0.95) 16 A	0.55(0.85) 17 A
TR 75mg	0.31(0.52) 39	0.59(0.72) 39 AB	0.62(0.85) 26 BC	0.38(0.85) 19 C	0.38(0.78) 11 AB	0.23(0.58) 10 B	0.18(0.51) 8 BC
APAP/PROP	0.47(0.65) 38	0.89(0.73) 38 A	0.89(0.83) 32 AB	0.79(0.87) 25 AB	0.68(0.81) 20 A	0.58(0.79) 16 A	0.39(0.72) 15 AB
CO 60mg	0.29(0.57) 38	0.55(0.69) 38 BC	0.63(0.82) 23 B	0.47(0.80) 16 BC	0.18(0.51) 12 B	0.21(0.53) 6 B	0.13(0.41) 5 C
Placebo	0.24(0.54) 41	0.32(0.57) 41 C	0.27(0.50) 20 C	0.22(0.52) 10 C	0.12(0.40) 7 B	0.05(0.22) 4 B	0.05(0.22) 2 C
P-VALUE	0.432	0.011	0.000	0.002	0.001	0.000	0.001
RMS ERROR	0.591	0.748	0.801	0.809	0.726	0.661	0.583

CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TZA

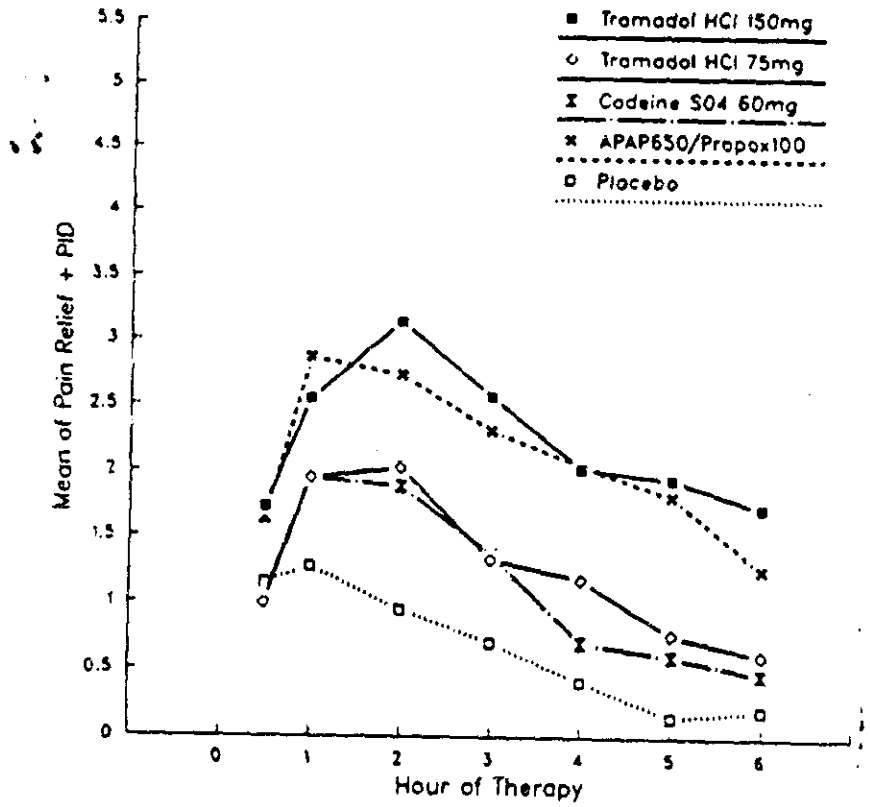
Cumulative Percent of Patients Terminating Prematurely



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour
TR 150mg	40(100.0%)	30(75.0%)	25(62.5%)	21(52.5%)	17(42.5%)	17(42.5%)
TR 75mg	39(100.0%)	26(66.7%)	19(48.7%)	11(28.2%)	10(25.6%)	8(20.5%)
APAP/PROP	38(100.0%)	32(84.2%)	25(65.8%)	20(52.6%)	16(42.1%)	15(39.5%)
CO 60mg	38(100.0%)	24(63.2%)	16(42.1%)	12(31.6%)	6(15.8%)	5(13.2%)
Placebo	41(100.0%)	20(48.8%)	10(24.4%)	7(17.1%)	4(9.8%)	2(4.9%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TZA



Treatment	SPRID (extrapolated) 3-hour	6-hour
TR 150mg	7.86(6.79) A	13.56(13.05) A
TR 75mg	4.83(5.62) B	7.40(10.30) B
APAP/PROP	7.30(5.36) A	12.43(11.04) A
CO 60mg	4.75(5.37) B	6.54(8.61) B
Placebo	2.87(3.78) B	3.62(5.61) B
P-VALUE	0.000	0.000
RMS ERROR	5.465	10.022

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 150mg	1.73(1.81) 40	2.55(2.46) 40 AB	3.15(2.73) 30 A	2.58(2.71) 25 A	2.03(2.66) 21 A	1.95(2.63) 16 A	1.73(2.41) 17 A
TR 75mg	1.00(1.36) 39	1.95(2.04) 39 BC	2.03(2.39) 26 B	1.33(2.32) 19 BC	1.18(2.20) 11 AB	0.77(1.72) 10 B	0.62(1.53) 8 BC
APAP/PROP	1.63(1.65) 38	2.87(1.91) 38 A	2.74(2.37) 32 AB	2.32(2.53) 25 A	2.05(2.45) 20 A	1.92(2.45) 16 A	1.26(2.13) 15 AB
CO 60mg	1.03(1.37) 38	1.95(1.89) 37 BC	1.89(2.33) 23 BC	1.37(2.31) 16 BC	0.71(1.59) 12 B	0.61(1.52) 6 B	0.47(1.37) 5 C
Placebo	1.15(1.35) 41	1.27(1.50) 41 C	0.95(1.63) 20 C	0.71(1.66) 10 C	0.41(1.32) 7 B	0.15(0.65) 4 B	0.20(0.87) 2 C
P-VALUE	0.092	0.005	0.000	0.002	0.001	0.000	0.001
RMS ERROR	1.519	1.982	2.314	2.327	2.103	1.926	1.746

PROTOCOL TZA

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	17	13	26
TR 75mg	30	21	53
APAP/PROP	18	14	27
CO 60mg	29	20	51
Placebo	26	19	41

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	3:45	2:20	> 6:00
TR 75mg	2:40	1:50	3:30
APAP/PROP	3:45	2:40	> 6:00
CO 60mg	2:15	1:40	3:20
Placebo	1:50	1:35	2:25

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Demographic Frequencies and Means

	Sex		___Race___					_Baseline Pain_		_____Surgical Procedure_____					_Reason for Discontinuation_		
Drug	M	F	Wht	Blk	Oth	Mean Age	Mean Weight	Moderate	Severe	Cesarean Section	Hysterectomy/ Oophorectomy	Other	Adv Exp	Patient Choice	Proto Viol	Other	
Tramadol 150 MG	0	40	28	12	0	35.33	159.90	34	6	9	30	1	0	0	0	1	
Tramadol 75 MG	0	40	30	10	0	34.03	151.74	34	5	10	28	2	0	0	0	0	
Codeine SO4	0	40	30	10	0	35.13	155.76	33	6	4	34	2	1	0	0	0	
APAP/Propoxyhene	1	38	27	12	0	36.10	161.87	34	4	10	26	3	0	0	0	0	
Placebo	0	42	31	11	0	35.45	164.29	35	6	14	24	4	0	0	0	0	

This display includes all patients, including those who were not included in the analysis.

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Frequencies of Diagnosis

Drug	Diagnosis											
	Hernia-Inguinal	Cholecystectomy	Genito Urinary Surgery	Oophorectomy	Cyst Ovarian	Oophorectomy &Salpingectomy	Cesarean & Part. Bilateral Salping	Laparotomy/ Oophorectomy	Hysterectomy/ Salpingo Oophorectomy	Abdominal Surgery	Abdominal /Pelvic Surgery	General Surgery
Tramadol 150 MG	0	0	0	0	0	0	0	1	0	0	1	1
Tramadol 75 MG	0	1	1	0	0	0	1	2	0	0	1	0
Codeine SO4	0	1	0	0	1	1	0	0	1	1	2	0
APAP/Propoxyhene	1	0	0	0	0	0	0	0	0	0	0	1
Placebo	0	0	2	1	0	1	0	0	0	0	2	0

Diagnosis		
Cesarean Section	Hysterectomy	Cesarean Section/ Tubal Ligation
8	28	1
8	25	1
3	29	1
10	27	0
13	22	1

00 0077

This display includes all patients, including those who were not included in the analysis.

Study: TR Investigator:	Pain Model: Cesarean Section Study Design: si, sd, db, r, p* Duration: 6 hours Tx: Tramadol (TR) 150 mg and 75 mg Acetaminophen 650 mg/ dextropropoxyphene napsylate 100mg (APAP/propoxyphene) Placebo
A single investigator, randomized, double-blind, single-dose, parallel group inpatient study of tramadol hydrochloride 150 mg and 75 mg (tramadol), acetaminophen 650 mg with dextropropoxyphene napsylate 100 mg (APAP/propoxyphene) and placebo in patients with moderate or severe baseline pain following Cesarean section.	
TR 150 mg: 40 pts. APAP/propoxyphene: 41 pts. Placebo: 40 pts. TR 75 mg: 40 pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5, and 6 hours Remedication allowed: None before 60 minutes after study drug administration Rescue medication: Not specified	

* si=single-investigator; sd=single-dose; db=double-blind; r=randomized; p=parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

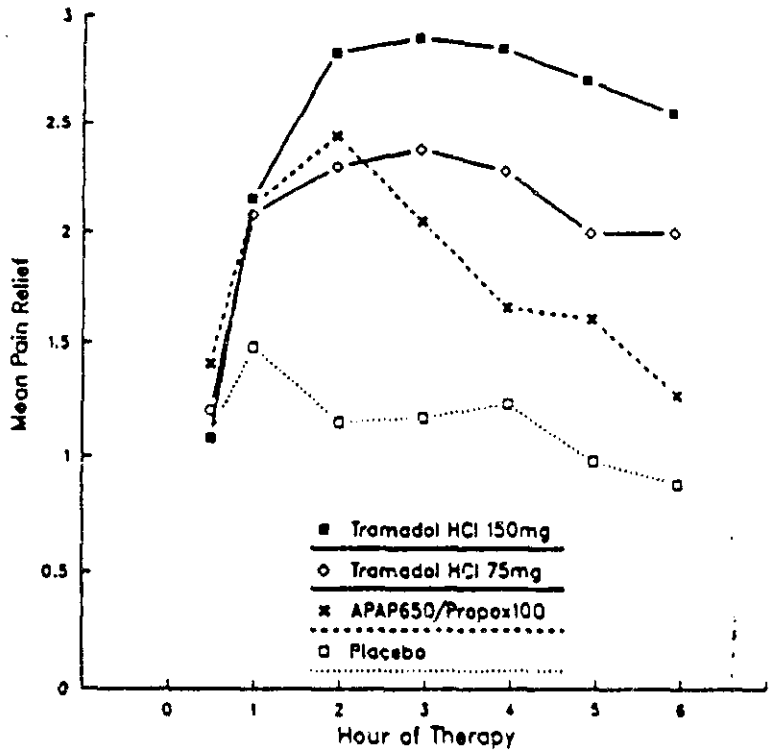
Of the 161 patients who completed the study, eight patients remedicated with additional analgesic during the study and 153 patients did not remedicate during the entire 6-hour period. No patient discontinued the study prematurely.

APAP/propoxyphene treatment group was statistically superior to placebo with respect to all efficacy variables. Tramadol 150 mg was statistically superior to placebo with respect to all efficacy variables. Tramadol 75 mg was statistically superior to placebo with respect to these efficacy variables.

Comparing the three active treatment groups with respect to all efficacy variables, tramadol 150 mg was favored numerically but was not necessarily statistically superior to the other treatments. The three active treatments did not differ statistically for TOTPAR (Total Pain Relief) during the 0 - 3 hour time period but tramadol 150 mg was statistically superior to both the other active treatments during the 0 - 6 hour time period. Tramadol 150 mg was also statistically superior over APAP/propoxyphene for SPID (Sum of the Pain Intensity Difference) scores during the 0 - 3 hour time period and superior over the other active treatments during the 0 - 6 hour time period. Tramadol 150 mg was favored over the 0 - 6 hour time period because of a more prolonged effect compared to APAP/propoxyphene. Tramadol 75 mg was generally numerically favored over APAP/propoxyphene for all efficacy variables although not statistically superior.

This study showed model sensitivity and demonstrated statistically superior pain relief for tramadol 150 mg and 75 mg when compared to placebo.

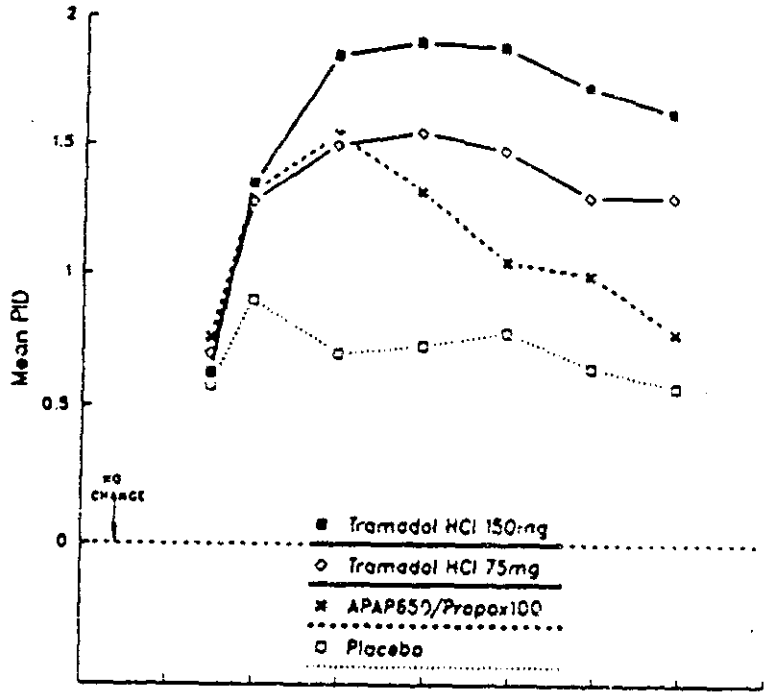
MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TR



	TOTPAR (extrapolated)	
Treatment	3-hour	6-hour
TR 150mg	7.34(1.34) A	15.44(1.95) A
TR 75mg	6.31(2.97) A	12.59(6.24) B
APAP/PROP	6.26(2.38) A	10.79(4.91) B
Placebo	3.61(2.99) B	6.69(5.85) C
P-VALUE	0.000	0.000
RMS ERROR	2.509	5.028

	Assessment Time-Points (in hours)						
Treatment	1/2	1	2	3	4	5	6
TR 150mg	1.08(1.07) 40	2.15(0.95) 40 A	2.83(0.59) 40 A	2.90(0.30) 40 A	2.85(0.53) 40 A	2.70(0.61) 40 A	2.55(0.78) 40 A
TR 75mg	1.20(1.18) 40	2.08(1.10) 40 A	2.30(1.11) 40 B	2.38(1.15) 40 B	2.28(1.20) 39 B	2.00(1.3.) 39 B	2.00(1.36) 38 B
APAP/PROP	1.41(1.02) 41	2.12(1.10) 41 A	2.44(0.87) 41 AB	2.05(1.18) 41 B	1.66(1.35) 41 C	1.61(1.32) [illegible]	1.27(1.32) 38 C
Placebo	1.10(1.08) 40	1.48(1.26) 40 B	1.15(1.29) 40 C	1.17(1.32) 40 C	1.23(1.29) 40 C	[illegible]7)	0.88(1.32) 37 C
P-VALUE	0.487	0.020	0.000	0.000	0.		0.000
RMS ERROR	1.091	1.107	1.001	1.067	1		1.222

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TR

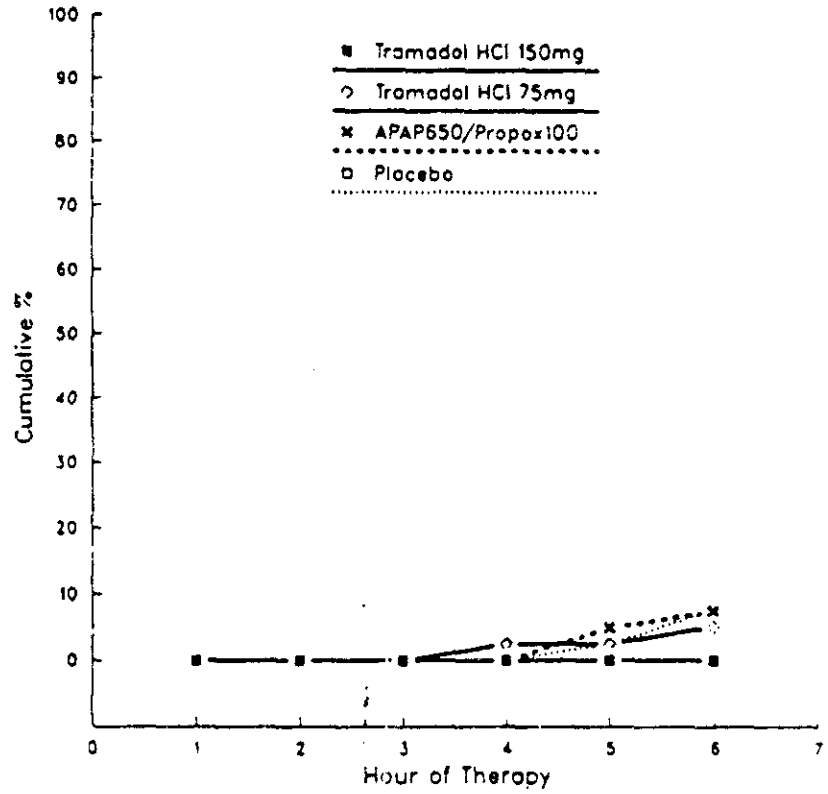


Treatment	SPID (extrapolated) 3-hour	6-hour
TR 150mg	4.74(0.98) A	9.96(1.55) A
TR 75mg	4.04(1.99) AB	8.11(4.14) B
APAP/PROP	3.89(1.60) B	6.72(3.17) B
Placebo	2.16(1.89) C	4.16(3.79) C
P-VALUE	0.000	0.000
RMS ERROR	1.659	3.316

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 150mg	0.63(0.63) 40	1.35(0.66) 40 A	1.85(0.48) 40 A	1.90(0.30) 40 A	1.88(0.40) 40 A	1.73(0.51) 40 A	1.63(0.59) 40 A
TR 75mg	0.70(0.72) 40	1.28(0.75) 40 A	1.50(0.75) 40 B	1.55(0.78) 40 B	1.48(0.82) 39 B	1.30(0.88) 39 B	1.30(0.91) 38 A
APAP/PROP	0.76(0.58) 41	1.32(0.76) 41 A	1.54(0.64) 41 B	1.32(0.79) 41 B	1.05(0.89) 41 C	1.00(0.87) 39 B	0.78(0.85) 38 B
Placebo	0.58(0.59) 40	0.90(0.81) 40 B	0.70(0.82) 40 C	0.73(0.85) 40 C	0.78(0.83) 40 C	0.65(0.83) 39 C	0.58(0.87) 37 B
P-VALUE	0.588	0.027	0.000	0.000	0.000	0.000	0.000
RMS ERROR	0.634	0.747	0.685	0 715	0.762	0.788	0.816

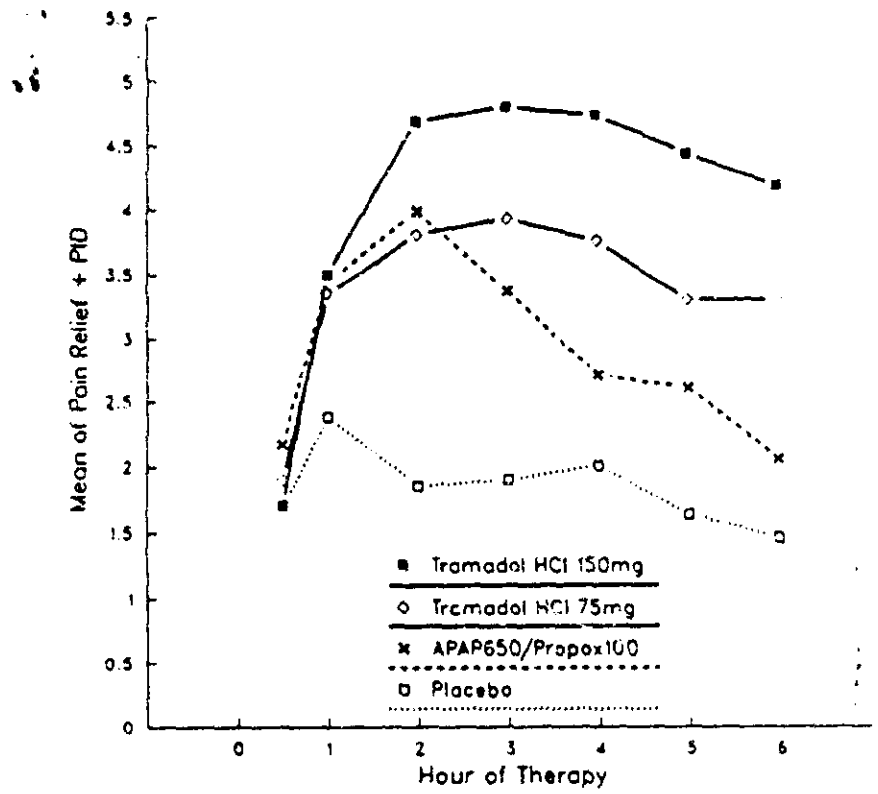
CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TR



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour
TR 150mg	40(100.0%)	40(100.0%)	40(100.0%)	40(100.0%)	40(100.0%)	40(100.0%)
TR 75mg	40(100.0%)	40(100.0%)	40(100.0%)	39(97.5%)	39(97.5%)	38(95.0%)
APAP/PROP	41(100.0%)	41(100.0%)	41(100.0%)	41(100.0%)	39(95.1%)	38(92.7%)
Placebo	40(100.0%)	40(100.0%)	40(100.0%)	40(100.0%)	39(97.5%)	37(92.5%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TR



	SPRID (extrapolated)	
Treatment	3-hour	6-hour
TR 150mg	12.08(2.30) A	25.40(3.48) A
TR 75mg	10.35(4.94) AB	20.70(10.37) B
APAP/PROP	10.15(3.96) B	17.51(8.06) B
Placebo	5.78(4.86) C	10.85(9.62) C
P-VALUE	0.000	0.000
RMS ERROR	4.152	8.323

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 150mg	1.70(1.68) 40	3.50(1.59) 40 A	4.68(1.07) 40 A	4.80(0.61) 40 A	4.73(0.93) 40 A	4.43(1.11) 40 A	4.18(1.36) 40 A
TR 75mg	1.90(1.89) 40	3.35(1.83) 40 A	3.80(1.86) 40 B	3.93(1.93) 40 B	3.75(2.01) 39 B	3.30(2.20) 39 B	3.30(2.27) 38 A
APAP/PROP	2.17(1.60) 41	3.44(1.84) 41 A	3.98(1.49) 41 AB	3.37(1.96) 41 B	2.71(2.24) 41 C	2.61(2.18) 39 B	2.05(2.17) 38 B
Placebo	1.68(1.67) 40	2.38(2.06) 40 B	1.85(2.11) 40 C	1.90(2.16) 40 C	2.00(2.11) 40 C	1.63(2.10) 39 C	1.45(2.19) 37 B
P-VALUE	0.536	0.021	0.000	0.000	0.000	0.000	0.000
RMS ERROR	1.713	1.838	1.676	1.774	1.899	1.951	2.032

PROTOCOL TR

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	18	13	26
TR 75mg	16	12	23
APAP/PROP	14	11	18
Placebo	18	14	26

Approximated Duration of Pain Relief*
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 150mg	> 6:00	> 6:00	> 6:00
TR 75mg	> 6:00	> 6:00	> 6:00
APAP/PROP	> 6:00	> 6:00	> 6:00
Placebo	> 6:00	> 6:00	> 6:00

* More than 50% of the patients in each group were active in the trial throughout the study. Therefore a mean Duration, Lower and Upper Confidence Limits could not be calculated.

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Demographic Frequencies and Means

	_Sex__		___Race____					_Baseline Pain__		Surgical Procedure	__Reason for Discontinuation__			
Drug	M	F	Wht	Blk	Oth	Mean Age	Mean Weight	Moderate	Severe	Cesarean Section	Adv Exp	Patient Choice	Protocol Violation	Other
Tramadol 150 MG	0	40	18	6	16	25.93	132.11	0	40	40	0	0	0	0
Tramadol 75 MG	0	40	14	11	14	26.45	136.18	0	40	40	0	0	0	0
APAP/Propoxyhene	0	41	12	20	9	25.78	129.86	0	41	41	0	0	0	0
Placebo	0	40	14	17	9	25.68	139.33	0	40	40	0	0	0	0

This display includes all patients, including those who were not included in the analysis.

Study: TV Investigators:	Pain Model:Cesarean Section Study Design: ti, sd, db, r, p* Duration: 6 hours Tx: Tramadol (TR) 100 and 50 mg Aspirin 650mg/Codeine Phosphate 60 mg (ASA/Codeine) Codeine Sulfate 60 mg (Codeine) Placebo
This was a two investigator, randomized, double-blind, single-dose, parallel group, inpatient study of tramadol hydrochloride 100 mg and 50 mg (tramadol), aspirin 650 mg with codeine phosphate 60 mg (ASA/codeine), codeine sulfate 60 mg (codeine) and placebo in patients with moderate or severe baseline pain following cesarean section.	
TR 100 mg: 31 pts. ASA /Codeine: 30pts Codeine: 29pts. Placebo: 30 pts. TR 50 mg: 31pts.	
Time-observation points: 0.5, 1, 2, 3, 4, 5 and 6 hours Remedication allowed: None before 60 minutes after study drug administration. Rescue medication: Not specified	

* ti = two investigator; sd = single-dose; db = double-blind; r = randomized; p = parallel

NOTE: The following descriptions relate only to this synopsis format as other variables were included in the complete analysis and report.

Of the 151 patients enrolled, 150 (99%) completed the study either by finishing the 6-hour protocol or by receiving a rescue analgesic, and one patient (1%) discontinued the study prematurely. Two placebo patients were excluded from the efficacy analyses due to significant protocol violations.

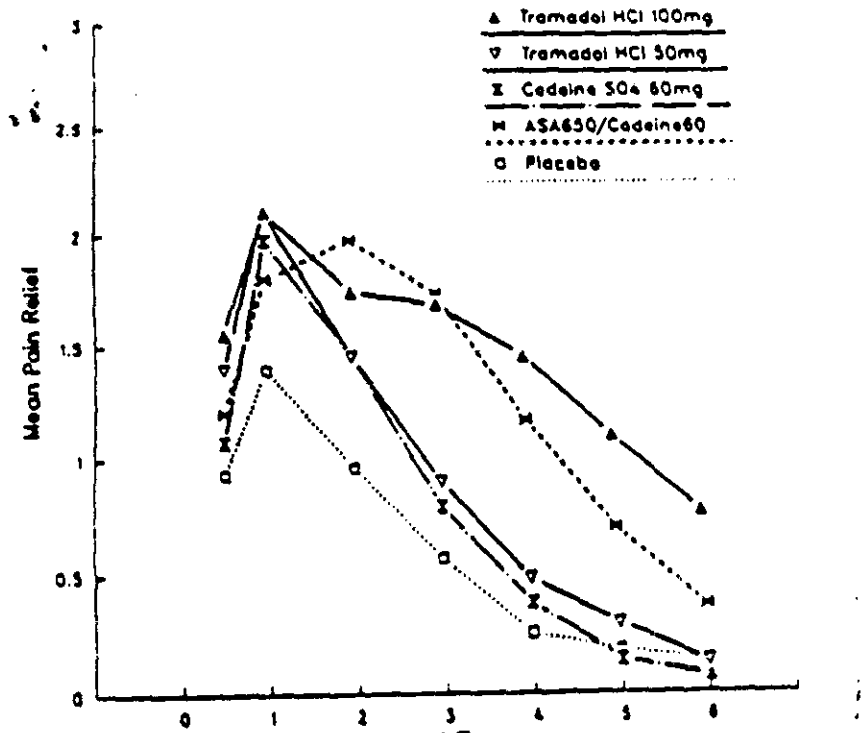
ASA/codeine was statistically superior to placebo with respect to TOTPAR (Total Pain Relief; sum of 0 - 3 and 0 - 6 hour scores), SPID (Sum of the Pain Intensity Difference; 0 - 3 and 0 - 6 hour scores) and time to remedication. Codeine was numerically favored over placebo with respect to all efficacy variables, although this was not statistically significant.

Tramadol 100 mg was statistically superior to placebo with respect to TOTPAR (sum of 0 - 3 and 0 - 6 hour scores), SPID (0 - 3 and 0 - 6 hour scores) and time to remedication. Tramadol 50 mg was numerically favored over placebo with respect to all efficacy variables, although this was not statistically significant. A significant tramadol dose-response was observed for TOTPAR (sum of 0 - 6 hour scores), SPID (0 - 3 and 0 - 6 hour scores) and time to remedication.

Comparing the four active treatment groups with respect to all efficacy variables, tramadol 100 mg and ASA/codeine were numerically superior to the other treatments. These two treatments were not statistically different with respect to TOTPAR (sum of 0 - 3 and 0 - 6 hour scores), SPID (0 - 3 and 0 - 6 hour scores) and time to remedication. Mean TOTPAR scores were identical for ASA/codeine and tramadol 100 mg during the 0 - 3 hour time period and numerically favored tramadol 100 mg over ASA/codeine during the 0 - 6 hour time period. Mean TOTPAR scores numerically favored tramadol 50 mg over codeine during both time intervals, although this was not statistically significant. Mean SPID scores numerically favored ASA/codeine over tramadol 100 mg during the 0 - 3 hour time interval, while tramadol 100 mg was numerically favored over ASA/codeine during the 0 - 6 hour time interval. Mean SPID scores for the tramadol 50 mg and codeine groups were identical during both time periods. The time to remedication for all active treatment groups was not statistically different.

This study showed model sensitivity, and tramadol 100 mg provided pain relief statistically superior to that of placebo. In this study, the order of relative efficacy in each variable was tramadol 100 mg and ASA/codeine > tramadol 50 mg and codeine > placebo.

MEAN SCORES OF PAIN RELIEF (Extrapolated) - PROTOCOL TV

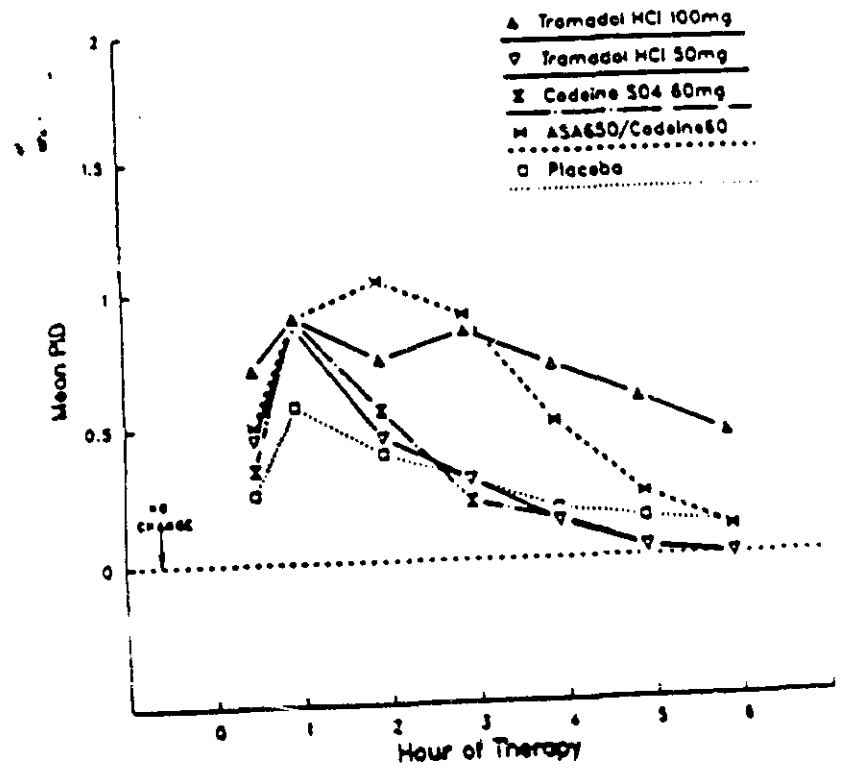


Treatment	TOTPAR (extrapolated) 3-hour	6-hour
TR 100mg	5.24(3.89) A	8.56(8.01) A
TR 50mg	4.10(3.06) AB	5.00(4.60) BC
ASA/COD	5.20(4.10) A	7.43(6.88) AB
CO 60mg	3.76(2.86) AB	4.34(3.86) C
Placebo	2.70(2.61) B	3.27(4.37) C
P-VALUE	0.023	0.003
RMS ERROR	3.370	5.810

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	1.55(1.15) 31	2.10(1.40) 31	1.74(1.50) 27	1.68(1.72) 21 A	1.45(1.61) 18 A	1.10(1.60) 16 A	0.77(1.52) 9 A
TR 50mg	1.39(1.02) 31	2.10(1.33) 31	1.45(1.34) 25	0.90(1.14) 18 B	0.48(1.03) 13 B	0.29(0.69) 7 BC	0.13(0.43) 4 B
ASA/COD	1.20(1.21) 30	1.80(1.35) 30	1.97(1.59) 23	1.73(1.62) 22 A	1.17(1.53) 17 A	0.70(1.24) 12 AB	0.37(0.76) 8 AB
CO 60mg	1.07(0.92) 29	1.97(1.09) 29	1.45(1.35) 26	0.79(1.24) 19 B	0.38(0.82) 8 B	0.14(0.44) 5 C	0.07(0.37) 3 B
Placebo	0.93(0.86) 28	1.39(1.20) 28	0.96(1.20) 20	0.57(1.00) 11 B	0.25(0.84) 7 B	0.18(0.77) 2 BC	0.14(0.76) 1 B
P-VALUE	0.165	0.199	0.086	0.002	0.000	0.002	0.012
RMS ERROR	1.046	1.280	1.406	1.377	1.224	1.044	0 879

MEAN SCORES OF PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TV

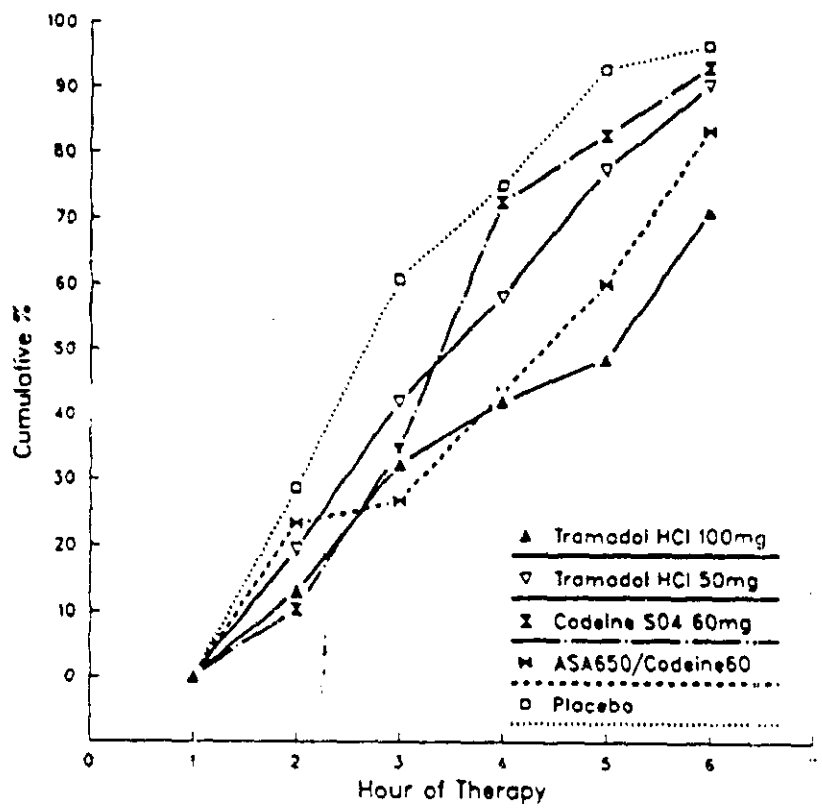


Treatment	SPID (extrapolated) 3-hour	6-hour
TR 100mg	2.39(2.46) AB	4.13(5.01) A
TR 50mg	1.40(1.70) BC	1.56(1.99) B
ASA/COD	2.63(2.43) A	3.47(3.61) A
CO 60mg	1.38(1.63) BC	1.55(2.08) B
Placebo	1.09(1.84) C	1.52(3.32) B
P-VALUE	0.013	0.003
RMS ERROR	2.050	3.406

Treatment	Assessment Time-Points (in hours) 1/2	1	2	3	4	5	6
TR 100mg	0.71(0.74) 31	0.90(0.94) 31	0.74(1.00) 27 AB	0.84(1.00) 21 A	0.71(0.97) 18 A	0.58(0.99) 16 A	0.45(0.93) 9 A
TR 50mg	0.45(0.57) 31	0.87(0.85) 31	0.45(0.85) 25 B	0.29(0.53) 18 B	0.13(0.43) 13 C	0.03(0.18) 7 B	0.00(0.00) 4 B
ASA/COD	0.50(0.73) 30	0.90(0.80) 30	1.03(0.93) 23 A	0.90(0.[illegible]) 22 A	0.50(0.78) 17 AB	0.23(0.50) 12 B	0.10(0.31) 8 B
CO 60mg	0.34(0.61) 29	0.90(0.67) 29	0.55(0.78) 26 B	0.21(0.73) 19 B	0.14(0.52) 8 C	0.03(0.19) 5 B	0.00(0.00) 3 B
Placebo	0.25(0.44) 28	0.57(0.84) 28	0.39(0.83) 20 B	0.29(0.76) 11 B	0.18(0.67) 7 BC	0.14(0.59) 2 B	0.11(0.57) 1 B
P-VALUE	0.066	0.487	0.041	0.001	0.003	0.001	0.003
RMS ERROR	0.631	0.827	0.884	0.824	0.702	0.579	0.507

CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TV

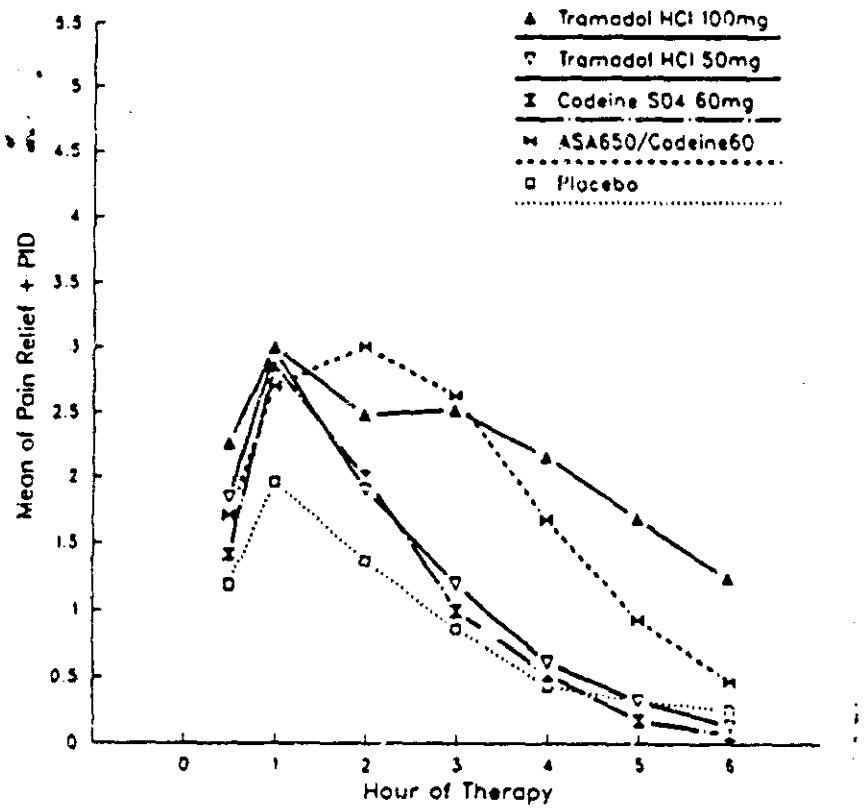
CUMULATIVE DATA OF PATIENTS-IN-THE-TRIAL - PROTOCOL TV



Number of Patients in Study at Time-Observation Point

Treatment	1-hour	2-hour	3-hour	4-hour	5-hour	6-hour
TR 100mg	31(100.0%)	27(87.1%)	21(67.7%)	18(58.1%)	16(51.6%)	9(29.0%)
TR 50mg	31(100.0%)	25(80.6%)	18(58.1%)	13(41.9%)	7(22.6%)	3(9.7%)
ASA/COD	30(100.0%)	23(76.7%)	22(73.3%)	17(56.7%)	12(40.0%)	5(16.7%)
CO 60mg	29(100.0%)	26(89.7%)	19(65.5%)	8(27.6%)	5(17.2%)	2(6.9%)
Placebo	28(100.0%)	20(71.4%)	11(39.3%)	7(25.0%)	2(7.1%)	1(3.6%)

MEAN SCORES OF PAIN RELIEF COMBINED WITH PAIN INTENSITY DIFFERENCE (Extrapolated) - PROTOCOL TV



Treatment	SPRID (extrapolated) 3-hour	6-hour
TR 100mg	7.63(6.18) AB	12.69(12.81) A
TR 50mg	5.50(4.54) ABC	6.56(6.32) BC
ASA/COD	7.83(6.36) A	10.90(10.18) AB
CO 60mg	5.14(4.30) BC	5.90(5.67) C
Placebo	3.79(4.30) C	4.79(7.58) C
P-VALUE	0.015	0.002
RMS ERROR	5.239	8.967

Assessment Time-Points (in hours)

Treatment	1/2	1	2	3	4	5	6
TR 100mg	2.26(1.77) 31	3.00(2.25) 31	2.48(2.42) 27	2.52(2.68) 21 A	2.16(2.53) 18 A	1.68(2.55) 16 A	1.23(2.43) 9 A
TR 50mg	1.84(1.46) 31	2.97(2.09) 31	1.90(2.12) 25	1.19(1.56) 18 B	0.61(1.41) 13 B	0.32(0.79) 7 B	0.13(0.43) 4 B
ASA/COD	1.70(1.88) 30	2.70(2.09) 30	3.00(2.45) 23	2.63(2.54) 22 A	1.67(2.22) 17 A	0.93(1.70) 12 AB	0.47(0.97) 8 B
CO 60mg	1.41(1.38) 29	2.86(1.64) 29	2.00(2.05) 26	1.00(1.85) 19 B	0.52(1.24) 8 B	0.17(0.54) 5 B	0.07(0.37) 3 B
Placebo	1.18(1.16) 28	1.96(1.95) 28	1.36(1.97) 20	0.86(1.72) 11 B	0.43(1.50) 7 B	0.32(1.36) 2 B	0.25(1.32) 1 B
P-VALUE	0.086	0.280	0.061	0.001	0.001	0.001	0.006
RMS ERROR	1.558	2.020	2.216	2.126	1.860	1.572	1.348

PROTOCOL TV

Approximated Onset of Pain Relief
(minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	13	10	18
TR 50mg	16	13	23
ASA/COD	18	13	30
CO 60mg	21	16	33
Placebo	25	19	40

Approximated Duration of Pain Relief
(hours:minutes)

Treatment	Mean	Lower 95% CL	Upper 95% CL
TR 100mg	4:25	2:40	5:40
TR 50mg	3:10	2:20	4:15
ASA/COD	4:00	2:35	5:05
CO 60mg	3:15	2:35	3:45
Placebo	2:25	1:50	3:10

Tramadol Protocol TV 11:25 Tuesday, June 7, 1994 1

Demographic Frequencies and Means

Drug	Sex M	Sex F	Race Wht	Race Blk	Race Oth	Mean Age	Mean Weight	Baseline Pain Moderate	Baseline Pain Severe	Surgical Procedure Cesarean Section	Reason for Discontinuation Adv Exp	Reason for Discontinuation Patient Choice	Reason for Discontinuation Protocol Violation	Reason for Discontinuation Other
Tramadol 100 MG	0	31	28	0	3	26.74	188.67	20	11	31	0	0	0	0
Tramadol 50 MG	0	31	30	0	1	25.[illegible]	182.03	21	10	31	0	0	0	0
Codeine SO4	0	29	29	0	0	26.93	188.86	19	10	29	0	0	0	0
ASA / Codeine	0	30	28	0	2	25.27	181.70	20	10	30	0	0	0	0
Placebo	0	30	26	2	0	26.73	174.53	20	10	30	0	0	1	0

0070 00

This display includes all patients, including those who were not included in the analysis.

Tramadol Study TKB:
Three Month Study of Chronic Pain

MEDICAL OFFICER REVIEW

NDA #: 20-281
NAME: ULTRAM (Tramadol Hydrochloride).
SPONSOR: R.W. Johnson
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.
REVIEW DATE: June 30, 1994.
CSO: C. Moody

GENERAL DESIGN: This was a multicenter, randomized, 3-month, double-blind, parallel, active-controlled, outpatient study of tramadol vs. aspirin with codeine in patients with chronic non-malignant pain.

STUDY POPULATION: Patients enrolled in this study had to be at least 18, have acceptable liver and kidney function, and have a consistent chronic painful condition that did not result from malignancy and that required a prescription analgesic almost every day. Conditions included, but were not limited to: trigeminal neuralgia, post-herpetic neuralgia, chronic low-back syndrome, marginally controlled RA, diabetic neuropathy, or primary fibrositis. Dysmenorrhea and recurrent headache were not included.

Subjects were excluded for active peptic-ulcer disease, history of a seizure disorder, current abuse of narcotics or alcohol, tolerance to narcotics, or if they were suicidal.

TREATMENT: The capsules compared were:

Tramadol Hydrochloride 50 mg, vs.
Aspirin 325 mg with Codeine Phosphate 30 mg.

Patients were instructed to take one or two capsules of their assigned study medication every 4 to 6 hours as needed for pain, up to 8 capsules/day, for three months. A maximum of eight capsules was permitted in any 24-hour period. After completion of the double-blind treatment period, or after the double-blind, withdrawal period, patients could elect to receive tramadol open-label.

EFFICACY ASSESSMENT: On Day 1 of Weeks 1, 3, 5 and 9, patients rated their pre-treatment pain (4 point scale), as well as pain relief (5 point scale) and medication acceptability (5 point scale) at 1, 2, 3 and 4 hours after the first dose of study medication on that day. They also rated minimum pain intensity experienced the day before. On Day 2 of the same study weeks, patients rated pain before and four hours after the first dose. They also rated maximum pain relief and medication acceptability. Daily during Weeks 1, 3, 5 and 9, patients recorded the number of capsules taken and completed an overall medication acceptability rating. At the conclusion of double-blind treatment, patients and investigators provided an overall assessment of therapy.

CONCOMITANT MEDICATIONS: No other analgesics were permitted for patients taking fewer than eight capsules of study drug per day. Patients taking 8 capsules per day could supplement with up to 4 g/day of acetaminophen. Patients who could not tolerate the maximum study medication per day were allowed to supplement with sponsor's permission. Prednisone therapy of not more than 10 mg/day prednisone or its equivalent could be continued if it was to remain constant. Chronic use of steroids was permitted for no more than half of the patients at each study site.

SPECIAL STUDIES: At the end of the double-blind period, patients were given the option of participating in a double-blind, 3-day withdrawal period. Patients who chose to participate were randomized to receive the same study medication as during the preceding 3-month period or 500 mg of acetaminophen. The Weak-Opiate Withdrawal Questionnaire was taken at the initiation of this withdrawal period and again three days later.

SAFETY: Safety was evaluated by reported adverse experiences, vital signs including supine and standing blood pressure, and clinical laboratory parameters. Electrocardiograms and ophthalmologic examinations were done at baseline and at the end of the double-blind period.

RESULTS

BASELINE DEMOGRAPHICS: Thirty-one investigators from private clinics participated. A total of 260 patients were enrolled in the study (195 tramadol, 65 ASA/codeine). Two tramadol patients were lost to follow-up after enrollment, with no efficacy and safety data recorded and these patients were excluded from the analyses of demographic characteristics. Distributions of demographic features are given in the following table:

Baseline Demographic Characteristics by Treatment Group

	Tramadol (N = 193)		ASA/Codeine (N = 65)	
Male	76	39%	24	37%
Female	117	61%	41	63%
White	178	92%	61	94%
Black	11	6%	2	3%
Other	4	2%	2	3%
Mean Age (years)	53.3		54.6	
Mean Wgt Male (lb)	192		182	
Mean Wgt Female (lb)	163		155	
Mean Hgt Male (in)	69.1[a]		70.0	
Mean Hgt Female (in)	63.3[a]		63.8[a]	
Baseline Pain[b]				
None	1	1%	1	2%
Mild	21	11%	7	11%
Moderate	115	62%	32	49%
Severe	49	26%	25	38%
Diagnosis				
Arthritis, Conn. Tissue	53	27%	15	23%
Musc/Skel Low Back Pain	88	46%	27	42%
Neuropathic Pain	39	20%	17	26%
Surgery, Trauma	11	6%	6	9%
Other	2[c]	1%	0	0%

[a] Height missing for 1 pt. in each group.
[b] Tramadol N = 186; Baseline pain missing for 7 tramadol patients
[c] Pelvic adhesions; ileitis.

The tramadol group tended to be heavier by 8 to 10 lbs., and there was a larger fraction with severe baseline pain in the ASA/codeine group. It is of interest that one patient in each group had no baseline pain.

DISPOSITION OF PATIENTS: The following table shows reasons for discontinuation:

	Tramadol (N = 195)[a]		ASA/Codeine (N = 65)	
	N	%	N	%
Lost after Enrollment, No Data	2		0	
Discontinued	96	50%	23	35%
Drug-Related[b]	71	37%	16	25%
Adverse Experience	46	24%	12	18%
Drug Ineffective	25	13%	4	6%
Intercurrent Illness	3	2%	2	3%
Failed to Return	5	3%	0	0%
Other	17	9%	5	8%
Incl/Excl Violation	4	2%	2	3%
Rec'd Contraindicated Med	4	2%	2	3%
Noncompliance	2	1%	0	0%
Patient Request	5	3%	0	0%
Other[c]	2	1%	1	2%
Completed double-blind	97	50%	42	65%
Completed Withdrawal Study	36	19%	16	25%
Went into Open-Label Study	82	42%	34	52%

[a] Percentages of patients completing the study and discontinuing for each reason are based on the total number of tramadol patients who enrolled and contributed data (N = 193).

[b] Tramadol vs. ASA/codeine: p = .10 by Chi-squared test.

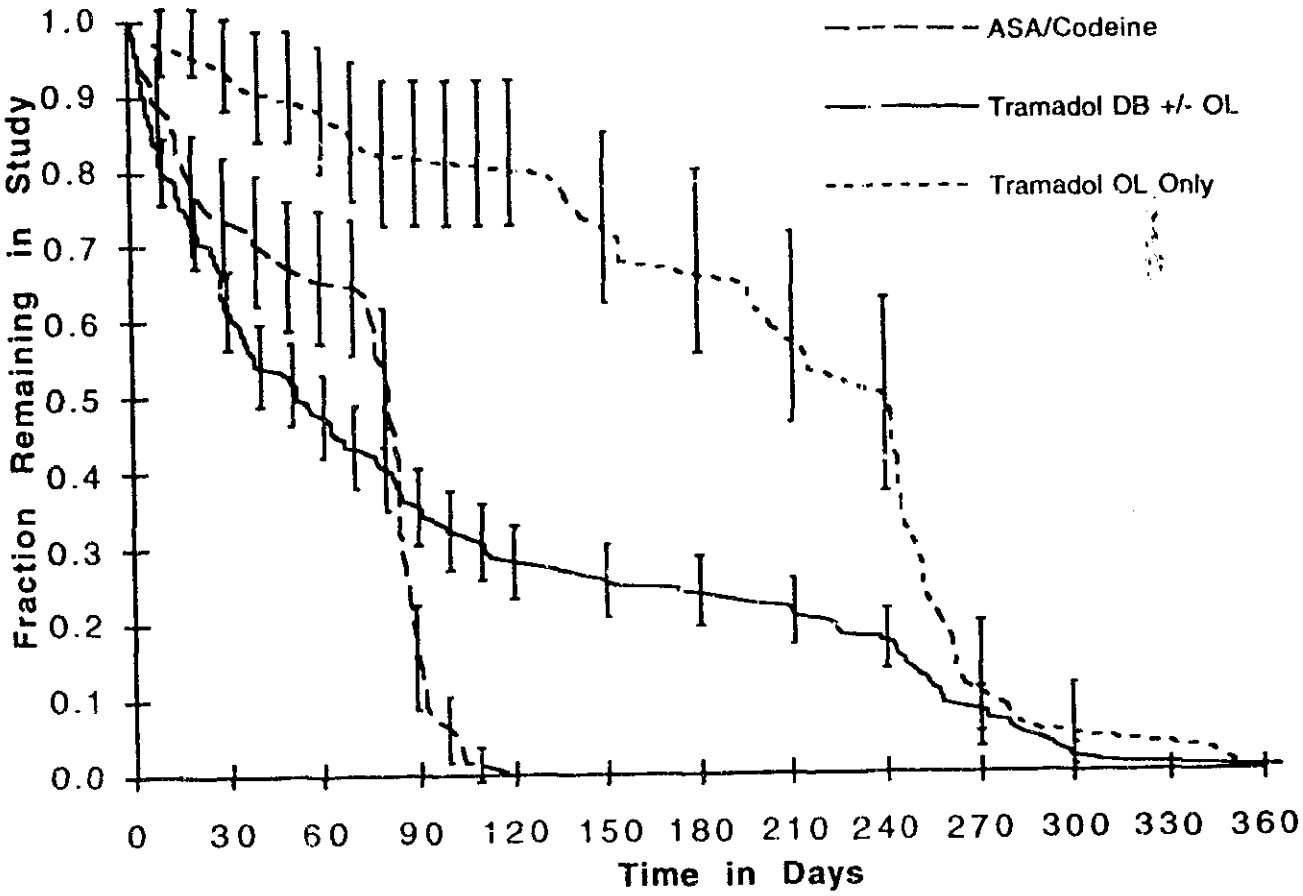
[c] Tramadol: 1 suicide attempt, 1 transient illness; ASA/codeine: 1 administrative

Half of the tramadol patients completed the double-blind period compared to about two-thirds of the ASA/codeine group. The main contributor to the difference was the greater tendency to leave the study for drug-related reasons.

OTHER DATA LOSS: Efficacy analyses included data from 257 of the 260 patients who were enrolled in the study. The two tramadol patients who were lost to follow-up had no efficacy data recorded, and were excluded. All efficacy data from one other tramadol patient were excluded from the analyses because the patient took a disallowed concomitant analgesic throughout the study. Partial efficacy data from two additional tramadol patients and one ASA/codeine patient were also excluded from the analyses because of a significant protocol violation.

The following table and graph show the fractions of patients remaining in the study over time for the ASA/codeine group and the tramadol group (including any open-label extension). The graph also shows the tramadol OL Only group (ASA/codeine patients who switched to tramadol for the open-label period)

Study TKB: Patients Remaining in Study



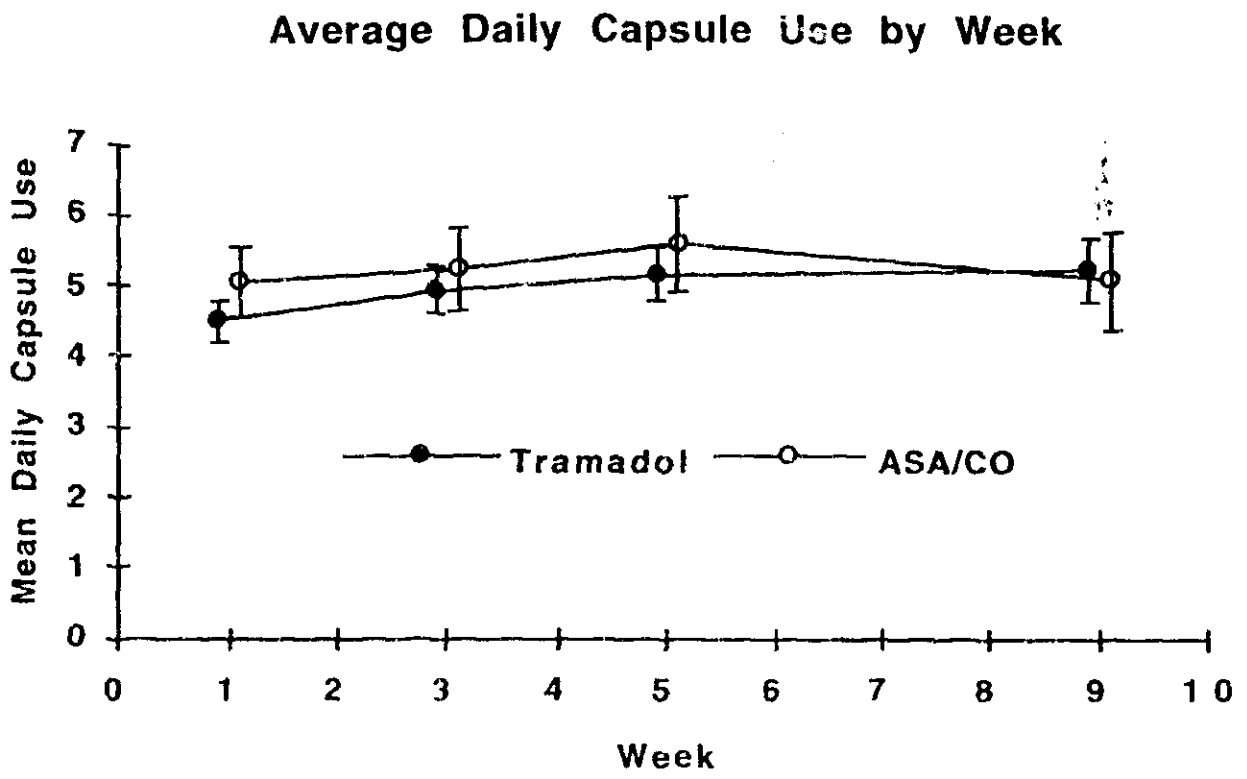
Error bars show +/- 1.5 s.e.m., so that statistically significant differences (at .05 two-sided) approximately correspond to lack of overlap of the error bars.

Fraction Remaining in Study

Days	ASA/Codeine	Tramadol	p-value
10	0.892	0.800	.13
20	0.769	0.718	.54
30	0.738	0.615	103
40	0.708	0.544	.030
50	0.677	0.518	.037
60	0.662	0.477	.015
70	0.646	0.436	.005
80	0.523	0.405	.13
90	0.154	0.354	.004

These data show that there was a higher attrition rate in the tramadol group. Differences in participation rate were statistically significant after 1 month to near the end of the double-blind period. The tramadol OL group showed lower attrition, as did the tramadol group after the end of the double-blind period, probably reflecting a selection effect.

MEDICATION USE: The average number of capsules used daily as recorded at each visit are plotted and tabulated below:



Error bars show +/- 1.5 s.e.m., so that statistically significant differences (at .05 two-sided) approximately correspond to lack of overlap of the error bars.

Treatment[a]		Week 1[b]	Week 3	Week 5	Week 9[b]
Tramadol	Mean No. of Caps	**4.50**	**4.94**	**5.14**	**5.25**
	95% CI	4.2 - 4.8	4.6 - 5.3	4.8 - 5.5	4.8 - 5.6
	Range	0.8 - 8.0	1.3 - 8.0	0.6 - 8.0	1.0 - 9.7
	% ≥ 8 caps/day	3%	10%	11%	13%
	N	172	137	115	94
ASA/Codeine	Mean No. of Caps	**5.05**	**5.24**	**5.59**	**5.09**
	95% CI	4.5 - 5.6	4.67 - 5.8	4.9 - 6.3	4.4- 5.8
	Range	1.7 - 8.0	0.89 - 8.0	0.67 - 10.7	0.89 - 8.3
	% ≥ 8 caps/day	10%	16%	20%	19%
	N	60	50	44	42

[a] No statistically significant difference between treatment groups (two-sided $p > 0.05$).
[b] Significant treatment-by-investigator interaction (two-sided $p \leq 0.10$).

Since the patient population is not constant in the above table, difference from week to week could be affected by selection. The reviewer computed average capsule use for the cohort that contributed mean capsule use data at all 4 visits. The values were similar:

Mean Capsule Use, for Cohort Contributing Data at All 4 Visits

		Week 1	Week 3	Week 5	Week 9
Tramadol	(N=89)	**4.49**	**4.88**	**5.07**	**5.21**
ASA/Codeine	(N=41)	**4.99**	**5.39**	**5.58**	**5.14**

There was a tendency toward increased capsule use over the 3 months of the study: tramadol use rose by 16% from week 1 to week 9, ASA/codeine use rose by 3% between those weeks, but peaked at 12% above baseline at week 5. The fraction using maximum dose jumped in the first two visits, and rose more slowly afterward. There were only three reports of the average daily use exceeding the 8 capsule limit: one tramadol patient at week 9, and one ASA/codeine patient at each of weeks 5 and 9.

EFFICACY -- DAY 1 RATINGS: Following administration of the first dose of study drug on Day 1 of Weeks 1, 3, 5 and 9, patients were instructed to record the intensity of their starting pain, as well as pain relief and medication acceptability at hourly intervals for four hours. Summary results are shown in the following tables. Total Pain Relief and Total Medication Rating are the sums of the 4 hourly values.

Mean Values and Treatment Comparisons
of Day 1 First Dose Efficacy Variables

Efficacy Variable/ Evaluation Period	Treatment Group[a]					
	Tramadol			ASA/Codeine		
	N	Mean	95% CI	N	Mean	95% CI
Starting Pain[b]						
Week 1	185	**2.1**	2.0 - 2.2	65	**2.2**	2.1 - 2.4
Week 3	142	**1.9**	1.8 - 2.1	51	**2.0**	1.8 - 2.2
Week 5	116	**1.9**	1.8 - 2.1	44	**2.0**	1.8 - 2.2
Week 9	95	**2.0**	1.8 - 2.1	42	**1.9**	1.6 - 2.1
Total Pain Relief[c]						
Week 1	182	**5.8**	5.3 - 6.3	64	**5.8**	4.9 - 6.8
Week 3	137	**6.7**	6.1 - 7.3	50	**7.2**	5.9 - 8.5
Week 5	114	**7.3**	6.6 - 7.9	43	**7.0**	5.8 - 8.2
Week 9	93	**7.0**	6.3 - 7.7	40	**6.5**	5.4 - 7.6
Total Medication Rating[d]						
Week 1	180	**9.0**	8.5 - 9.4	63	**9.1**	8.2 - 10.0
Week 3	136	**10.0**	9.4 - 10.6	49	**10.4**	9.2 - 11.6
Week 5	112	**10.9**	10.2 - 11.6	42	**11.5**	10.1 - 12.8
Week 9	92	**11.2**	10.4 - 12.0	40	**10.9**	9.5 - 12.3

a No statistically significant difference between treatment groups (two-sided p > 0.05).
b Scale: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe.
c Scale: 0 = No relief; 16 = Complete relief at every evaluation.
d Scale: 4 = Poor at every evaluation; 20 = Excellent at every evaluation.

The average Day 1 starting pain at each week during on both treatments was moderate. The Day 1 first dose starting pain, Day 1 first dose total pain

relief, and Day 1 first dose total medication rating in the tramadol and ASA/codeine groups were similar for the two groups at all evaluations.

Day 2 data are not presented here, but they also showed similarity of the two treatments.

EFFICACY -- OVERALL RATINGS: Patients were instructed to complete a rating of medication acceptability daily during Weeks 1, 3, 5 and 9. At the conclusion of the study, investigators completed a global evaluation of efficacy for each patient, and patients completed an overall assessment of medication.

Mean Overall Average Medication Rating[a]

Evaluation Period	Treatment Group[b]					
	Tramadol			ASA/Codeine		
	N	Mean	95% CI	N	Mean	95% CI
Week 1	167	**2.7**	2.6-2.9	60	**2.8**	2.5-3.0
Week 3	137	**2.8**	2.7-3.0	50	**2.9**	2.6-3.2
Week 5	113	**3.0**	2.8-3.2	43	**3.0**	2.7-3.4
Week 9	94	**2.9**	2.7-3.1	40	**3.1**	2.7-3.4

a Scale: 1 = Poor, 2 = Fair, 3 = Good, 4 = Very Good, 5 = Excellent.
b No statistically significant difference between treatment groups (two-sided p > 0.05).

Distribution and Mean Values of Global Ratings

	Number (%) of Patients	
	Tramadol	ASA/Codeine
Investigator's Global Evaluation[a]		
Marked (6)	16 (9%)	7 (11%)
Moderate (5)	82 (45%)	28 (46%)
Minimal (4)	51 (28%)	17 (28%)
None (3)	21 (12%)	9 (15%)
Worse (2)	11 (6%)	0 (0%)
Mean Rating	4.4	4.5
95% CI	4.2-4.5	4.3-4.8
Total No. Patients	181	61
Patient's Overall Assessment[a]		
Excellent (6)	10 (6%)	6 (10%)
Very Good (5)	28 (16%)	9 (14%)
Good (4)	47 (26%)	19 (30%)
Fair (3)	48 (27%)	15 (24%)
Poor (2)	47 (26%)	14 (22%)
Mean Rating	3.5	3.7
95% CI	3.3-3.7	3.3-4.0
Total No. Patients	180	63

a No statistically significant difference between treatment groups (two-sided p > 0.05).

OPIATE WITHDRAWAL STUDY: A total of 36 tramadol and 16 ASA/codeine patients chose to participate in a double-blind, 3-day

withdrawal period were randomized to receive the same study medication or 500 mg of acetaminophen (APAP). The Weak Opiate Withdrawal Questionnaire was to be completed at the beginning and end of the period. Numerically higher scores correspond to greater withdrawal symptoms.

Weak Opiate Withdrawal Questionnaire Results

Treatment Sequence	Visit[a]	N	Mean Score	Mean Change Score
Tramadol - Tramadol	Preliminary	22	28.0	0.8
	Withdrawal	22	28.9	
Tramadol - APAP	Preliminary[b]	14	31.4	0.7
	Withdrawal	14	32.1	
ASA/Codeine - ASA/Codeine	Preliminary	9	33.6	-1.9
	Withdrawal	9	31.7	
ASA/Codeine - APAP	Preliminary	7	32.3	2.0
	Withdrawal	7	34.3	

a Preliminary visit = at initiation of withdrawal period; withdrawal visit = at conclusion of 3-day, double-blind withdrawal period.

b One patient did not have a preliminary score and was excluded from the questionnaire analysis.

None of the changes from baseline or difference between groups were statistically significant. Although the data suggest less distinction between study drug and APAP for those on tramadol, the small sample size and resulting lack of precision make comparisons unreliable.

SAFETY

The safety experience is considered in more detail in the Integrated Safety Review. For each adverse event, the table below shows the number of patients who experienced that event at least once. The only events reported here are those that occurred in at least 5% of patients in at least one of the groups. Events with statistically significant differences are indicated with an asterisk.

	Tramadol		ASA/Codeine	
	N	%	N	%
Any AE	182	94.3	60	92.1
Body as Whole	95	49.2	29	44.6
Asthenia	17	8.8	7	10.8
Headache	61	31.6	19	29.2
Edema*	3	1.6	6	9.2
Cardiovascular System	12	6.2	5	7.7
Central Nervous System	96	49.7	30	46.2
Somnolence	38	19.7	16	24.6
Sleep Disorder	12	6.2	2	3.1
Dizziness	57	29.5	14	21.5
Paresthesia	7	3.6	6	9.2
GI System	138	71.5	55	84.6
Dyspepsia*	26	13.5	18	27.7
Nausea	75	38.9	27	41.5
Vomiting	26	13.5	10	15.4
Mouth Dry	25	13.0	9	13.9
Diarrhea	10	5.2	2	3.1
Abdominal Pain*	13	6.7	12	18.5
Constipation*	55	28.5	32	49.2
Musc/Skel System	25	13.0	8	12.3
Psychiatric	36	18.7	7	10.8
Nervous	10	5.2	0	0.0
Respiratory System	24	12.4	6	9.2
URI Infection	8	4.1	4	6.2
Skin*	46	23.8	5	7.7
Pruritus	23	11.9	3	4.6
Sweating	14	7.3	1	1.5
Special Senses	28	14.5	5	7.7
Tinnitus	11	5.7	1	1.5
Urogenital System	34	17.6	7	10.8
Menopausal Symp	8	6.8	1	2.4

* statistically significantly different at p = .05

The adverse event profile of tramadol resembled that of an opioid: dizziness, somnolence, constipation and nausea, vomiting, dry mouth and pruritus were common; sweating was seen as well. The tramadol group had less edema, dyspepsia, constipation and abdominal pain, but more skin complaints, than the ASA/codeine group.

Serious Adverse Event

One patient in the tramadol group attempted suicide while receiving study medication. This

patient, a 34-year-old white man weighing 144 lb, attempted suicide on Day 74 by taking an overdose of tramadol (approximately 60 capsules). According to the patient, he vomited everything after 30 minutes. No other adverse sequelae from the attempted overdose were noted by the patient. The patient informed the study site of the incident on Day 77. The patient was discontinued from the study at this time. He was psychologically evaluated, but not hospitalized. The patient had entered the trial for the treatment of back pain and his average daily dose of tramadol during Weeks 1, 3, 5 and 9 were 114.3 mg, 121.4 mg, 171.4 mg and 214.3 mg, respectively. The patient experienced several adverse experiences prior to this suicide attempt, including euphoria, difficulty in urination, urinary hesitancy, sinus pain, disorientation, constipation, itchy eyes, metallic taste, neuralgia, ear infection, nausea and vomiting. The amount of pain relief the patient received from the study medication diminished throughout the study. The patient reported withdrawal symptoms (unspecified) on Day 76. He was placed on acetaminophen with hydrocodone for low back pain on Day 78.

Orthostatic hypotension was reported in two patients treated with tramadol: blood pressure measurements recorded on the day, but not necessarily the time of the orthostatic episodes, failed to indicate any significant reduction in pressure relative to previous measurements. Other adverse experiences noted by these patients were not consistent with an orthostatic fall.

Ophthalmologic exams found 5.5% of 91 tramadol patients with a change from baseline and 5.1% of 39 ASA/codeine patients. One tramadol patient was diagnoses with cataracts, another with glaucoma.

There were no clinically significant changes in average values for vital signs, laboratory values or ECG parameters.

SUMMARY

Tramadol and ASA/codeine provided essentially the same analgesia during the double blind period. However, there tended to be more drug-related discontinuations in the tramadol group, and attrition from the tramadol group was significantly higher during the double blind period.

The daily capsule usage trended higher over time in both groups, with tramadol use rising 16% from week 1 to week 9. There was little evidence of use exceeding recommendations.

The withdrawal study did not establish any difference between tramadol and ASA/codeine.

The adverse event profile of tramadol resembles that of an opioid: nausea, vomiting, constipation, dizziness and somnolence as well as some pruritus and sweating. One suicide attempt with the drug was unsuccessful. The tendency of the drug to produce vomiting may have provided beneficial it that case.

CONCLUSIONS

This study provides substantial evidence of the utility of tramadol for treating chronic pain, and provides supporting evidence of its analgesic effect. The adverse event profile is similar to that of an opioid.

John E. Hyde

John E. Hyde, Ph.D., M.D

Phm. Wdmcal 2-28-95

Tramadol Study TKM:
One Month Study of Pain of Malignancy

MEDICAL OFFICER REVIEW

NDA #: 20-281
NAME: ULTRAM (Tramadol Hydrochloride).
SPONSOR: R.W. Johnson
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.
REVIEW DATE: June 30, 1994.
CSO: C. Moody

GENERAL DESIGN: This was a multicenter, randomized, 1-month, double-blind, parallel, active-controlled, outpatient study of tramadol vs. acetaminophen with oxycodone in patients with pain due to malignancy.

STUDY POPULATION: Patients enrolled in this study had to be at least 18, have reasonable liver and kidney function, and have consistent moderate or severe pain that was attributed to diagnosed malignancy and that required a prescription analgesic almost every day.

Subjects were excluded for symptomatic urethral stricture, symptomatic prostatic hyperplasia, taking anticholinergic medications or monoamine oxidase inhibitors, history of a seizure disorder, current abuse of narcotics or alcohol, tolerance to narcotics, or if they were suicidal. Patients were also excluded if they were taking prestudy opioid-containing analgesics indicated for moderate or moderately severe pain

TREATMENT: The capsules compared were:

Tramadol Hydrochloride 50 mg, vs.

Acetaminophen 250 mg with Oxycodone Hydrochloride 2.5 mg

Patients were instructed to take one or two capsules of their assigned study medication every six hours as needed for pain for four weeks. A maximum of eight capsules was permitted in any 24-hour period. After completion of the double-blind period, patients could elect to receive open-label tramadol.

EFFICACY ASSESSMENT: On Day 1 of Weeks 1 and 3, patients rated their pre-treatment pain (4 point scale) as well as pain relief (5 point scale) and medicine acceptability (5 point scale) at 1, 2, 3 and 4 hours after the first dose of study medication on that day. On Day 2 of the same study weeks, patients rated pain before and four hours after the first dose. They also rated minimum pain intensity and medicine acceptability. Daily during Weeks 1 and 3, patients completed a daily overall medicine acceptability rating. At the conclusion of double-blind treatment, patients and investigators provided an overall assessment of therapy.

CONCOMITANT MEDICATIONS: During the double-blind period, patients taking the full 8-capsule per day allotment of study drug or who took their

maximum tolerated dose (if at least four capsules per day) could supplement with up to 4 g of aspirin per day or maximal NSAID. Moderate use of steroids was permitted by patients who still required analgesia and who had been receiving no more than 10 mg/day prednisone or its equivalent without significant side effects. Therapy was to remain constant through the double-blind period. Steroids were not to be used in conjunction with NSAID's or for pain relief. Steroids also could be prescribed for anti-emetic use or with a chemotherapy regimen.

SAFETY: Safety was evaluated by reported adverse experiences, vital signs, clinical laboratory evaluations, electrocardiograms and ophthalmologic examinations.

RESULTS

BASELINE DEMOGRAPHICS: Thirty-eight investigators participated. One hundred seventy patients were enrolled in the study and took study drug (101 tramadol, 69 APAP/oxycodone). All patients (N = 170) were included in the analysis of baseline demographic characteristics. Distributions of demographic features are given in the following table:

Baseline Demographic Characteristics by Treatment Group

	Tramadol (N = 101)		APAP/Oxycodone (N = 69)	
Male	57	56%	31	45%
Female	44	44%	38	54%
White	93	92%	66	96%
Black	8	8%	2	3%
Other	0	0%	1	1%
Mean Age (years)	62.6		66.4[a]	
Mean Weight - Male (lb)	166.8[b]		165.0[b]	
Mean Weight - Female (lb)	146.5		142.6	
Mean Height - Male (in)	70.0[c]		68.7[c]	
Mean Height - Female (in)	63.4		63.7	
Baseline Pain[d]				
None	3	3%	1	2%
Mild	21	22%	15	23%
Moderate	56	58%	36	55%
Severe	16	17%	13	20%

[a] Statistically significantly higher than tramadol group (two-sided $p \leq 0.05$).
[b] Weight missing for 1 pt. in each group.
[c] Height missing for 2 pts in each group;
tramadol statistically greater than: APAP/oxycodone group, (two-sided $p \leq 0.05$).
[d] Tramadol N = 96; APAP/oxycodone N = 65

The tramadol group mean age was almost 4 years younger. The difference in male height is not clinically significant. The distribution of baseline

pain is comparable between the groups. It is of interest that 3 tramadol patients and 1 APAP/oxycodone patient reported no baseline pain.

DISPOSITION OF PATIENTS: The following table shows reasons for discontinuation:

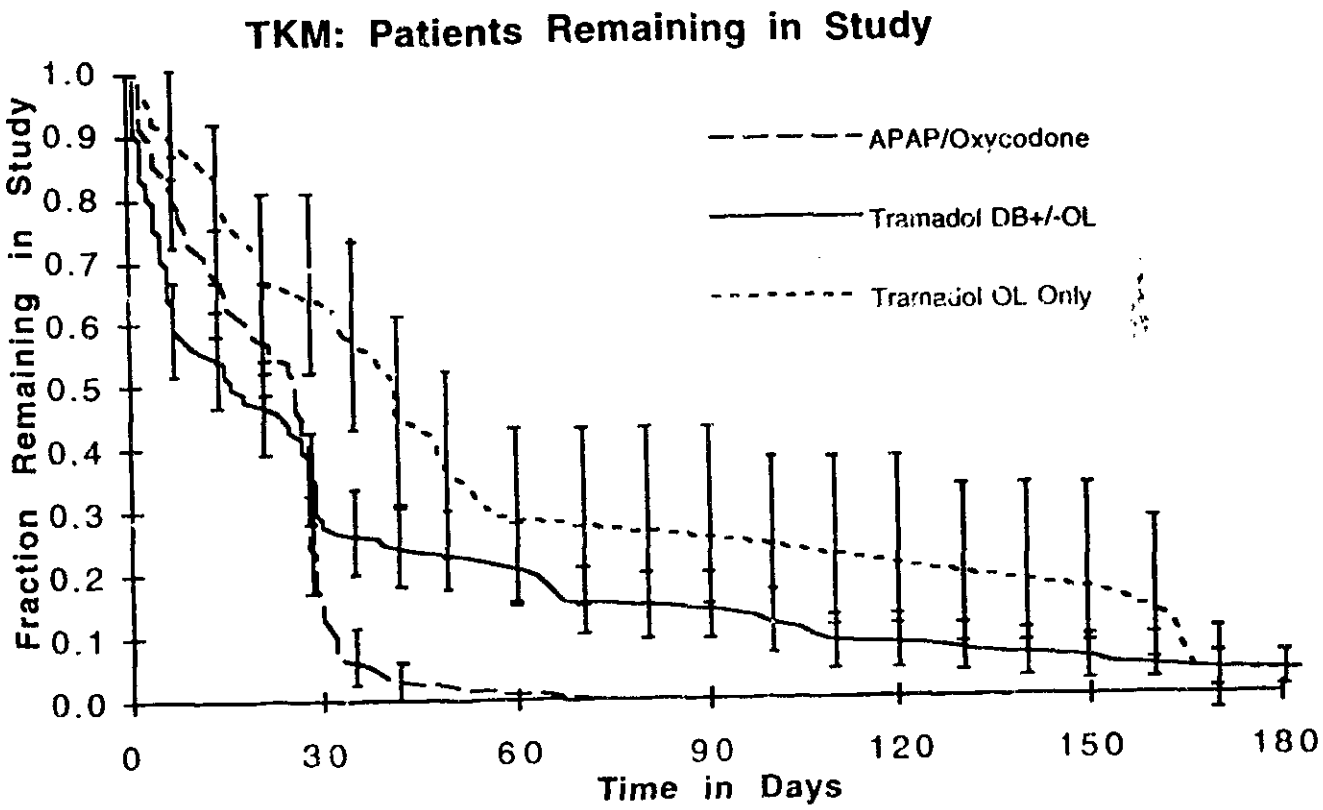
	Tramadol (N = 101)		APAP/Oxycodone (N = 69)	
	N	%	N	%
Discontinued	47	47%	32	46%
Drug-Related	33	33%	23	33%
Adverse Experience	18	18%	8	12%
Drug Ineffective	15	15%	15	22%
Intercurrent Illness	3	3%	2	3%
Patient Choice	5	5%	2	3%
Other	6	6%	5	7%
Death	1	1%	0	0%
Hospitalized	0	0%	3	4%
Rec'd Contraindicated Med	1	1%	0	0%
Insufficient pain/ No analgesia need	2	2%	1	1%
Patient Request	1	1%	0	0%
Other[a]	1	1%	1	1%
Completed double-blind	54	53%	37	54%
Went into Open-Label Study	40	40%	24	35%

[a] Tramadol: 1 extended vacation; APAP/oxycodone: 1 disease progression.

Just under half of the patients in each group failed to complete the double blind period. The distributions of reasons seem comparable, although the drug related reasons were tilted towards adverse events in the tramadol group and toward ineffectiveness in the APAP/oxycodone group.

OTHER DATA LOSS: Efficacy analyses include data from 168 of the 170 patients who were enrolled in the study and received study medication. The diaries for two patients in the APAP/oxycodone group were not returned and thus no efficacy data was available for these patients. Only limited efficacy data (just global evaluations) were recorded for four tramadol patients and two APAP/oxycodone patients.

The following table and graph show the fractions of patients remaining in the study over time for the APAP/oxycodone group and the tramadol group (including any open-label extension). The graph also shows the experience while on tramadol of the tramadol OL Only group (APAP/oxycodone patients who switched to tramadol for the open-label period)



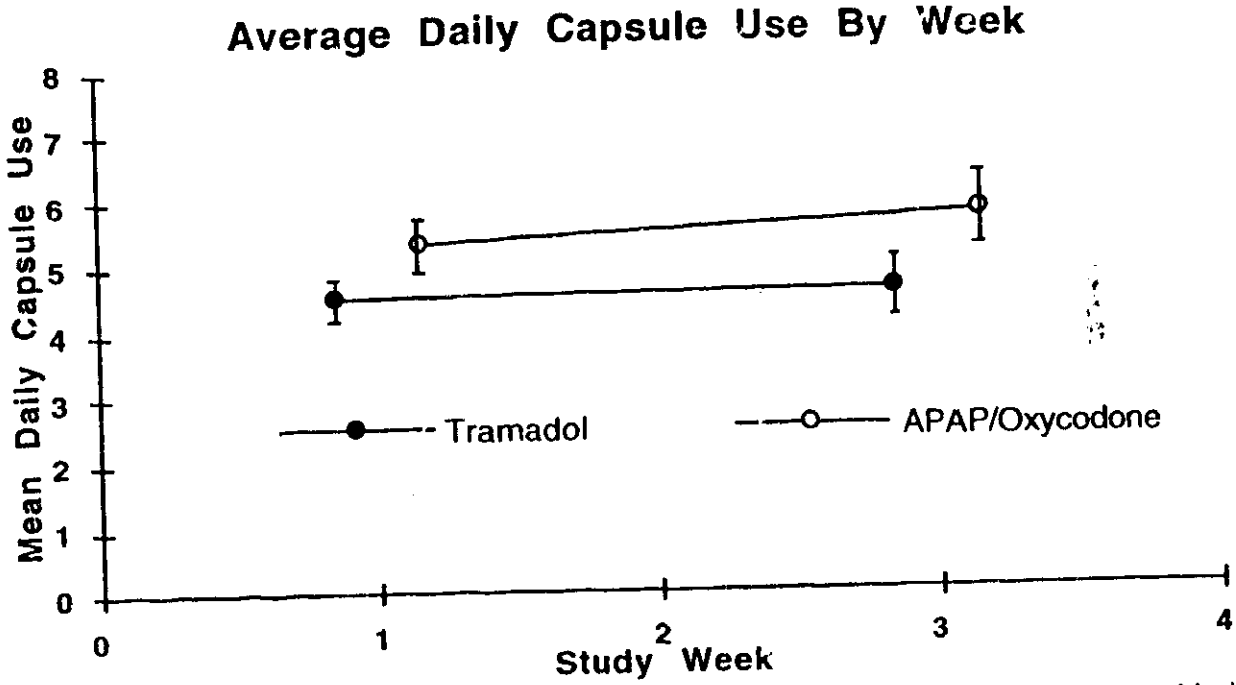
Error bars show +/- 1.5 s.e.m., so that statistically significant differences (at p≤.05 two-sided) approximately correspond to lack of overlap of the error bars.

Fraction Remaining in Study

Days	APAP/Oxycodone	Tramadol	p-value
7	0.797	0.594	0.009
14	0.667	0.545	0.152
21	0.580	0.465	0.191
28	0.246	0.356	0.176

These data show that there was a higher attrition rate in the first week for the tramadol group, and participation tended to remain lower during the rest of the double blind period. The tramadol OL group showed lower attrition, as did the tramadol group after the end of the double-blind period, probably reflecting a selection effect.

MEDICATION USE: The average number of capsules used daily as recorded at each visit are plotted and tabulated below:



Error bars show +/- 1.5 s.e.m., so that statistically significant differences (at $p \leq .05$ two-sided) approximately correspond to lack of overlap of the error bars.

		Week 1[a]	Week 3[a]
Tramadol	Mean No. of Caps	**4.49**	**4.63**
	95% CI	4.1 - 4.9	4.0 - 5.2
	Range	0.6 - 8.0	0.4 - 8.0
	% ≥ 8 caps/day	11%	13%
	N	80	56
APAP/Oxycodone	Mean No. of Caps	**5.31**	**5.79**
	95% CI	4.8 - 5.8	5.1 - 6.5
	Range	0.4 - 8.9	1.7 - 8.0
	% ≥ 8 caps/day	8%	23%
	N	59	35

[a] Tramadol and APAP/oxycodone groups differ (two-sided $p \leq .05$).

Since the patient population is not constant in the above table, difference from week to week could be affected by selection. The reviewer computed average capsule use for the cohort that contributed mean capsule use data at both visits. The values were similar:

Mean Capsule Use, for Cohort Contributing Data at Both Visits

		Week 1	Week 3
Tramadol	(N=53)	**4.43**	**4.76**
APAP/Oxycodone	(N=35)	**5.39**	**5.79**

There was a slight tendency toward increased capsule use over the course of the study: tramadol use and APAP/oxycodone use both rose by 7% from week 1 to week 3. There were no reports of the average daily use exceeding

the 8 capsule limit in the tramadol group, and only 1 report in the APAP/oxycodone group.

EFFICACY -- DAY 1 RATINGS: Following administration of the first dose of study drug on Day 1 of Weeks 1 and 3, patients were instructed to record the intensity of their starting pain, as well as pain relief and medication acceptability at hourly intervals for four hours. Summary results are shown in the following tables. Total Pain Relief and Total Medication Rating are the sums of the 4 hourly values.

Mean Values and Treatment Comparisons
of Day 1 First Dose Efficacy Variables

	Treatment Group[a]					
	Tramadol			APAP/Oxycodone		
	N	Mean	95% CI	N	Mean	95% CI
Starting Pain[b]						
Week 1	96	1.9	1.7 - 2.0	65	1.9	1.8 - 2.1
Week 3	58	1.7	1.5 - 1.9	35	1.8	1.7 - 2.0
Total Pain Relief[c]						
Week 1	92	7.6	6.7 - 8.5	62	7.9	6.7 - 9.0
Week 3	51	9.1	8.1 - 10.1	35	9.0	7.5 - 10.4
Total Medicine Rating[d]						
Week 1	91	10.0	9.3 - 10.7	61	11.0	9.9 - 12.0
Week 3	50	12.4	11.4 - 13.5	35	12.4	10.9 - 13.9

a No statistically significant difference between treatment groups (two-sided $p > 0.05$).
b Scale: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe
c Scale: 0 = No relief; 16 = Complete relief at every evaluation
d Scale: 4 = Poor at every evaluation; 20 = Excellent at every evaluation

The average Day 1 starting pain at each week during on both treatments was moderate. The Day 1 first dose starting pain, Day 1 first dose total pain relief, and Day 1 first dose total medication rating in the tramadol and APAP/oxycodone groups were comparable at all evaluations.

Day 2 data are not presented here, but they also showed similarity of the two treatments.

EFFICACY -- OVERALL RATINGS: Patients were instructed to complete a rating of medication acceptability daily during Weeks 1 and 3. At the conclusion of the study, investigators' completed a global evaluation of efficacy for each patient, and patients completed an overall assessment of medication.

Mean Overall Average Medication Rating[a]

	Treatment Group[b]					
	Tramadol			APAP/Oxycodone		
	N	Mean	95% CI	N	Mean	95% CI
Week 1	79	**3.0**	2.8 - 3.2	58	**2.9**	2.7 - 3.2
Week 3	55	**3.4**	3.2 - 3.7	35	**3.3**	2.9 - 3.6

a Scale: 1 = Poor, 2 = Fair, 3 = Good, 4 = Very Good, 5 = Excellent
b No statistically significant difference between treatment groups (two-sided p > 0.05).

Distributions and Mean Values of Global Ratings

Global Evaluation/ Rating	Number (%) of Patients	
	Tramadol	APAP/Oxycodone
Investigator's Global Evaluation[a]		
Marked (6)	18 (19%)	12 (19%)
Moderate (5)	39 (41%)	25 (40%)
Minimal (4)	24 (26%)	14 (23%)
None (3)	10 (11%)	8 (13%)
Worse (2)	3 (3%)	3 (5%)
Mean Rating	4 6	4.6
95 % CI	4.4 - 4.8	4.3 - 4.8
Total No. Patients	94	62
Patient's Overall Assessment[a]		
Excellent (6)	12 (12%)	6 (9%)
Very Good (5)	21 (21%)	11 (17%)
Good (4)	25 (26%)	17 (26%)
Fair (3)	19 (19%)	15 (23%)
Poor (2)	21 (21%)	16 (25%)
Mean Rating	3.8	3.6
95 % CI	3.6 - 4.1	3.3 - 3.9
Total No. Patients	98	65

a No statistically significant difference between treatment groups (two-sided p > 0.05).

SAFETY

The safety experience is considered in more detail in the Integrated Safety Review. All patients (N=170) were included in the analysis of safety. For each adverse event, the table below shows the number of patients who experienced that event at least once. The only events reported here are those that occurred in at least 5% of patients in at least one of the groups. Events with statistically significant differences are indicated with an asterisk.

	Tramadol		APAP/Oxycodone	
	N	%	N	%
Any AE	93	92.1	56	81.2
Body as a Whole	46	45.5	32	46.4
Asthenia	9	8.9	4	5.8
Edema*	0	0.0	5	7.2
Headache	21	20.8	8	11.6
Hospitalization	9	8.9	9	13.0
Cardiovascular System	9	8.9	2	2.9
Central Nervous System	35	34.7	17	24.6
Dizziness	20	19.8	8	11.6
Somnolence	15	14.9	6	8.7
GI System	73	72.3	44	63.8
Anorexia	8	7.9	3	4.3
Constipation	37	36.6	28	40.6
Diarrhea	4	4.0	5	7.2
Dyspepsia	7	6.9	3	4.3
Nausea	44	43.6	20	29.0
Pain, Abdominal	2	2.0	4	5.8
Vomiting*	26	25.7	6	8.7
Musc/Skel System	5	5.0	5	7.2
Psychiatric	10	9.9	5	7.2
Respiratory System	12	11.9	8	11.6
Cough	5	5.0	5	7.2
Skin	15	14.9	4	5.8
Sweating*	9	8.9	1	1.4
Special Senses	6	5.9	4	5.8
Urogenital System	9	8.9	5	7.2

* Statistically significantly different at $p \leq .05$.

The adverse event profile of tramadol resembled that of an opioid: dizziness, somnolence, constipation, nausea and vomiting were common; sweating was seen as well. The tramadol group had less edema, but more vomiting and sweating than the APAP/oxycodone group. The tramadol group also tended to have more nausea.

Deaths

One tramadol patient died during this study, and a second tramadol patient died just after completing the study. One APAP/oxycodone patient died after being hospitalized. The deaths were all considered to be secondary to underlying diseases. A detailed discussion of these patients follows:

Inv. 098, Pt. 010, death (tramadol) - This 56-year-old, 134.2 lb, black man died on Day 4 of the

study. This patient is listed in the 1990 IND Annual Report (Serial No. 094). The patient entered the trial with non-small cell lung cancer. The patient received 200 mg, 200 mg and 300 mg of tramadol on Days 1, 2 and 3, respectively. The patient died as the result of a cardiac arrest. The investigator noted that this was probably due to hypercalcemia (screening calcium level was elevated, 11.3 mg/dL) brought on by the patient's cancer. The investigator considered this adverse experience to be unrelated to treatment.

Inv. 096, Pt. 006, death (tramadol) - This 70-year-old, 153.5 lb, white man died one day after completing the double-blind study during which he had received 29 days of treatment. This patient is listed in the 1990 IND Annual Report (Serial No. 094). The patient had entered the trial for the treatment of pain in his lungs, kidneys and pelvis secondary to lung, skin and groin cancer. Approximately two weeks prior to study entry, the patient was placed on lorazepam for anxiety. On Day 18, the patient reported a fever and cough and was given acetaminophen. On Day 22, the patient reported a sore mouth and throat and hemoptysis, and was given ketoconazole and ciprofloxacin. The patient was unable to come into the office for the follow-up visit and subsequently died on Day 30. During Weeks 1 and 3, the patient received an average daily dose of 185.7 mg and 300 mg of tramadol, respectively. The investigator noted that the patient died as the result of a progression of metastatic non-small cell lung cancer. All of the adverse experiences reported during the study were rated as moderately severe and considered to be unrelated to treatment.

Inv. 133, Pt. 003, death (APAP/oxycodone) - This 82-year-old, 115.5 lb, white woman died on Day 4 due to intracerebral hemorrhage. This patient is listed in the 1990 IND Annual Report (Serial No. 094). The patient received two capsules of APAP/oxycodone on Days 1 and 2. The patient was noted as being less responsive at this time, and study medication was discontinued. On Day 3, the patient was comatose with a blood glucose of 47 mg/dL; an amp of dextrose was given. There was no clinical improvement and the patient was hospitalized. The patient showed no clinical improvement, and on Day 4, her respirations ceased and no heart rate or palpable pulse was found. Due to the patient's advanced age and advanced malignancy, the patient was not resuscitated. The patient entered the trial with colon cancer with lung and liver metastases and was receiving warfarin, furosemide, diltiazem HCl, docusate sodium, ranitidine, doxepin HCl and chemotherapy. The investigator considered this death to be due to the to the progression of the patient's disease and not to study medication.

Other Serious Adverse Experiences

One patient attempted suicide 16 days after discontinuing tramadol therapy and one tramadol patient was hospitalized for a possible cardiovascular accident. These patients are discussed in detail below:

Inv. 155, Pt. 005, suicide attempt (tramadol) - A 41-year-old, 127 lb, white woman attempted suicide on Day 21 of the study with triazolam and multiple lacerations. The patient had been hospitalized one week prior to the screening visit for pain secondary to metastatic breast cancer and extensive bone cancer, during which time it was noted that the patient complained of depression. The patient was discharged on furosemide, prednisone and triazolam. The patient reported stopping study medication on Day 5 and resumed treatment with oxycodone with acetaminophen (PERCOCET®) on Day 6. She failed to return her diary, and her daily dose of tramadol is unknown. The investigator rated the adverse experience as marked in severity and unrelated to treatment.

Inv. 103, Pt. 002, coronary artery disease, hospitalization (tramadol) - This 57-year-old, 120 lb, white man with a past history of chronic obstructive pulmonary disease and who was taking theophylline and prednisone was hospitalized on Day 33 for a possible cardiovascular accident. On Days 21 to 23, the patient began experiencing dizziness, confusion, weakness of the extremities and numbness. A CT scan done on Day 25 revealed a small stroke. A physical examination revealed decreased sensation in the right arm and leg. On Day 32, the patient experienced a seizure and was given phenytoin. He was hospitalized the next day. A CT scan

on Day 38 revealed a small focus of abnormality in the left parietal lobe which was probably an infarction. An angiogram performed on Day 40 showed internal carotid stenosis. The patient received a total of 28 days of therapy and the average daily dose of tramadol was 371.4 mg and 400 mg during Weeks 1 and 3, respectively. These adverse experiences were rated as marked in severity and unrelated to treatment.

Ophthalmologic evaluations were to be completed within two weeks of the baseline visit and at the end of the double-blind period. but no ophthalmology examinations were performed at the end of the double-blind period.

There were no clinically significant changes in average values for vital signs, laboratory values or ECG parameters.

SUMMARY

Tramadol and APAP/oxycodone provided essentially the same analgesia during the double blind period. However, attrition from the tramadol group was higher during the initial week of treatment.

The daily capsule usage showed a slight rising trend over time in both groups, with tramadol use increasing 7% from week 1 to week 3. There was no evidence of use exceeding recommendations.

The two deaths and the two serious adverse events for patients on tramadol did not appear to be related to treatment.

The adverse event profile of tramadol resembles that of and opioid; nausea, vomiting, constipation, dizziness and somnolence as well as some sweating.

CONCLUSIONS

This study provides substantial evidence of the utility of tramadol for treating chronic pain of malignancy, and provides supporting evidence of its analgesic effect. The adverse event profile is similar to that of an opioid.

John E Hyde
John E. Hyde, Ph.D., M.D

Pam Wildman 2-28-95

Tramadol Study TL2:
One Month Study of Chronic Pain in Elderly

MEDICAL OFFICER REVIEW

NDA #: 20 281
NAME: ULTRAM (Tramadol Hydrochloride).
SPONSOR: R.W. Johnson
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.
REVIEW DATE: June 30, 1994.
CSO: C. Moody

GENERAL DESIGN: This was a multicenter, randomized, 1-month, double-blind, parallel, active-controlled outpatient study of tramadol vs. acetaminophen with codeine in elderly patients with chronic pain.

STUDY POPULATION: Patients enrolled in this study had to be at least 65 years of age or older, have acceptable liver and renal function, and have consistent pain requiring a prescription analgesic almost every day. Conditions included, but were not limited to: trigeminal neuralgia, post-herpetic neuralgia, chronic low-back syndrome, rheumatoid arthritis, diabetic neuropathy, primary fibrositis, osteoarthritis, Paget's disease, and malignancy. Recurrent headache was not included.

Patients were excluded for painful bony metastases (unless they could not take NSAID's), history of a seizure disorder, current abuse of narcotics or alcohol, tolerance to narcotics, of if they were suicidal.

TREATMENT: The capsules compared were:
Tramadol Hydrochloride 50 mg, vs.
Acetaminophen 300 mg with Codeine Phosphate 30 mg
Patients were instructed to take one or two capsules of their assigned study medication every 4 to 6 hours as needed for pain, for 4 weeks. A maximum of 8 capsules was permitted in any 24-hour period. After completion of the double-blind period, patients could elect to receive open-label tramadol.

EFFICACY ASSESSMENT: On Day 1 of Weeks 1 and 3, patients rated their pre-treatment pain (4 point scale), as well as pain relief (5 point scale) and medication acceptability (5 point scale) at 1, 2, 3 and 4 hours after the first dose of study medication on that day. On Day 2 of the same study weeks, patients rated pain before and four hours after the first dose. They also rated minimum pain intensity and medication acceptability. Daily during Weeks 1 and 3, patients recorded the number of capsules taken and completed an overall medication acceptability rating. At the conclusion of double-blind treatment, patients and investigators provided an overall assessment of therapy.

CONCOMITANT MEDICATIONS: During the double-blind period, patients taking the full 8-capsule per day allotment of study drug or who

took their maximum tolerated dose (if at least four capsules per day) could supplement with up to 4 g of aspirin per day or maximal NSAID. Chronic use of steroids was permitted by patients who still required analgesia and who had been receiving no more than 10 mg/day prednisone or its equivalent without significant side effects. Therapy was to remain constant through the double-blind period. Bulk laxatives and stool softeners were permitted. The chronic use of aspirin up to 325 mg/day for anticoagulation and the use of stimulant laxatives required the sponsor's permission. Prescribing of centrally-acting drugs was to be done with caution.

SAFETY: Safety was evaluated by reported adverse experiences, vital signs, clinical laboratory evaluations and ECG's.

RESULTS

BASELINE DEMOGRAPHICS: Thirty-four investigators participated. Three hundred ninety patients were enrolled in the study and took study drug (234 tramadol, 156 APAP/codeine). All patients (N = 390) were included in the analysis of demographic characteristics. Distributions of demographic features are given in the following table:

Baseline Demographic Characteristics by Treatment Group

	Tramadol (N = 234)		APAP/Codeine (N = 156)	
Male	76	32%	39	25%
Female	158	68%	117	75%
White	212	91%	145	93%
Black	15	6%	9	6%
Other	7	3%	2	1%
Mean Age (years)	72.1		72.0	
Mean Weight - Male (lb)	182		184	
Mean Weight - Female (lb)	160[a]		158	
Mean Height - Male (in)	68.2		68.9	
Mean Height - Female (in)	63.3[a]		62.9	
Baseline Pain[b]				
None	1	0%	0	0%
Mild	29	13%	13	9%
Moderate	120	53%	82	54%
Severe	77	34%	56	37%
Diagnosis				
Low Back Pain	23	10%	22	14%
Arthritis	169	72%	112	72%
OA	115	49%	69	44%
RA	13	6%	7	4%
Neuropathic Pain	22	9%	11	7%
Cancer	1	0%	0	0%
Orthopedic Pain	14	6%	9	6%
Other	5[c]	2%	2[d]	1%

a Weight and height missing for pt.
b Tramadol N = 227; APAP/codeine N = 151.
c Chronic mouth pain; restless leg syndrome; cervical muscle spasms; 2 with fibrositis.
d Bilateral testicular pain; osteoporosis and osteoarthritis.

The groups appear reasonably balanced. The predominant condition studied was arthritis, primarily osteoarthritis. This was essentially a study of non-malignant pain, as there was only one cancer patient.

DISPOSITION OF PATIENTS: The following table shows reasons for discontinuation:

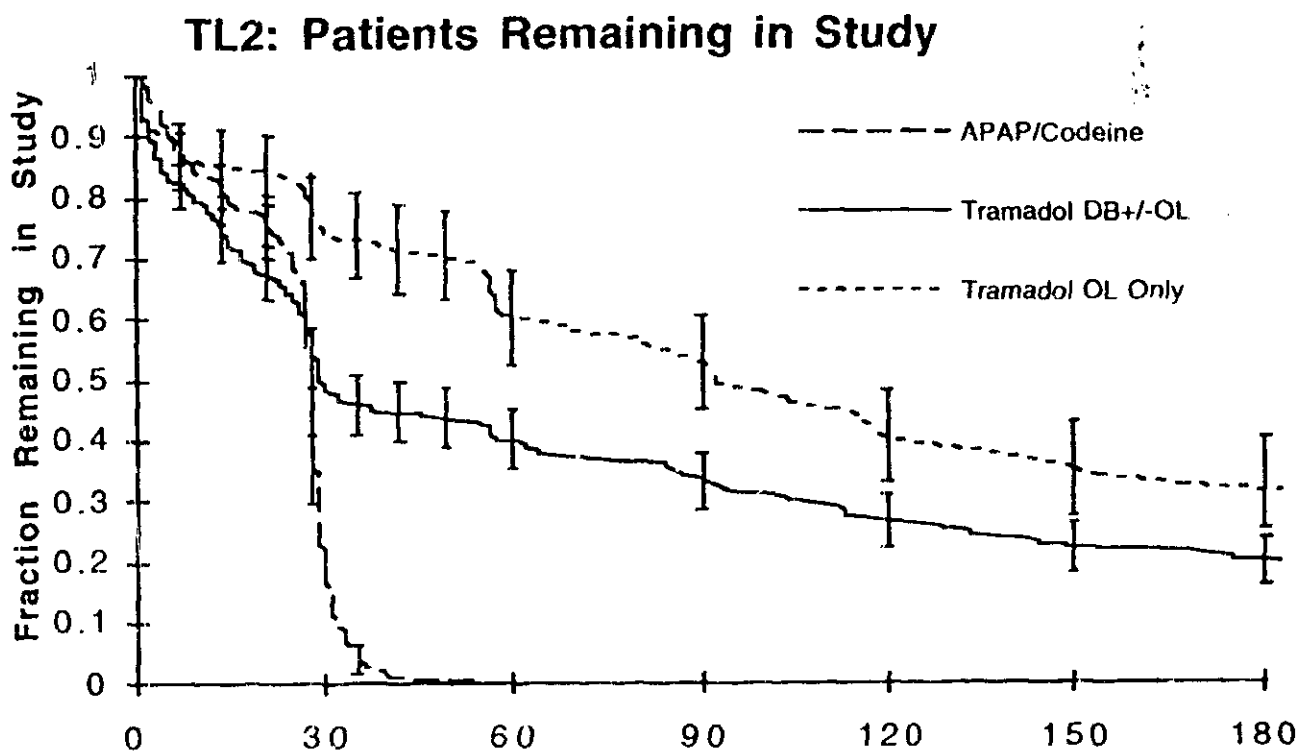
	Tramadol (N = 234)		APAP/Codeine (N = 156)	
	N	%	N	%
Discontinued	71	30%	45	29%
Drug-Related	53	23%	25	16%
Adverse Experience[a]	44	19%	15	10%
Drug Ineffective	9	4%	10	6%
Intercurrent Illness	4	2%	5	3%
Patient Choice	7	3%	4	3%
Failure to Return	1	0%	2	1%
Other	6	3%	9	6%
Hopitalized	1	0%	1	1%
Poor compliance	2	1%	2	1%
Incl/Excl Violation	1	0%	3	2%
Insufficient Pain	0	0%	2	1%
Other[b]	2	1%	1	1%
Completed double-blind	163	70%	111	71%
Went into Open-Label Study	140	60%	91	71%

a Significant between group difference (two-sided $p \leq 0.05$).
b Tramadol: alcohol abuse; took contraindicated medication. APAP/codeine: got wrong study bottle.

There was the same completion rate in both groups, however, there were more discontinuations due to adverse events in the tramadol group.

OTHER DATA LOSS: Efficacy analyses include data from 385 of the 390 patients who were enrolled in the study and received study medication. One patient in the tramadol group was excluded from all efficacy analyses for repeatedly taking rescue medication before completing the prescribed tramadol regimen (eight capsules per day). No efficacy data were recorded for 3 tramadol patients and 1 APAP/codeine patient. Only global evaluations were recorded for four tramadol patients and one APAP/codeine patient. Other patients were missing data on some efficacy variables at one or more time points.

The following table and graph show the fractions of patients remaining in the study over time for the APAP/codeine group and the tramadol group (including any open-label extension). The graph also shows the experience while on tramadol of the tramadol OL Only group (APAP/codeine patients who switched to tramadol for the open-label period)

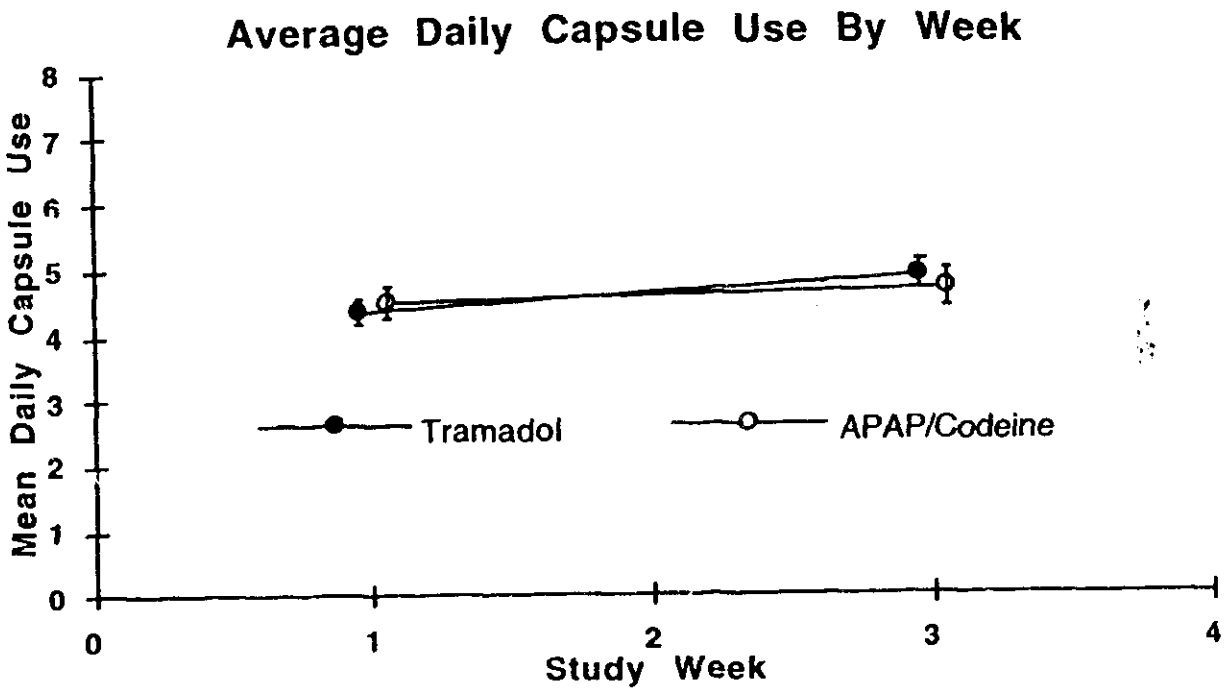


Error bars show +/- 1.5 s.e.m., so that statistically significant differences (at .05 two-sided) approximately correspond to lack of overlap of the error bars.

Days	APAP/Codeine	Tramadol	p-value
7	0.865	0.821	0.299
14	0.808	0.739	0.149
21	0.750	0.675	0.141
28	0.353	0.539	0.000

The tramadol group tended to have more attrition during the double blind period, but he difference was not statistically significant. The tramadol OL group showed lower attrition, as did the tramadol group after the end of the double-blind period, probably reflecting a selection effect.

MEDICATION USE: The average number of capsules used daily as recorded at each visit are plotted and tabulated below:



Error bars show +/- 1.5 s.e.m., so that statistically significant differences (at $p \leq .05$ two-sided) approximately correspond to lack of overlap of the error bars.

		Week 1[a]	Week 3[a]
Tramadol	Mean No. of Caps	**4.37**	**4.90**
	95% CI	4.1 - 4.6	4.6 - 5.2
	Range	1.0 - 8.1	0.3- 8.0
	% ≥ 8 caps/day	3%	6%
	N	205	168
APAP/Codeine	Mean No. of Caps	**4.51**	**4.69**
	95% CI	4.2 - 4.8	4.3 - 5.1
	Range	0.4 - 8.3	0.6 - 8.0
	% ≥ 8 caps/day	4%	7%
	N	145	116

a No statistically significant difference between treatment groups (two-sided $p > 0.05$)

Since the patient population is not constant in the above table, differences from week to week could be affected by selection. The reviewer computed average capsule use for the cohort that contributed mean capsule use data at both visits. The values were similar:

Mean Capsule Use, for Cohort Contributing Data at Both Visits

		Week 1	Week 3
Tramadol	(N = 167)	**4.36**	**4.91**
APAP/Codeine	(N = 116)	**4.46**	**4.69**

There was a tendency toward increased capsule use over the course of the study: tramadol use rose by 13% from week 1 to week 3 while APAP/codeine use rose 5%. There was 1 report in each group of the average daily use exceeding the 8 capsule limit during week 1.

EFFICACY -- DAY 1 RATINGS: Following administration of the first dose of study drug on Day 1 of Weeks 1 and 3, patients were instructed to record the intensity of their starting pain, as well as pain relief and medication acceptability at hourly intervals for four hours. Summary results are shown in the following tables. Total Pain Relief and Total Medication Rating are the sums of the 4 hourly values.

Mean Values and Treatment Comparisons
of Day 1 First Dose Efficacy Variables

	Treatment Group[a]					
	Tramadol			APAP/Codeine		
	N	Mean	95% CI	N	Mean	95% CI
Starting Pain[b]						
Week 1	224	2.2	2.1 - 2.3	150	2.3	2.2 - 2.4
Week 3	170	2.0	1.9 - 2.1	113	2.0	1.9 - 2.2
Total Pain Relief[c]						
Week 1	221	6.1	5.6 - 6.6	147	6.1	5.4 - 6.7
Week 3[d]	169	7.4	6.8 - 7.9	111	6.7	6.0 - 7.4
Total Medicine Rating[e]						
Week 1	217	9.3	8.8 - 9.8	146	8.9	8.3 - 9.4
Week 3	168	10.4	9.9 - 11.0	111	10.2	9.5 - 10.9

a No statistically significant difference between treatment groups (two-sided $p > 0.05$).
b Scale: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe
c Scale: 0 = No relief; 16 = Complete relief at every evaluation
d Significant treatment-by-investigator interaction (two-sided $p \leq 0.10$).
e Scale: 4 = Poor at every evaluation; 20 = Excellent at each evaluation.

Day 2 data are not presented here, but they also showed very similar efficacy ratings for the two treatments.

EFFICACY -- OVERALL RATINGS: Patients were instructed to complete a rating of medication acceptability daily during Weeks 1 and 3. At the conclusion of the study, investigators completed a global evaluation of efficacy for each patient, and patients completed an overall assessment of medication.

Mean Overall Average Medication Rating[a]

	Treatment Group[b]					
	Tramadol			APAP/Codeine		
	N	Mean	95% CI	N	Mean	95% CI
Week 1[c]	204	**2.7**	2.6 - 2.8	144	**2.6**	2.4 - 2.7
Week 3	164	**2.8**	2.7 - 3.0	116	**2.7**	2.6 - 2.9

a Scale: 1 = Poor, 2 = Fair, 3 = Good, 4 = Very Good, 5 = Excellent
b No statistically significant difference between treatment groups (two-sided $p > 0.05$).
c Significant treatment-by-investigator interaction (two-sided $p \leq 0.10$).

Distributions and Mean Values of Global Ratings

Global Evaluation/ Rating	Number (%) of Patients	
	Tramadol	APAP/Codeine
Investigator Global Evaluation		
Marked (6)	25 (11%)	12 (8%)
Moderate (5)	91 (41%)	75 (50%)
Minimal (4)	62 (28%)	32 (21%)
None (3)	32 (15%)	23 (15%)
Worse (2)	10 (5%)	7 (5%)
Mean Rating	4.4	4.4
95% CI	4.3 - 4.5	4.3 - 4.6
Total No. Patients	220	149
Patient Overall Assessment		
Excellent (6)	15 (7%)	7 (5%)
Very Good (5)	37 (16%)	25 (16%)
Good (4)	71 (32%)	52 (34%)
Fair (3)	49 (22%)	38 (25%)
Poor (2)	53 (24%)	31 (20%)
Mean Rating	3.6	3.6
95% CI	3.5 - 3.8	3.4 - 3.8
Total No. Patients	225	153

SAFETY

The safety experience is considered in more detail in the Integrated Safety Review. All patients (N = 390) were included in the analyses of safety. For each adverse event, the table below shows the number of patients who experienced that event at least once. The only events reported here are those that occurred in at least 5% of patients in at least one of the groups. Events with statistically significant differences are indicated with an asterisk.

	Tramadol		APAP/Codeine	
	N	%	N	%
Abnormal Labs	12	5.1	7	4.5
Body As A Whole	86	36.8	66	42.3
Asthenia	25	10.7	17	10.9
Edema*	5	2.1	12	7.7
Headache	56	23.9	31	19.9
Cardiovascular System	25	10.7	9	5.8
Central Nervous System	123	52.6	76	48.7
Dizziness	72	30.8	41	26.3
Somnolence	57	24.4	43	27.6
Vertigo	13	5.6	4	2.6
GI System	164	70.1	122	78.2
Anorexia	16	6.8	4	2.6
Constipation*	91	38.9	90	57.7
Diarrhea	16	6.8	13	8.3
Dyspepsia*	10	4.3	17	10.9
Flatulence	7	3.0	11	7.1
Mouth, Dry	13	5.6	14	9.0
Nausea	83	35.5	52	33.3
Pain, Abdominal*	12	5.1	17	10.9
Vomiting*	32	13.7	10	6.4
Musc/Skel System	22	9.4	13	8.3
Psychiatric	21	9.0	14	9.0
Respiratory System	24	10.3	13	8.3
Skin	43	18.4	23	14.7
Pruritus	26	11.1	10	6.4
Sweating	14	6.0	6	3.8
Special Senses	18	7.7	9	5.8
Urogenital System	25	10.7	16	10.3

* Statistically significantly different at $p \leq .05$.

The adverse event profile of tramadol resembled that of an opioid: dizziness, somnolence, constipation and nausea and vomiting were common; pruritus and sweating were seen as well. The tramadol group had less edema, dyspepsia and constipation, but more vomiting, than the APAP/codeine group.

Other Notable Adverse Experiences

Angina pectoris (myocardial ischemia) was reported in one tramadol patient and two APAP/codeine patients during the study. One tramadol patient was receiving chlorpropamide, nifedipine and isosorbide at study entry and had a previous history of angina. His prescriptions ran out on

Day 12 and were not refilled. This precipitated the episode of angina pectoris that was accompanied by swelling and ankle edema. Following refill of his prescriptions, the adverse experiences resolved. Both APAP/codeine patients had a history of angina pectoris and were treated with nitroglycerin for this adverse experience.

SUMMARY

Tramadol and APAP/codeine provided essentially the same analgesia during the double blind period. Attrition from the tramadol group tended to be higher.

The daily capsule usage showed a rising trend over time in both groups, with tramadol use increasing 13% from week 1 to week 3. There was little evidence of use exceeding recommendations.

The adverse event profile of tramadol resembles that of and opioid: nausea, vomiting, constipation, dizziness and somnolence, as well as some pruritus and sweating.

CONCLUSIONS

This study provides substantial evidence of the utility of tramadol for treating chronic pain, and provides supporting evidence of its analgesic effect. The adverse event profile is similar to that of an opioid.

John E Hyde
John E. Hyde, Ph.D., M.D

Rm. Wdward 2-28-95

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Pharm

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PHARMACOLOGY REVIEW - NDA #20-281

NDA 20-281

Trade name: ULTRAM **Dosage form:** oral tablet

Generic name: tramadol hydrochloride
Sponsor:
R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

Date of Submission: NOVEMBER 1, 1993

Date of Review: January 6, 1995

Date of Receipt:
CDER: November 1, 1993
Reviewer: March 20, 1994

CATEGORY: Analgesic, narcotic

INDICATIONS: acute and long term pain-management

RELATED DRUG/INDs/NDAs/DMFs:

s)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

Tramadol is the trans-isomer of 1-(m-methoxy-phenyl)-2-(dimethylaminomethyl)-cyclohexan-1-ol and molecular modelling has shown that the trans-isomer can overlap the morphine ring-structure much better than the cis-form (V21NDA/083). The trans form, apparently more potent in analgesic tests with less acute toxicity, is the only form used in studies presented in the following review and is used as the racemic mixture unless otherwise noted. The racemic trans-isomer is the form for clinical use and marketing.

PRECLINICAL STUDIES RELATING TO ABUSE POTENTIAL

The following is a review of the effects of tramadol in preclinical tests and because of the magnitude of accumulated internal and

literature reports, this review attempts to address major themes of tramadol action. An extensive review of the preclinical data was compiled with the IND in 1985 but due to the time interval and study accumulation, there will be some repetition.
One important factor that has surfaced since the original report is the potency of the metabolite, O-desmethyltramadol, M1. This metabolite appears to play a major role in the opioid binding and analgesic effects, 4 times to nearly 200 times as potent as the parent tramadol and is often present at equivalent blood levels. The pharmacologic effects will be addressed as encountered and in the ADME section of the review.

I. *IN VITRO* RECEPTOR-BINDING STUDIES:

The μ-opioid receptor is considered the site of analgesia, tolerance and addiction and *in vitro*, racemic tramadol is less potent than morphine, d-propoxyphene and codeine by factors of 6000, 60 and 13, respectively (Table I/a).

The binding to α_1, α_2, NMDA and benzodiazepine sites was insignificant up to 10-100μM. This was also true of 5-HT_2 sites although ritanserin antagonized the analgesia of intrathecal tramadol, but not intrathecal morphine (V18NDA/p088). The following table is a synopsis of significant in vitro binding.

NDA# 20-281

TABLE I/a
(V8/19:p109-110) (V18NDA/P079) (V21NDA/p244)

IN VITRO - RECEPTOR BINDING

COMPOUND	$\mu^{a,b}$	^3H - nal^{a,c}	δ^a	NE^a	5-HT^a
(±)-TRAMADOL	2.1 x E^{-6}	1.9 x E^{-5}	5.8 x E^{-5}	7.9 x E^{-7}	9.9 x E^{-7}
(+)-TRAMADOL	1.3 x E^{-6}	1.0 x E^{-5}	6.2 x E^{-6}	2.5 x E^{-6}	5.3 x E^{-7}
(-)-TRAMADOL	2.5 x E^{-5}	1.9 x E^{-4}	2.1 x E^{-4}	4.3 x E^{-7}	2.4 x E^{-6}
(±) M1^d	1.2 x E^{-8}	1.1 x E^{-7}	-	1.5 x E^{-6}	5.2 x E^{-6}
(+) M1	6.0 x E^{-9}	-	-	1.4 x E^{-5}	3.0 x E^{-6}
(-) M1	4.3 x E^{-7}	-	-	8.6 x E^{-7}	1.8 x E^{-5}
MORPHINE	3.5 x E^{-10}	1.5 x E^{-8}	9.3 x E^{-8}	-	-
d-PROPOXYPHENE	3.5 x E^{-8}	-	3.8 x E^{-7}	-	-
CODEINE	1 .6 x E^{-7}	3.6 E^{-6}	5.1 x E^{-6}	na	na
IMIPRAMINE	3.7 x E^{-6}	-	1.3 x E^{-5}	6.6 x E^{-9}	2.1 x E^{-8}

a. K_i (M) ^{b}= DAGO-H^3 as ligand ^{d} M1 = mono-O-desmethyltramadol
^{c} naloxone binding: FO-PH/269 IND SUB.#104 3/8/91
na = not active at 10μM - = not tested NE = norepinephrine

The μ-receptor binding, the principle binding site of narcotic analgesics, is usually most closely associated with analgesia and addiction. The delta receptors bind with the greatest affinity for the enkephalins and have a more discrete distribution in the brain than the mu or kappa receptors. Although morphine mainly interacts with the mu receptor, the administration of morphine can induce the release of enkephalins and the delta receptors are activated and play a role in analgesia.

This in vitro data suggests that tramadol has less intrinsic ability to produce analgesia and/or dependence than dextropropoxyphene or codeine in relation to mu-receptor activity. However, the M1 metabolite is more potent than either of these weak opiates. As discussed later in metabolism and pharmacokinetics, the M1 metabolite is often quantitatively greater than the parent tramadol. This is

most evident in the rats and mice, but also in humans where the M1 can be a third of the parent compound serum concentration.

In relation to the displacement of tritiated naloxone, the M1 metabolite was 30 X as potent as codeine and more than 100 X as potent as the parent tramadol. These results indicate analgesic potency can be time-dependent, due to the formation of active metabolites.

The sponsor suggests that the inhibition of noradrenaline and/or 5-HT may play a role in a non-narcotic analgesic component. However, the potency as presented in the table above indicates at least two orders of magnitude separate the most potent enantomer, M1(-), from imipramine. In an article by the originator, Grunenthal (Biochem. Pcol 31:1654-1655(1982)), narcotic toxicity was found to increase when rats were pretreated with an MAO-inhibitor. However, this increase was greatest for morphine, which has no amine uptake inhibition, and tramadol was grouped with methadone and meperidine, both of which are 10X as potent as tramadol in inhibiting norepinephrine and serotonin uptake. As stated in this article, the blood levels found in humans are below the concentrations effectively inhibiting uptake. The following table was derived from this study:

TABLE I/b
(Biochemical Pharacology 31:1654-55 (1982)

MONOAMINE UPTAKE INHIBITION

COMPOUND	5-HT Uptake Inhibition IC_{50} (M)	Norepinephrine Uptake Inhibition IC_{50} (M)
tramadol	4.05×10^{-5}	1.38×10^{-5}
L-methadone	4.22×10^{-6}	3.23×10^{-6}
meperidine	3.73×10^{-6}	2.83×10^{-6}
morphine	$>5 \times 10^{-4}$	$>5 \times 10^{-4}$
imipramine	2.89×10^{-6}	6.85×10^{-8}

NDA# 20-281

II. ANALGESIC ACTIVITY

The analgesic tests in mice provide a comparison between tramadol and the narcotic analgesics and data in the following tables demonstrate that the oral absorption is better with tramadol than the other narcotic analgesics. The potency of tramadol is less than morphine and comparable to codeine and d-propoxyphene.

Table II/a
(V9/p0032)

MOUSE TAIL FLICK (radiant heat)

COMPOUND	ED_{50} (mg/kg) i.p.	ED_{50} (mg/kg) p.o.	Ratio p.o./i.p.
TRAMADOL (±)	16.0	31.2	1.9
MORPHINE	4.7	16.1	3.5
CODEINE	20.2	64.8	3.2
d-PROPOXYPHENE	21.1	67.1	3.2

Table II/b
(V9/18:p00053)

Analgesic Effects in Haffner tail-clamp Test

ED_{50} mg/kg s.c.	tramadol	morphine	codeine	dextro-propoxyphene
	22.7	7.41	40.3	24.0

NDA# 20-281

Table II/c
(V9/p00042)

PHENYLQUINONE-INDUCED WRITHING (PQW -mice)

COMPOUND	ED_{50} (mg/kg) s.c.	ED_{50} (mg/kg) p.o.	Ratio p.o. / s.c.
TRAMADOL	5.0	7.8	1.6[a]
MORPHINE	0.24	2.8	11.7
CODEINE	11.8	34.6	2.9
d-PROPOXYPHENE	4.1	-	-

[a] No significant difference between doses.

The potency of the racemic tramadol is in the range of other weak opiates and the stereo-selectivity of enantiomers of both parent and M1 metabolites are presented in the following table.

Table II/d (V1*/P0169,0171,0184) [V11/19dal:p0054+] (V21NDA/p128)
*9/30/93 submission

ANALGESIA IN MICE WITH TRAMADOL, METABOLITE AND ISOMERS

COMPOUND	ED_{50} (mg/kg) Tail-flick po	ED_{50} (mg/kg) Tail-flick iv	ED_{50} (mg/kg) PQW-writhing po
TRAMADOL (±)	31.2	-	3.69
TRAMADOL (+)	12.0	-	3.90
TRAMADOL (-)	106.0	-	5.00
M1-METABOLITE (±)	5.43	1.94	2.59
M1-METABOLITE (+)	3.75	1.41	1.87
M1-METABOLITE (-)	103.0	27.8	5.83

This table demonstrates that the M1(+) isomer is the more active in vivo than both the parent compound and the M1(-) metabolite. This differentiation is prominent in the tail-flick assay and reflects the rank-order in vitro binding data for the tramadol isomers and the M1 isomer in μ binding (Table I/a). This rank-order correlation also holds true for the M1 isomers in the PQW assay However, the magnitude of in vitro potency difference is not seen in the PQW-induced writhing assay.

The tail-flick analgesic test was done in rats after intrathecal administration of tramadol(±), tramadol(+) and tramadol(-) (V21NDA/p173-236). The analgesia measured was below 50% at all doses and there was little differentiation between enantiomers and the racemate. No significant formation of the M1 metabolite was found. This experiment did not show the differences between isomers but the relevance to oral administration is not clear, for there is more than an order of magnitude difference in the latter situation.

The sponsor makes the point that the tail-flick analgesia is reversed by naloxone for both morphine and tramadol, but not the analgesia in PQW-induced writhing when produced by tramadol (V1/19:p0168-171[9/30/93]). This naloxone resistant analgesia is also seen in the tail-flick analgesia at early time points. i.e. 20 minutes post administration versus 40 minutes (V1/19:0190) or 30 versus 60 minutes (V21NDA/p125).

The sponsor presents the PQW naloxone resistance as an example of non-narcotic analgesia. However, the time-dependency of naloxone-resistant analgesia in the tail-flick assay invites an examination of the time-course in other analgesic tests. Although the data does not seem to exist for naloxone challenges at extended times after tramadol administration and therfore the question remains open: is the resistance of tramadol analgesia to naloxone challenge time-dependent or test dependent or both?

The agonist action of tramadol at the opiate receptor has been well documented in the analgesic tests and in the naloxone sensitivity. However, the inability of tramadol to completely replace morphine in some narcotic withdrawal tests provided some question of possible antagonistic effects at the opiate receptor (V9/19:p00094).

The ability of naloxone to antagonize the analgesic effects of morphine, tramadol and its M1 metabolite were examined. As presented in Table IIe, the slopes of the curves are presented, as progressive doses of naloxone shift the dose-response curves in the Shild-Plot analysis.

Table II/e (V11/00033)

Schild Plot Analysis of Naloxone Shift in Tail-Flick Analgesia

COMPOUND	Slope	pA_2 value of naloxone
TRAMADOL	-0.86 ± 0.17[a]	7.76 ± 0.10[b]
O-desmethyltramadol	-0.81 ± 0.28[a]	7.79 ± 0.19[b]
MORPHINE	-1.09 ± 0.18[a]	7.94 ± 0.16[b]

[a] not statistically different from 1

[b] not statistically different from each other

This data analysis indicates the three compounds are reacting at the same receptor and no mixed agonist-antagonist properties are evident.

This indication that tramadol has no opioid antagonist properties was supported when tramadol at 30, 60 and 90 mg/kg was administered to morphine-dependent mice and no withdrawal jumping was observed (V9/18:p00084).

III. TOLERANCE (Tachyphylaxis)

Tolerance to the analgesic effects is a characteristic of opiates and tramadol studies have generally shown less tolerance development than other narcotic analgesics, although the following table suggests that tramadol may produce more tolerance than dextropropoxyphene.

At the doses of 20 mg/kg/day of tramadol and 9.5 mg/kg/day of d-

propoxyphene, the tolerance appears to develop for both compounds. However, the tramadol ED_{50} changes by a factor of 3X and d-propoxyphene by a factor of 2X.

Table III/a:
(V24NDA/p082 p047)

Analgesia ED_{50} Changes with Repeated Subcutaneous Administration in Mice [a]

Compound s.c. inj.	control	1st week	2nd week	3rd week	4th week
Tramadol	11.0	10.5	21.0	27.0	34.0
d-propoxyphene	6.8	9.0	9.9	11.0	14.0

[a]Dose: tramadol= 20 mg/kg/day, propoxyphene = 9.5 mg/kg/day, both injected during 5 day weeks; route = s.c. in ♀ NMRI mice. Analgesic test = electrical stimulation

This contrasts to the study presented in the following table when the dose of tramadol was doubled. The route of administration was oral and the analgesia test was reaction to radiant heat.

Table III/b:
(V9/19:p00140)

Analgesia Changes with Repeated Administration in Female Mice[a]

Compound	Acute ED_{50} po	1st week $ED_{50\ po}$	2nd week $ED_{50\ po}$	3rd week $ED_{50\ po}$
Tramadol	17.4 mg/kg	19.6 mg/kg	20.1 mg/kg	21.8 mg/kg

[a] 20 mg/kg po X 2 / day chronic dosing: tail-flick analgesia

In this study, no significant tolerance developed; however, there were no standards included for comparative effects.

IV. WITHDRAWAL - DEPENDANCE - SUBSTITUTION

One measure of dependance is the jumping response in mice after naloxone induced withdrawal. After two days of progressive dosing of morphine, tramadol or pentazocine, mice were injected with naloxone and the number of jumping response were counted during the following 10 minutes. The results indicated that naloxone induced withdrawal jumping after tramadol only after higher doses than either morphine or pentazocine. However, the intensity of the jumping (severity of withdrawal?) was least in the pentazocine group. Tramadol treated mice, at all doses, 12.5 to 100 mg/kg, had fewer number of jumps than morphine except at the 6 mg/kg dose. Again, tramadol was shown to be different from the strong narcotic, but not the weak opioid.

Table IV/a
(V 09/19:p00075)(V15NDA/p063)

NALOXONE INDUCED JUMPING IN DEPENDENT MICE

dose (mg/kg)	MORPHINE		TRAMADOL		PENTAZOCINE	
	PERCENT >10 JUMPS	MEAN # JUMPS > 10[a]	PERCENT >10 JUMPS	MEAN # JUMPS >10[a]	PERCENT >10 JUMPS	MEAN # JUMPS >10[a]
100	90.5	47.1	42.7	34.8	-	-
50	84.0	52.6	51.3	33.1	31.4	23.1
25	70.0	53.1	18.0	21.5	16.0	26.0
12.5	76.0	43.1	16.0	25.3	24.0	21.8
6.0	42.0	28.5	0	0	16.0	19.5
3.0	0	0	-	-	4.0	15.0

[a] mean number of jumps of the mice which jumped at least 10x in 10 minutes.

Another measure of withdrawal severity has been the loss of body weight after abstinence or antagonist precipitated withdrawal.

The loss of body weight has usually been found to be less after chronic tramadol than after morphine and the substitution of tramadol during morphine withdrawal has been reported to reduce, but not prevent, the loss of body weight in dependent rats (V09/19:p00084+).

In another experiment, rats had been treated with morphine, 100 mg/kg/24hrs, or tramadol, 120 mg/kg/24 hrs for 62 days (four divided doses/day). When tramadol, 60 and 120 mg/kg/day, was substituted for morphine, the weight loss in the morphine group was equivalent to spontaneous withdrawal. However, if morphine, 20 and 40 mg/kg/day, was substituted for tramadol, the rats gained a slight amount of weight (V9/19:p00115+).

However, tramadol has a much weaker effect than either codeine or morphine in preventing prostaglandin-induced diarrhoea, 1/4 and 1/17th, respectively. This suggests that tramadol, by having less intrinsic effect on the intestinal tract, may also produce less weight loss upon withdrawal due the relative lack of diarrhoea (V09/19:p00279).

Table IV/b
(V09/19:p00277)

INHIBITION OF PROSTAGLANDIN INDUCED DIARRHOEA IN MICE

COMPOUND	Antidiarrheal Effect ED_{50} (mg/kg) s.c.
TRAMADOL	49.8
MORPHINE	2.9
CODEINE	12.3

The low intrinsic activity of tramadol on intestinal motility may also be the reason it has little ability to reverse the weight loss in morphine dependent rats when withdrawal has been precipitated by naloxone administration (V9/19:p094).

In addicted monkeys, no administration of tramadol was able to

suppress the morphine withdrawal symptoms. This also indicates that tramadol is not equivalent to morphine but there is no comparative data for codeine or dextropropoxyphene and therefore no evidence that tramadol is in any other drug class.

Table IV/c (V24NDA/p92) (NIH study 1967?)

Suppression of Withdrawal Symptoms in Morphine Dependant Monkeys[a]

Tramadol (mg/kg)[b]	Number of Monkeys	Effects
2	2	no suppression
4	2	no suppression
8	2	slight suppression
16	2	no suppression
32	2	no suppression
64	2	no suppression
128	2	convulsions
4/8/32[c]	6	no precipitated withdrawal

a. dependant @ 3 mg/kg/day morphine sulfate and withdrawn for 12-24 hours.
b. administered 12-24 hrs post morphine
c. attempt to precipitate in non-withdrawn monkeys

A rat study with formalin induced pain compared morphine at 1 mg/kg s.c. versus tramadol at 100 mg/kg p.o. and showed both compounds were antagonized by low doses of naloxone and the analgesic potency of tramadol was greatly reduced in rats tolerant to morphine (V13NDA/p166).

In a study in arthritic rats, no cross-tolerance was observed for tramadol when rats were made tolerant to morphine but buprenorphine and nalbuphine did show cross-tolerance (V13NDA/p175). In this model, naloxone only blocks about 50% of the analgesic effects of tramadol, but the naloxone effect on the other compounds was not presented.

V. SELF-ADMINISTRATION

In a rat study (V09/18:p00094)(V15NDA/p070) groups of rats were forced to drink water with various concentrations of either morphine or tramadol. Over a four week period, the ingestion of both compounds increased in the groups at the highest concentrations, 1 mg/ml morphine and 2 mg/ml tramadol. These rats lost weight when withdrawal was precipitated with naloxone or when a quinine solution was substituted for the opiate solution. Tramadol solution did not completely prevent the body weight loss in the morphine dependent group, however there was no information on the effects of morphine solution on the weight loss of tramadol dependent rats. The weight loss measure may be a reflection of the low intrinsic activity on GI musculature by tramadol as previously noted. The withdrawal symptoms of wet-dog shakes, jumping, teeth chattering, writhing and sensitivity to touch were observed in both morphine and tramadol treated rats after naloxone injection and no qualitative differences were observed between morphine and tramadol.

Tramadol was self administered by monkeys previously trained to self-administer the stimulant lefetamine and in two naive monkeys. The data are presented in the following table:

Table V/a
(V09/19:p123-130)(T.Yanagita Artzneim.-Forsch. 28:158-163(1978))

SELF-ADMINISTRATION IN MONKEYS
AVERAGE DAILY NUMBER OF INJECTIONS

MONKEY	Control saline	0.1 mg/kg/inj 4 to 6 weeks	1.0 mg/kg/inj 1st two weeks[a]	1.0 mg/kg/inj 2nd 3 weeks
naive #1	2.7	3.1	97.0	193.7
naive #2	1.9	3.1	48.1	129.9
experienced #1	10.7	11.5	39.9	51.4
experienced #2	12.7	2.3	188.9	DIED[b]

[a] 2 weeks after initiation of self-administration
[b] became emaciated; anorexia, nausea, vomiting and convulsions noted during first 2 weeks of administration: died in third week.

This monkey study indicated that tramadol could support self-administration and this was expanded when two monkeys were put on a self-administration program with a progressive ratio of lever presses to injection. This estimates the motivational power of tramadol reward and self-administration extinguished at ratios of 1:32 and 1:64. This was probably quite early however, there were no comparative compounds cited and the number of subjects was limited to two.

SUMMARY OF PRE-CLINICAL ABUSE POTENTIAL

The efficacy of tramadol as an analgesic is well supported in the animal studies. This has been shown for both tramadol and its M1 metabolite, O-desmethyltramadol. The potency of M1 exceeds the parent compound in analgesia, with a parallel increase in opioid binding. Tramadol efficacy is in the range of the weaker opiates, codeine and dextropropoxyphene.

Tolerance to tramadol appears to be much weaker than morphine but equal to propoxyphene. The withdrawal symptoms appear to be qualitatively similar to morphine but quantitatively similar to pentazocine. Tramadol does not substitute well for morphine although this has been judged in relation to weight loss and tramadol is an order of magnitude weaker than morphine in terms of gastrointestinal stimulation. Morphine can reverse weight loss upon tramadol withdrawal. There appears to be no narcotic antagonism by tramadol in rodents or monkeys, supporting its activity as a narcotic agonist without antagonist properties.

The claim of significant non-narcotic analgesic effects are rather weak and may depend upon the time interval between administration and testing. The amine uptake inhibition probably plays no significant role in tramadol analgesia.

Although the monkeys will not press a lever beyond a low number of repetitions for tramadol self-administration, this was with few subjects and no comparative compounds. Rodents will increase tramadol

intake and monkeys will self-administer tramadol into the toxic range.

Although tramadol has some unique properties, it appears to remain in the category of weak opiates like codeine, pentazocine and dextropropoxyphene.

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION OF TRAMADOL

Tramadol Absorption:

The oral absorption of tramadol has been examined in mice, rats and dogs and percents absorbed were 87%, 85% and 87%, respectively (V61NDA/p25,p262)(V64NDA/p047).

Tramadol Tissue Distribution:

The binding of the parent compound to plasma proteins is not a major factor and is species dependent. The extent ranges for 7.6% in the rabbit and 10.2% in the rat to 20.2% in humans (V60NDA/p002).

The tissue distribution of ^{14}C-tramadol was determined in rats (3 Wistar males) following the intravenous administration of a 20 mg/kg dose. The following table lists the results.

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Table ADME/1:
(V61NDA/p187)

TISSUE DISTRIBUTION

ORGAN	Rate of dissappearance $t_{1/2}$ (hr)	Ratio of tissue/serum	
		2 hr concentration	16 hr concentration
Liver	6	8.6	20.0
Kidney	3	7.6	4.7
Heart	3	1.6	1.0
Lung	3	6.1	2.9
Spleen	3	3.9	4.3
Brain	3	1.6	0.3
Serum	3	-	-

Tramadol Metabolism and Excretion:

Tramadol metabolism studies have identified 5 major metabolites, M1 through M5. The conjugates of M1, M4 and M5 also constitute major metabolites found in the urine. The studies of intrinsic activity in analgesia and at the opioid binding sites, in vitro, have been limited to the M1, an O-desmethyltramadol. This metabolite has opioid binding and analgesic activity, 10 to nearly 200 times the parent compound and with conjugate, constituted about 29% of the labeled compound in the mouse urine. Unidentified metabolites accounted for about 28% of the dose . In rats, the M1 and its conjugate accounted for 20% of the dose and another 20% was unidentified. Similar percentages were found in hamsters and dogs and in humans the M1, with conjugate, amounted to 12 to 26% in the two human subjects (V72NDA/p44). In rabbits and guinea pigs both M1 plus conjugate and fraction unknown increased. A synopsis of the metabolite content of the 0-72 hour urine of six animal species and man is presented in the following tables (V60NDA/p056)(V61NDA/p25-44:p45-68)(V61NDA/p263-284) (V62NDA/p1-26):

Table ADME/2:

Urine Metabolites as Percent Total Radioactivity

Oral Administration	mouse	hamster	rat	guinea pig
DOSE (mg/kg)	34	31	30	26
No. / group	3	5	5	7
Tramadol	1.1	1.3	0.9	1.4
M1	11.9	5.3	9.1	38.8
M2	10.3	1.3	16.9	0.6
M3	1.2	3.1	9.8	0.9
M4	1.5	2.3	1.7	2.0
M5	14.6	8.9	12.8	7.3
M1-conjugate	17.3	14.3	10.5	3.7
M4-conjugate	1.5	3.2	3.6	0.4
M5-conjugate	12.7	25.9	13.6	1.7
fraction unknown	28.1	34.3	20.2	43.0

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Table ADME/3:
(V19/19:p493-500 NDA refile) (V060/p056)

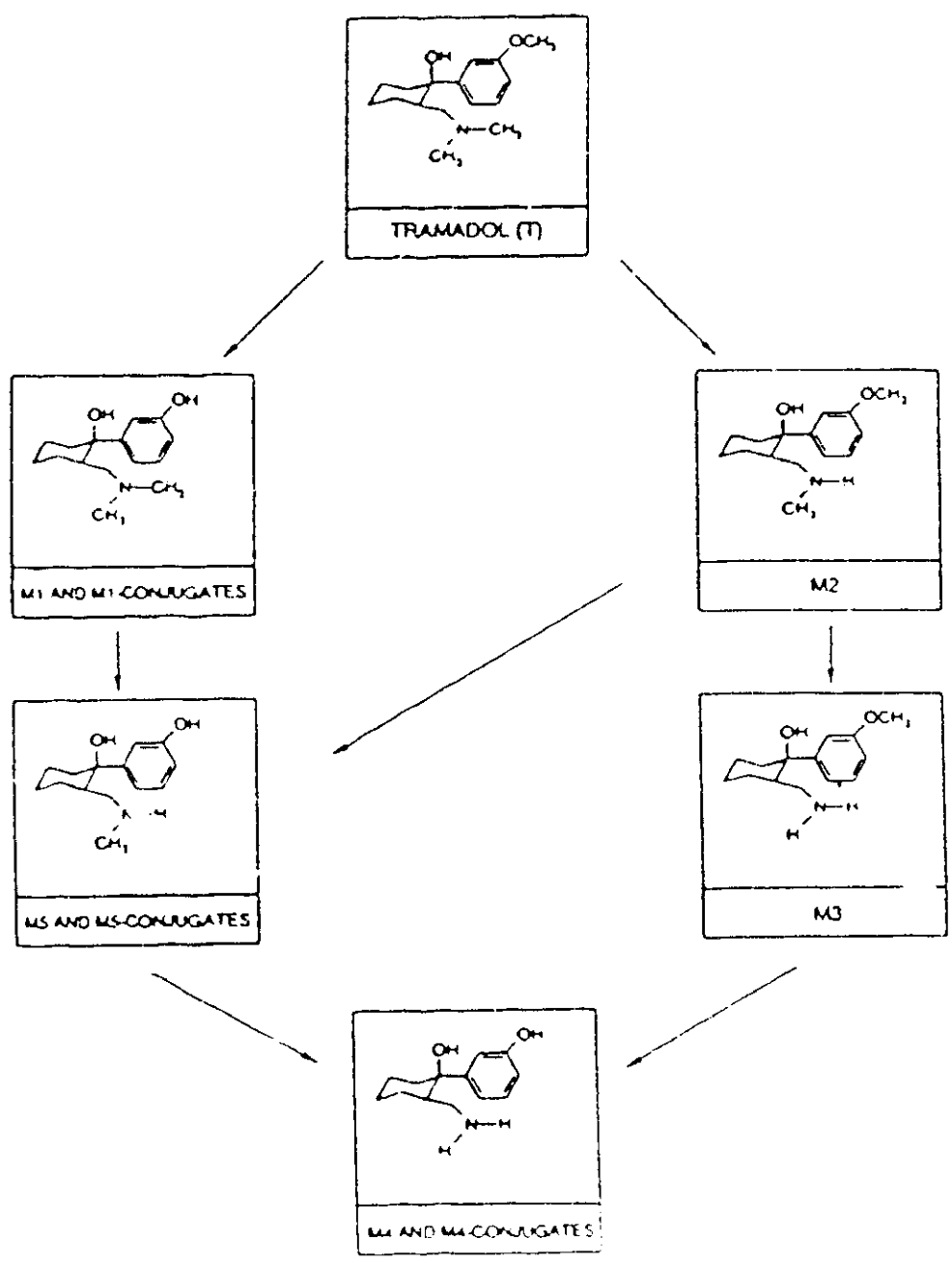
Urine Metabolites as Percent Total Radioactivity

	rabbit	dog	human	
			A1	A2
DOSE (mg/kg)	30	10.5	1.25	1.06
No. / group	3	3	1	1
Tramadol	1.3	1.0	25.1	31.7
M1	11.4	1.9	10.4	4.9
M2	0.9	5.4	2.4	31.4
M3	0.7	2.4		0.8
M4	2.4	3.6	0.1	0.8
M5	5.2	9.6	12.8	6.0
M1-conjugate	20.3	12.2	15.5	7.6
M4-conjugate	3.0	6.0	0.8	0.2
M5-conjugate	8.6	32.9	15.1	5.8
fraction unknown	46.2	25.1	17.8	10.7

The metabolism of tramadol is primarily by hepatic P_{450} microsomal enzymes. These were inhibited in mice by pretreatment with SKF 525-A and serum levels of tramadol increased and M1 levels decreased with an apparent decrease in analgesic potency (V21NDA/p140-170). At 10 minutes after administration of 21.5 mg/kg iv of tramadol, the serum level of tramadol was 3.2 μg /ml and analgesia was about 90%. After metabolic inhibition, the serum concentration at 90% analgesia was about 6 μg/ml, indicating a substantial role for the M1 metabolite in analgesia. The analgesic potency of M1 at 6.81 mg/kg iv at 10 minutes was comparable to the potency of tramadol at 21.5 mg/kg iv at 30 minutes. As stated by the sponsor, after oral administration, the role of unchanged tramadol is even less.

The sponsor examined hepatic enzyme induction and no substantial increases were observed after 28 days of 30 mg/kg/day in mice or 10 or 50 mg/kg/day for 10 days in rats (V61NDA/p1-16 + p225-236 + p240-262). In the dog, after one year of 24 or 40 mg/kg/day, tramadol induced a slight increase in hepatic P_{450}; 10 to 11% in males and 26 to 34% in females. This treatment also inhibited hepatic microsomal glucuronyltransferase, 25 to 55% (V63NDA/p1-22).

These values indicate that the M1 metabolite can have a significant role in the analgesic activity of tramadol. The metabolic pathways for tramadol are presented below (V13NDA/p372):



Tramadol Pharmacokinetics

The pharmacokinetics of tramadol in various species are briefly outlined in the following table.

Species No.	Dose rt	Compound	$T_{(max)}$ hrs	AUC_{0-24hr} ng.h /ml	$t_{1/2}$ hrs	NDA Vol/pg
Rat 3	30 i.v. (mg/kg)	tramadol	0.5	7279	2.9	61/100
		M1	0.5	1046	1.6	
		M1-conj	1.0	4183	4.7	
Dog 3	10 p.o. (mg/kg)	tramadol	1.7	323	2.1	63/023
		M1	1.3	427	1.7	
		M1-conj	2.7	5867	2.4	
Dog 3	10 i.v (mg/kg)	tramadol	0.3	2191	1.5	63/023
		M1	0.4	343	2.5	
		M1-conj	2.7	4192	2.6	
Human 2	100 mg oral	tramadol	2.0	265 C_{max}[a] AUC nd	9	72/124
		M1	4-6	37 C_{max}[a] AUC nd	14	72/188
		M1-conj	6-8	140 C_{max}[a] AUC nd	9	72/224

[a] C_{max} values
nd = not determined

Tramadol is a racemic mixture and both the parent enantiomers and the M1 metabolite isomers provide different potencies in a variety of assays as well as different profiles in pharmacokinetics. The following graphs depict the pharmacokinetics in mice and dogs (V1/1:3-30-94/p 4-5;v-vi).

Table PK/1:
Study DM-94301

Single Administration of Racemic Tramadol to NMRI Mice

Single dose po	tramadol male		tramadol female		M1 male		M1 female	
30mg/kg	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)
C_{MAX} (ng/ml)	78.2	39.6	80.5	25.3	85.4	147.4	112.1	158.5
T_{MAX} (hr)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
$t_{1/2}$ (hr)	2.2	2.8	3.5	nd	1.9	2.4	1.1	1.4
$AUC_{(0-10hr)}$	117.7	63.3	113.5	34.1	128.8	195.1	107.6	151.2

In the single administration experiment, the plasma concentrations of the active metabolite (M1) are equal to or greater than those observed for the parent tramadol. This is true for both C_{max} and AUC. The $t_{1/2}$ is somewhat longer for the parent nevertheless, a large portion of the analgesia is probably due to the M1 metabolite.

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Table PK/2: Study #: DM-94301

Pharmacokinetics after 14 Days Administration of Racemic Tramadol to Mice

Multiple oral dose 30 mg/kg /day x 14	tramadol male		tramadol female		M1 male		M1 female	
	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)
C_{MAX} (ng/ml)	147.4	69.2	184.8	80.5	155.0	311.5	94.2	187.1
T_{MAX} (hr)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
$t_{1/2}$ (hr)	1.6	1.9	1.7	2.3	2.4	2.4	0.9	1.5
$AUC_{(0-10hr)}$	238.7	190.9	161.9	66.4	272.8	465.1	106.8	174.6

Although not evident after a single administration, male mice have greater plasma concentrations of the enantiomers of both tramadol and the M1 metabolite after repeated administration.. This was in terms of both AUC's and C_{MAX}.

After repeated administration, the M1 metabolite of tramadol continues to equal or exceed the concentrations of the parent. The AUC values for all compounds increased with repeated administration and this increase was greater than two-fold for the males and less than two fold for the females.

Although the relative concentrations of M1 to parent are less in human studies, the M1 metabolite can still have an AUC as much as 1/3 the parent compound. The above data indicate that the M1 metabolite is a major contributor to tramadol activity.

In the rat, there is an apparent sex difference in the pharmacokinetics of tramadol:

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Table PK 3:(V19/19:p0541:11/01/93)

Single Administration of Racemic Tramadol to Wistar Rats

Single dose po	tramadol male		tramadol female		M1 male		M1 female	
30mg/kg	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)
C_{MAX} (ng/ml)	192	73	712	224	151	256	287	255
T_{MAX} (hr)	0.67	0.58	0.50	0.50	0.50	0.50	0.58	0.50
$t_{1/2}$ (hr)	3.04	5.76	3.90	4.24	4.23	5.24	4.77	6.24
$AUC_{(0-10hr)}$	519	153	2677	888	385	835	1512	608

The female rats have greater AUC values than the males both after single as well as multiple administrations. The trend is consistent in rats, dogs and in man.

Table PK 4:

Multiple Oral Administrations of Racemic Tramadol to Wistar Rats

dose 30 mg/kg /day	tramadol male		tramadol female		M1 male		M1 female	
x 14	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)
C_{MAX} (ng/ml)	343	158	906	596	121	206	166	149
T_{MAX} (hr)	0.50	0.50	0.50	0.50	0.50	0.50	1.08	0.58
$t_{1/2}$ (hr)	2.51	2.67	2.99	2.92	4.34	5.26	5.33	5.59
$AUC_{(0-10hr)}$	840	307	2942	1364	355	690	1089	671

In the dog the pharmacokinetics are different as there is an apparent sex difference and possible enzyme induction upon repeated administration (V1/1:p00052 doc.3-30-94).

Table PK/5:
Study#:DM-93379

Pharmacokinetic Parameters after Single or Multiple Oral Doses to Beagle Dogs

Tramadol racemate	Single dose - 20 mg/kg tramadol - racemate				14 X 20 mg/kg/day tramadol - racemate			
	male		female		male		female	
oral	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)
C_{MAX} (ng/ml)	431	428	632	681	160	161	268	321
T_{MAX} (hr)	0.75	0.75	0.88	0.88	0.75	0.75	0.88	0.88
$t_{1/2}$ (hr)	1.8	1.5	2.2	1.7	1.7	1.2	2.1	1.3
CL/F ml/min.kg	435	403	266	241	1821	1726	756	735
$AUC_{(0-10hr)}$	849	877	1451	1599	251	242	506	550

In the dog, the females had nearly twice the AUC's of the males for both optical isomers of tramadol. This was evident both with acute and with 14 days of administration. The greater clearance upon repeated administration was accentuated in the males as the ♂ / ♀ differences went from about 1.6 in acute to 2.4 upon repeated administration. These sex differences could not be quantified for the M1 metabolite as the levels of M1 were below assay limits at most time points in the males. The M1(-) levels in the females were also below assay limits at most time points and the M1(+) results are presented in the following table (V1/1:p00052 doc.3-30-94).

Table PK/6

Pharmacokinetics of M1(+) in Female Dogs

Tramadol 20 mg/kg oral	M1(+)	
	Single	Multiple
C_{max} ng/ml	56.2	18.1
T_{max} (hr)	1.0	0.88
$t_{1/2}$ (hr)	3.3	nd
AUC ng.hr/ml	191.9	76.2

The sponsor suggests the increased clearance with multiple dosing may be due to enzyme induction in the dog and this was observed after one year of dosing at 40 mg/kg day in chronic dog studies. However, only a maximum of 34% increase was observed in females and 11% in males.

This increased clearance was not observed in mice and the human data is similar to the mouse data where the AUC increases upon repeated dosing. In the rat, the AUC increase upon repeated dosing is evident with tramadol but not the M1 metabolite. The sex differences seen in the dog study are similar in the rat and human studies, as the females have higher AUC's and lower clearance than the males.

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GENERAL TOXICITY OF TRAMADOL

ACUTE TOXICITY

Table BI/a (V26NDA/p006)

LD_{50} VALUES (mg/kg)

Species	oral	s.c.	i.v.	i.m.	i.p.	rectal
Mouse	328-785	197-265	47-68	179-184	178-200	-
Rat	151-572	240-293	56	-	-	540-662
Rabbit	300-450	-	20 - 40	100-150	-	160
Guinea pig	850-897	23-250	-	-	-	-
Dog	100-450	-	>50<100	>50<100	-	-

Signs of toxicity of tramadol in ♂ mice: sedation in low doses followed by hypermotility, straub tail, slight tremor, exopthalmus, clonic convulsions, cyanosis.

Interactions in male mice:

COMPOUND	DOSE (mg/kg) i.p.	Tramadol LD_{50} (mg/kg, i.p.)
NONE	---	166
naloxone	30	157
phenobarbital	50	193[a]
diazepam	20	163[a]
haloperidol	5	166[b]
chlorpromazine	20	134[a]
imipramine	20	167
tranylcypromine	10	91 [b]
amphetamine	2	183
physostigmine	0.2	171
atropine	2	171

[a] convulsions decreased [b] convulsions increased

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The acute and sub-chronic toxicology studies have been extensively reviewed in the original IND of 11/28/85 (2/13/86). The synopsis of the acute toxicity is presented above and the following sub-chronic studies are essentially only new investigations.

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SUB-CHRONIC TOXICITY

STUDY: TWO-WEEK ORAL NEUROTOXICITY OF TRAMADOL HCl IN RATS

REPORT #: DS-93308 (Letter date 2/9/94 - doc. N(BP))

COMPOUND & LOT: RWJ-26898-002: tramadol monohydrochloride
Grunenthal/01 5651

FORMULATION:

ROUTE(S): oral by gavage

DOSE(S): 8, 20 and 40 mg/kg/day of tramadol HCl. [mazindol 0.3 mg/kg po or fenfluramine in saline s.c at 10 mg/kg/day]. Dosing was daily for 14 to 17 days.

STRAIN: Rat/Crl:CD BR, VAF/Plus

NUMBER/SEX/DOSE: 5♂ + 5♀ / dose : ♂ 219-263 g, ♀ 136-205 g at start of dosing.

STUDY SITE: R.W. Johnson Pharmaceutical Research Institute

DATE: June 14, 1993 to July 1, 1993.

PROCEDURE: Assignment to dosing groups was done using computer generated random selection by body weight. The rats were dosed daily for two-weeks. Clinical observations were made prior to daily dosing

and body weights were recorded prior to dosing on Days 1, 8 and 15 during dosing. Food consumption was recorded pre-dosing Day 0, 7 and 14 during the dosing period.

After termination of the study, the rats were sacrificed, perfused with 10% neutral buffered formalin, and the brain and spinal cord dissected and placed in fixative. A coronal section of one frontal lobe was removed and placed in 5% glutaraldehyde. All tissues were kept cold and shipped to Virginia Tech Laboratory for Neurotoxicity Studies (LNS). At LNS, the tissues were coronally sectioned: the cerebral hemispheres at three levels, the mid-brain and adjacent pons at two levels and three levels of the spinal cord. The tissues were imbedded in paraffin, sectioned and stained by hematoxylin and eosin (general tissue stain), Luxol fast blue-periodic Schiff-hematoxylin (for myelin and astrocytes, Holmes' silver (for neuritic processes) or the glial fibrillary acid protein (GAFP - for astrocytes) immunohistochemical procedure.

Smaller sections of frontal cortex, caudate-putamen, parietal cortex and midbrain were dissected, embedded in epoxy resin, sectioned at 1 μm and stained with a combination of toluidine blue and safranin.

The slides were examined non-blinded and qualitatively using a light-microscope. When appropriate, a semi-quantitative 0-3 evaluation was done, reflecting normal, minimal and moderate to severe changes respectively.

The epoxy-resin sections were evaluated for presence and extent of the following specific changes: "dark" neurons, densely-stained bodies in and adjacent to neuronal cell bodies, perivascular neuropil pale staining (parlor), degenerating nerve fibers and quality of perfusion.

RESULTS:

Clinical observations: No animals died during the study and the appearance of scabs at the sites of s.c. injection in the fenfluramine group were the only drug related observations reported.

Body weights and food consumption: Mean body weight gains were significantly reduced only in the fenfluramine group of males on days 8 and 15. The food consumption was significantly reduced the

fenfluramine group; ♂ and ♀ on day 7 and ♂ on day 14. Food consumption was also reduced in tramadol ♀ 's receiving 40 mg/kg /day on day 7.

Neurotoxicity:

No statistically significant changes were observed in numbers of "Dark" neurons or degenerating myelinated fibers.

The only statistically significant difference found between treatment groups in the parameter of Neuronal Dense Bodies was in the caudate-putamen. In this measure, the females in the tramadol 40 mg/kg/day and the mazindol female groups had significantly more dense bodies than the saline control females in the area of the caudate-putamen. The respective means were 5.0, 4.1 and 2.2 for the controls. However, there were no significant increases in the males in any brain region or changes in other areas in the females. The sponsor cited literature studies which had reported these bodies are determinants of lysosomes and degenerating axon terminals in the cerebral cortex after fenfluramine treatment. The data was "not considered to represent real change".

The perivascular staining pallor was significantly less in the saline controls than mazindol or fenfluramine only in the frontal cortex. However, there were no scores greater than 1, the "abnormal" threshold and the results were considered invalid. No changes in cerebral cortical astrocytes or the occurrence of incidental lesions were considered compound related.

CONCLUSIONS:

The twelve tables of data provided indicate that no extensive neuronal toxicity was produced by any compound and the data variablity indicates that larger sample sizes would be needed to uncover limited neurotoxicity.

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NDA# 20-281

CHRONIC TOXICITY

STUDY: CHRONIC TOXICITY OF TRAMADOL HCl IN RATS - 18 MONTH

STUDY SITE:

REPORT #: 500,362; 500,371; Accession No. 500,618
(V030/239:p001) (V031/239:p331)

DATE: 2/27/84 - 9/5/85

GLP STATEMENT: In spirit of GLP's but without QA inspections during in-life phase. Toxicology and Pathology reports were audited by testing facilities QA unit.

COMPOUND & LOT: tramadol HCl. batches 143, 148. The stability of tramadol in the drinking water was done retrospectively by analysis of respective concentrations after 7 days of storage at room temperature.

ROUTE(S): oral

DOSE(S): 7.5, 15, 30 mg/kg in the drinking water.

SPECIES/STRAIN: Wistar rats, 30-35 days old, 83g ♂, 78g ♀ at initiation.

NUMBER/SEX/DOSE: 20 ♂ + 20 ♀ / dose

PROCEDURE:
Housed 2/cage for initial 4 week and subsequently individually housed for duration of study. Stock solution of tramadol HCl and the drinking-water solutions were prepared twice weekly.
Animals were observed daily, body weights and food consumption recorded weekly and water consumption was checked 3-4 times per week until week four, weekly until week 61 and biweekly for the duration of the study.

RESULTS:

Mortality:

TRAMADOL EFFECTS ON SURVIVAL AT 18 MONTHS
(initial = 20/sex/group)

Dose (mg/kg/day)	0	7.5	15	30
males	16	19	18	19
females	20	20	18	18

No significant effects on survival were observed.

Body Weight:

BODY WEIGHTS AT WEEK 79
(grams/percent change from control)

Dose (mg/kg/day)	0	7.5	15	30
Males	529	479 -9.5%	481 -9.1%	480 -9.3%
Females	323	290 -10.2%	278* -13.9%	280* -13.3%

* $p<0.01$

The tramadol treated animals were lighter than controls, but no dose-response was evident.

Food and Water Consumption:

FOOD AND WATER CONSUMPTION - WEEK 78

Dose (mg/kg/day)		0	7.5	15	30
Male	food g	4.5	5.2*	5.5*	5.1*
	water ml	28.4	29.6	33.0	28.9
Female	food g	6.2	6.2	6.8	7.1*

	water ml	39.0	31.4	34.2	36.0

* P<0.01

The food and water consumption was slightly greater in the trmadol treated animals than in the control group.

Clinical Signs:

The only clinical sign which appeared increased in the treatment groups was trichophagia, mostly in the ♀s and this increase in hair biting is of limited biological significance. Palpation of tissue masses did not differ between treatment groups.

No treatment related effects were observed in the ophthamologic examinations at 12 or 18 months and the hearing test was also negative.

Clinical Chemistry:

Hematology:

No substance related differences were observed.

Fecal blood:

No treatment or dose-related differences were observed.

Urinalysis:

The examination of volume, specific gravity blood and biliruben did not show any significant changes related to either treatment or dose, although there were sporadic differences occuring in the 3, 6, 12 and 18 month measurements.

Organ Weights: (V19/19:p45,46)

Absolute organ weights were similar to control in both ♂ and ♀ treatment groups and statistical significance was sporadic and no dose-response relationship was evident. The relative organ weights were often higher than control, reflecting the dose-related body weight loss.

Histopathology:

No treatment related neoplastic or non-neoplastic changes were observed. The number of tumor-bearing ♂ was 7, 9, 12 and 1 in control, low, medium and high doses and in the ♀ groups the corresponding numbers were 4, 3, 3, and 8.

DISCUSSION:

Except for body weight loss and increased food and water consumption, no treatment dose-related effects were observed.

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STUDY: **FIFTY-TWO WEEK ORAL TOXICITY OF TRAMADOL HYDROCHLORIDE IN BEAGLE DOGS**

REPORT #: DS-90323 Access #500,046 (V036/p001)

COMPOUND & LOT: Tramadol HCl ?

FORMULATION:

ROUTE(S): oral, twice daily, five hours between daily dosings.

DOSE(S): 0, 10, 24 and 40 mg/kg/day

STRAIN: beagle dog, approximatly 11 months of age and body weights were: males = 10.4 -13.6 kg, female = 6.6 - 10.4 kg at start of testing. Supplier, Marshall Research Animals, NY.

NUMBER/SEX/DOSE: 4♂ and 4♀ per treatment group

STUDY SITE: McNeil Pharmaceuticals, Spring House PA

GLP STATEMENT; Conducted in compliance with GLP guidlines (V036\p030).

DATE: June 1987 to July 1988

PROCEDURE: The dogs were acclimatized to the oral dosing during week -1 and randomized into treatment groups based on body weights. The animals were individually housed and fed a certified Canine Diet #5007 after the morning dosing.

RESULTS:

Clinical Signs:
The only treatment related clinical sign was mydriasis and was considered an extention of the pharmacological action of the drug. The pupillary response to light was evaluated during weeks 2, 6 and 11. Other signs, such as emesis, diarrhea and salivation were not dose related and occured in controls to an equal extent.

Mortality:
All animals survived except one mid-dose ♂ was sacrificed, week 37, due to recurring urinary obstruction due to a large bladder stone. This was not considered treatment related.

Body Weight:
In the ♂, the body weight gain was 20% in the controls and only 7% in the high dose group, but not a statistically significant difference. In the ♀ dogs, all treatment groups gained less than controls and were significantly lighter, approximately 15%, during most of the last ten weeks of testing.

Food Consumption:
The food consuption was slightly lower than controls among high dose ♂ and mid and high dose ♀. The differences were occasionally statistically significant.

Morphological Examinations: No treatment related changes.

Ophthalmoscopic examinations: No treatment related changes.

Electrocardiographic Examinations (week 52): No treatment related changes.

Organ weights: Several significant increases in relative liver and heart weights were found in treated dogs but this was probably a reflection of the lower body weights. The brain weights in the high

dose ♂'s versus the controls was statistically significant, as was the relative brain weight. The sponsor attributes this to controls with lower than normal brain weights and high dose ♂ with higher than normal.

Hematology: No treatment related changes according to the sponsor. However, WBCS were elevated above control at last two testings (weeks 40 and 53) for all treatmet groups and statistically significant for the high dose group (combined ♂♀) at both time intervals. However, the results were not replicated in other parameters and probably of limited biological significance or may be related to the observation of minimal foci of chronic interstitial pnemonia seen in one control dog and four high-dose dogs (V026/p027).

Clinical Chemistry: No treatment related changes.

Histopathology: No treatment related changes except for the occurrence of minimal interstitial pnemonia in one control an four high dose dogs.

DISCUSSION:
No treatment related effects were observed except for slightly reduced weight gain and food intake in the ♀'s of all treatment groups.

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STUDY: CHRONIC TOXICITY OF TRAMADOL HCl IN BEAGLE DOGS - 12 MONTH - EFFECTS ON HEPATIC MICROSOMAL ENZYMES

STUDY SITE: R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

REPORT #: Accession No. 500,587 (V063/239:p001)
DATE: - December 19, 1991

COMPOUND & LOT: tramadol HCl. batches

ROUTE(S): oral

NDA# 20-281

DOSE(S): 0, 10, 24 and 40 mg/kg/day by two divided daily doses.

STRAIN: Beagle Dogs

NUMBER/SEX/DOSE: 3♂ and 3♀ / dose

PROCEDURE: At necropsy of dogs from 1 year chronic study, DS-90323 portions of the livers were excised and frozen. Subsequently, the hepatic microsomes were prepared and the following indicatiors of microsomal drug metabolism activity were determined: protein content, P450 content, 7-ethoxycoumarin O-deethylase (ECOD) activity, ethoxyresorufin O-deethylase (EROD) activity and acetaminophen glucuronlytransferase (AGT) activity.

RESULTS:

Hepatic Drug Metabolizm Enzymatic Activity
After 52 Weeks of Tramadol Treatment
Expressed as Mean Percent of Control Values

Sex	Dose[a]	Protein	P450	ECOD	EROD	AGT
M	10	89	104	183	110	104
M	24[b]	106	111	146	89	75
M	40	99	110	225	142	59
F	10	106	107	133	118	107
F	24	109	134	145	119	55
F	40	102	126	180	113	45

[a] Dose in mg/kg/day (N=4) [b] n=3

DISCUSSION:
Tramadol can be considered a mild inducer of hepatic microsomal P450 isozymes and a mild inhibitor of AGT. The differences from control were small but statistically significant.

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The original review, IND (2/12/86), included chronic toxicity in dogs:

1. #540041; Beagle dogs; 26 weeks, 8 animals per dose, oral dosing @ 0, 10, 25 and 60 mg/kg/day by capsule. Study was done by , May to October 1979.

2. One year, oral dosing in @ 0, 10, 30 and 60 mg/kg: 2♂ and 2♀/dose group. Study was done by Upjohn Laboratories, February 1968 to February 1969.

No changes in clinical chemistry, urinalysis, ophthalmologic measurements, hematology, EKGs or pulse rates were significantly drug related. No histopathological findings were noted.

The clinical symptoms of vomiting were noted in the high dose groups in both studies and convulsions were noted in the high dose group in the Grunenthal study (5/8) and 1/8 at 25 mg/kg/day but unlisted in the study by Upjohn.

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__Summary of Chronic and Subchronic Canine Studies__

The effects of oral tramadol has been studied in dogs at doses from 10 tc 60 mg/kg/day for durations from 26 to 52 week and at three ...aceutical companies. The only observed drug related changes were ...ly reduced body weignt gain and food intake (principly in ♀) ... adic convulsions from 25 through 60 mg/kg. The lack of ...ical, chemical and histopathological changes have indicated ...madol HCl is generally non-toxic to dogs upon chronic and sub... nic administration.

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NDA# 20-281

REPRODUCTIVE EFFECTS OF TRAMADOL

There were eight experiments of tramadol effects on the reproductive parameters reviewed in the original IND . . 2/12/86.

Segment I Studies (3):

Sprague-Dawley ♀ rats; 0, 25, 50 and 75 mg/kg by oral gavage; 14 days prior to mating through day 14 of pregnancy. Dose related reduction in corpus lutea formation (-20% at 75 mg/kg/day). No effect on implantation, fetal growth or fetal death.

Wistar rats (may be S-D); 0, 25, 50 and 75 mg/kg by oral gavage; 14 days prior to mating through day 14 of pregnancy. No effect on fertility, fetal growth or fetal deaths.

Sprague-Dawley ♂ rats; 0, 10 and 50 mg/kg by oral gavage; 60 days prior to mating through mating period. In the first week post-partum there was an increased mortality in both treatment groups. However, this was principally due to losses of total litters in these groups which may have been due to a failure of the dams to nurse. The number pregnant per number mated, the pregnancy duration, number of live fetuses, still births, pup weight gain and fetal malformations did not differ from control.

Segment II (Teratology studies) (4):

Sprague-Dawley rats; 0, 10, 50 mg/kg in food and 10 mg/kg s.c. injection; daily, day 8 through 14 of pregnancy. Unacceptable report due to lack of detail. This report is from an Upjohn report #147, February 1969 and submitted in the NDA (V058/p189). The details are still lacking and the report unacceptable.

Sprague-Dawley rats; 0, 25, 50 and 75 mg/kg p.o., daily day 7 to day 17 of gestation. No biologically significant differences were observed in the number of implantations, post-implantation losses or 21 day survival curves. Also no skeletal or major visceral abnormalities were treatment related or still-births or differences in

male/female ratios. Tramadol may have increased the percentage with ureter dilation and there was a decrease in aural openings in the pups reared by high dose dams.

Rabbits; New Zealand Whites and mixed breeds: 0, 10, 50 and 100 mg/kg in food and then by gavage, days 8 through 14 of gestation. Insufficient data and study was unacceptable.

Rabbit; Russian; 0, 25, 50 and 75 mg/kg po; days 7 to 19 of gestation. A decrease in food consumption and weight gain was observed in the high dose group and the ossification of the skull bones was delayed in the pups of this group. No malformations or fetal weight differences were observed. A statistically significant increase in fetal mortality was only found in the 50 mg/kg group and did not appear dose-related.

Segment III -Peri- and Post-natal development (1):

Rats, Wistar; 0, 10, 25, 50 mg/kg, po by gavage; day 16 of pregnancy through day 21 post-partum. A reduced weight gain was observed in the high dose group but there was no significant differences in litter size, live births or malformations. The number of dead fetuses was significantly increased in both 25 and 50 mg/kg groups, but the 25 mg/kg group was attributable to the loss of one complete litter. The weight gain in the pups was slightly less in the high dose group on day 4, but there was no significant differences in post-natal development or sex ratios across groups.

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SEGMENT I:

STUDY: Toxicity of Tramadol for Reproduction. Influence of Male and Female Fertility. Development and Reproductive Performance of Untreated F1-Generation.

REPORT #: FO-TE 308/A; 500,481 500,601. (V053/001-319)

NDA# 20-281

GLP STATEMENT: Conducted in the spirit of GLP, except for in-life QAU inspections.

DATE: July 1984 to May 1985

STUDY SITE:

COMPOUND & LOT: tramadol HCl, CG-315, ID# F13019; batches 137, 142.

FORMULATION: distilled water

ROUTE(S): Oral gavage, daily

DOSE(S): 0, 10, 25 and 50 mg/kg/day

STRAIN: Sprague-Dawley

NUMBER/SEX/DOSE: 30♂ + 30♀ /dose

PROCEDURE:

F0 ♂; dosed 85 to 92 days prior to mating and through mating.

F0 ♀; dosed 14 days prior to mating to 20 days post mating or delivery on day 22 post mating.

NDA# 20-281

RESULTS:

Conditions	F0 generation	F1 generation
Mortality	no effect	
Body weight	50 mg/kg = dec ♂+♀	No effect of F0 treatment
Food consumption	50 mg/kg = dec ♂+♀	not determined
Clinical Signs	no effect F0	-
Copulation rates	no effect	no effect
Fertility rates	no effect	no effect[a]
vaginal smears	no effect	-
gestation length	no effect	no effect
necropsy findings	no macroscopic find	no macroscopic find
testes weight	50 mg/kg relative ↑	no effect
reproductive changes	No dif. live or resorptions	no effect

[a] Slight reduction in fertility based on number pregnant in 50 mg/kg in F1 generation but not considered drug related due to high rate in controls (100%)(= Sponsors statement). However, dose related decreases in the fertility index were seen; 0%, -6.7%, -13.3%, and -26.7% for control, 10, 25 and 50 mg/kg, respectively (V053/313). However, the sponsor stated that there was no effect on fertility in the F1 generation (V053/p209).

There was a lack of pinna twitch reflex in 6/95 F2 pups of the 50 mg/kg group on the first examination, versus 0/139 in controls. At test 3-4, at the end of the testing, 4/95 had feeble pinna reflexes and 1 still had none. The 10 and 25 mg/kg doses were 0/73 and 0/89, respectively. (V053/p288)

The weight gain of F2 males was reduced significantly in the 50 mg/kg group (V053/p292) and only occasionally significant for the F2 females.

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NDA# 20-281

SEGMENT II - Teratogenicity / Developmental toxicity

STUDY: Teratogenicity Study In New Zealand White Rabbits

REPORT #: DS-90325 Acc.#500,624 (V055/239:p1-393)

STUDY SITE: R.W. Johnson Pharmaceutical Research Institute, Spring House, PA.

DATE: 12/10/90 Animals arrived for 11 week quarantine prior to study: dosing 3/4/91 - 3/26/91

GLP STATEMENT: The study was done under GLP regulations (V055/p393).

COMPOUND & LOT: tramadol HCl, batch B3989A

FORMULATION: tramadol HCl in 1% hydroxypropylmethylcellulose

ROUTE(S): oral gavage, once per day from day 7-19 of gestation

DOSE(S): 0, 10, 50, 125 and 175 mg/kg/day

NUMBER/SEX/DOSE: 18 impregnated females/dose group

PROCEDURE: The ♀ rabbits were artificially inseminated and treated daily with tramadol or vehicle from day 7 to 19 of gestation. The females were euthanized on day 29 of presumed gestation the ovaries, uteri and fetuses were examined.

RESULTS:

MATERNAL;
Mortality: One animal died shortly after insemination in the 10 mg/kg/day group, undetermined causes. One ♀ in the 50 and one in the 175 mg/kg/day group died from intubation injuries, one form the 125 mg/kg/day group was sacrificed after breaking a leg. The only drug related death was one in the 175 mg/kg/day group which died during convulsions after drug administration.

Clinical Observations: Increased incidences of rapid breathing, decreased urine and feces, and prostration were observed in 125 and 175 mg/kg/day groups.

Body Weights: Body weight gains were significantly decreased in the 125 and 175 mg/kg/day groups, both during treatment (gestation days 7-20) and at termination (days 7-29). The 10 and 50 mg/kg/day groups tended to have reduced weight gain compared to control but these differences were not significant.

Food Consumption: The food consumption was significantly reduced in the two high dose groups (125 and 175 mg/kg/day), both throughout the treatment period and from day 7 through day 29.

Necropsy findings: No significant differences were observed between treatment groups and controls.

REPRODUCTIVE PARAMETERS:

Dose (mg/kg)	0	10	50	125	175
No. pregnant	18	18[a]	18	18	18
No. aborted	0	0	0	0	1[b]
No. deaths[a]	0	1	1	1	2
No. total reabsorption	1	1	0	0	0
No. litters	17	16	17	17	15[c]
Mean # corpus lutea	11.0	9.6	9.1	10.1	9.4
Mean # implantations	8.0	8.6	7.2	7.2	6.6
% preimplantation loss	27.8	9.7*	19.7	28.2	28.2
Mean # total live fetuses	7.4	8.1	7.2	6.7	6.1
dead	0.1	0.0	0.0	0.0	0.0
% postimplantation loss	7.3	5.5	0.8	6.4	8.1
mean fetal body weights	46.6	45.1	45.0	42.8	41.8*

[a] deaths enumerated previously

[b] aborted on days 25 and 27 of gestation

[c] one of these dams received an extra dose and was subsequently removed - No. =14

* significantly less than control ($p<0.05$)

The above table indicates that tramadol had limited adverse effects on reproduction until toxicity to the dams was observed. The fetal body weights were significantly less in the high dose by 10.3%. However, there were very limited fetal malformations/alterations which appeared to be drug related in either skeletal, soft tissue or external observations. The only statistically significant observations in the treated groups, besides lower body weight, were increased numbers of full supernumerary ribs in the two high dose groups and an increase in rudimentary supernumerary ribs in the low dose group.

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STUDY: STUDIES ON TERATOGENESIS ON CG-315 (IN MICE, RATS)

REPORT

STUDY SITE: - Not stated, but mice and rats from Japan CLEA Co.

DATE: Not Stated

COMPOUND & LOT: Not Stated

FORMULATION:

ROUTE(S): oral and subcutaneous injection

DOSE(S): mice: 10, 120 mg/kg/day s.c. and 10, 140 mg/kg/day p.o.
rats: 10, 60 mg/kg/day s.c. and 10, 80 mg/kg/day p.o.

STRAIN: I.C.R. mice and Sprague-Dawley rats.

NUMBER/SEX/DOSE: Not stated, probably in the 60+ tables not included.

PROCEDURE: The female animals were mated, vaginal plug of spermatozoon in Smear test- signaled gestation day 0 and the dosing was from gestation day 7 to 12 in the mice and from gestation day 9 to 14 in the rats.

The pregnant animals were evidently divided into groups for cesarian

section and another group allowed to deliver and nurse the pups. However, this is not explained in the submission.

RESULTS: The following is abstracted from the Conclusion section of the report.

Mice- 120 mg/kg sc significantly reduced the body weight gain during pregnancy as well as the average fetus weight. However, no fetal malformations were attributable to treatment except for possible extra supernumerary ribs.

Rats: No noticeable abnormalities except for some extra ribs.

Conclusion: The data was too sparse to evaluate and the sponsor has been contacted regarding this deficiency.

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A test for teratogenicity in rabbits is cited in the labeling. This study (V058/p224) is represented by a single summary paragraph and the sponsor has been requested to supply the data. The used doses of 100 and 300 mg/kg were found to cause loss of body weight by the dams during treatment and increased intrauterine fetal mortality. Although there were no increases in visceral malformations observed, drug treatment did apparently decrease sternal ossification centers in the fetuses. The sponsors maintain that the fetal malformations are only at doses which cause maternal toxicity.

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SEGMENT III - PERINATAL AND POSTNATAL EFFECTS

STUDY **PERINATAL AND POSTNATAL REPRODUCTION STUDY IN CRL:CD BR VAF/PLUS RATS**

REPORT #: #DS-90337 (V057/239:p4-272)

STUDY SITE:

DATE: 2/5/91 TO 4/5/91

NDA# 20-281

COMPOUND & LOT: TRAMADOL HCl, Lot# 8807409

FORMULATION:

ROUTE(S): oral gavage

DOSE(S): 0, 8, 20, 40, 80 mg/kg/day

STRAIN: Sprague-Dawley

NUMBER/SEX/DOSE: 25 presumed pregnant females/dose

PROCEDURE: Presumed pregnant rats were dosed daily from day 15 of gestation through day 21 of lactation (or day 25 of presumed gestation if no litter is delivered).

RESULTS and **DISCUSSION**:

F0:

No females died and all 25 ♀/group delivered litters except for one non-pregnant ♀ in the 8 mg/kg/day group. The only clinical signs noted were increased occurrences of exophthalmos, dilated pupils, and alopecia of the abdominal area in the treated groups. The abdominal alopecia was significantly increased in the 40 and 80 mg/kg/day groups during the gestation and lactation treatment periods. Mean body weights were significantly lower during gestation in the groups receiving ≥ 20 mg/kg/day. There was a corresponding decrease in food consumption for these subjects. During the first week of lactation there was a significantly reduced weight gain in all tramadol treated groups but this reversed during second and third week. On lactation day 21, there were still significantly reduced mean maternal body weights in the 40 and 80 mg/kg/day groups. No necropsy findings were attributed to drug administration. The duration of gestation was significantly increased by tramadol doses ≥ 20 mg/kg/day, but the size of the increases were not dose related, as presented in the following table:

Effects on the F1 generation:

Dose (mg/kg)	0	8	20	40	80
Duration of gestation (d)	21.9	21.8	22.3	22.0	22.2
" in whole days	22.3	22.2	22.8*	22.8*	22.7*
implantation sites	15.0	14.2	14.3	14.6	15.3
dams ≥1 dead pup/total	2/25	4/24	4/25	4/25	9/25
dams w/ all pups dying (day 21)	0	1	0	0	3
mean pups / litter	14.1	13.4	13.2	13.8	14.8
viability index[a]	99.1	93.4	99.7	96.8	77.5*
pup weight/litter day 1	5.8	5.8	6.0	5.8	5.1*
pup weight/litter day 21	43.2	42.8	43.9	41.6	39.5*

* significantly different from control ($p<0.05$)
[a] number alive on day 4 (preculling)/ number live born day 1

The 80 mg/kg/day dose caused significant increases in pup mortality and a significant decrease in pup body weight, from day 1 through day 21. The high dose group pups also were most often found pale and/or cold to touch during the daily observations ($p<0.01$).

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SUMMARY

SEGMENT I

Male Fertility:

In rats, 10 or 50 mg/kg/day for 60 days prior to mating did not change the number pregnant per number mated, gestation length, number of live

fetuses or still-births, fetal malformations or pup weight gain. An additional test, with male rats receiving 10, 25 or 50 mg/kg/day for 85 to 92 days prior to mating, found decreased weight gain in the high dose group and an increase in relative testes weight. This probably has no biological significance. The Dominant Lethal test in mice is reviewed in the Mutagenicity section and no significant change in fertility was observed.

Female Fertility:

An early study in rats used doses of 25, 50 or 75 mg/kg for 14 days prior to mating through day 14 of pregnancy. No effect on implantation, fetal growth or fetal death were observed, however there was an apparent dose-related reduction in corpora lutea formation (-20 at 75 mg/kg/day). The latter was not considered drug related by the sponsor and did not occur in following studies at doses of 10, 25 or 50 mg/kg/day

SEGMENT II - TERATOGENICITY / DEVELOPMENTAL TOXICITY

In a rabbit study with maternal doses of 10,50, 125 and 175 mg/kg/day, the two high doses significantly reduced the maternal weight gain and at the highest dose, 175 mg/kg/day, the fetal body weights were also reduced compared to control. However, the only observed fetal malformations were an increased number of full supernumerary ribs in the two highest doses and rudimentary supernumerary ribs in the low dose. The excess ribs in the fetus were also observed in a study of rats (60 mg/kg/day sc and/or 80 po) and mice (120 mg/kg/day sc and/or 140 po). The latter study submission was incomplete but the similarity of results required inclusion.

SEGMENT III - Perinatal and Postnatal Effects

In a rat study with doses of 10, 25 and 50 mg/kg/day in both ♂ and ♀, there was an apparent decrease in fertility of F1 ♀ in the F0 50 mg/kg/day group. This was attributed to the high fertility rate in the controls, according to the sponsor. However, there was a dose related decline in fertility. In the F2 generation, from F0 50 mg/kg/day

group, there was delayed or absent pinna reflex in 6/95 pups versus 0/139, 0/73 and 0/89 in the control, 10 and 25 mg/kg/day groups, respectively The F2 ♂ of the 50 mg/kg/day FO group also had reduced weight gain.

When pregnant rats were dosed with 8, 20, 40 or 80 mg/kg/day, the 80 mg/kg/day dose caused a significant increase in pup mortality and decrease in body weight days 1 through 21. The high doses also caused a reduced food consumption and body weight of the F0 ♀ during gestation.

XXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

CONCLUSIONS:

In Segment I studies, tramadol HCl did not affect fertility in rats either the male (up to 50 mg/kg) or the female (up to 80 mg/kg). Although the 80 mg/kg dose slightly and significantly increased gestation time.

Tramadol HCl has little effect on embryo/fetal survival until the dose is maternally toxic. Increased fetal mortality was observed in rabbits at 300 mg/kg dose.

Increased supernumerary ribs were observed in rabbits at 125 and 175 mg/kg, in rats with high doses (60 sc, 80 po) and mice (120 sc and 140 po).

In peri- and post-natal rat studies, 80 mg/kg to pregnant and nursing dams resulted in significant decreases in pup body weights and increases in pup mortality. This was not observed at doses of 8, 20 or 40 mg/kg.

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NDA# 20-281

MUTAGENICITY

1.

MUTAGENICITY TESTING OF CG315 USING SALMONELLA/MICROSOME TEST ACCORDING TO AMES

STUDY SITE:

REPORT #: Accession No. 47570
(V059/NDA:P16)

DATE: OCTOBER 1978

GLP STATEMENT: Not GLP, done prior to regulations, variations from GLP's not stated.

COMPOUND & LOT: tramadol HCl. batches 143, 148.

DOSE(S): 0.1, 1, 10, 100, 1000 µg/plate ; +/- S9 mixture

VEHICLE: DMSO

STRAIN(s): TA98, TA100, TA1535, TA1537, TA1538
Histidine-auxotrophic strains

RESULTS:

Tramadol did not significantly increase the colonies/plate at any dose tested in either the -S9 or +S9 condition.

2. **DETERMINATION OF THE MUTAGENIC POTENCY OF TRAMADOL HCL IN THE SALMONELLA TYPHIMURIUM REVERSE MUTATION ASSAY (base pair substitutions/deletions or frame snift mutations)**

STUDY SITE:

NDA# 20-281

REPORT #: Accession No. 500, 043
(V059/NDA:p21)

DATE: February - March 1990

GLP STATEMENT: Not GLP, variations from GLP's: "1) report does not contain stability or characterization data for the test article/carrier mixture. 2) QA statement does not indicate study inspections or date report audit findings were reported to study director and management."

COMPOUND & LOT: Tramadol-HCl lot# 8C1160

DOSE(S): 0.1, 1.0, 10, 100, 1000μg ; +/- S9 mixture

VEHICLE: sterile demineralized water;

STRAIN(s): TA97, TA98, TA100, TA102

SOLVENT CONTROLS: sterile demineralized water, DMSO

POSITIVE CONTROLS: 4-Nitro-o-phenylenediamine (NPD), methyl methanesulfonate(MMS), sodium azide(NaN3), 2-aminofluorene(2AF), 2-aminoanthracene (2-AA).

PROCEDURE:
Each of the four strains was run in triplicate, both with and without the S9 activator. The concentration of the exogenous S9-mix for metabolic activation was increased from the standard of 20 μl/assay to 50 μl.

RESULTS:
The results indicate that tramadol did not have mutagenic activity in either the direct assay or with the S9 activation. The results are summarized on the following table:

		NUMBER OF REVERTANTS/PLATE							
STRAINS		TA97		TA98		TA100		TA102	
	µg/plate	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Tram	1000	51	103	8	19	123	137	164	290
	100	58	93	13	16	118	125	156	284
	10	46	93	7	18	116	130	160	277
	1	63	121	9	15	126	121	152	267
	0.1	60	106	9	21	112	111	151	228
DMSO		47	119	11	21	129	144	152	294
H2O		64	122	11	28	145	139	186	301
NPD	20.0	1105	-	1561	-	-	-	-	-
2-AF	10.0	-	844	-	1484	-	953	-	-
NaN3	1.5	-	-	-	-	1053	-	-	-
MMS	1300	-	-	-	-	-	-	2034	-
2-AA	10.0	-	-	-	-	-	-	-	1192

3.

ASSESSMENT OF MUTAGENIC POTENTIAL OF TRAMADOL HYDROCHLORIDE IN A MAMMALIAN CELL MUTATION ASSAY USING THE CHINESE HAMSTER OVARY/HGPRT LOCUS ASSAY

STUDY SITE:

REPORT #: GNL13/90864; Accession No. 500,482
(V059/NDA:P38)

NDA# 20-281

DATE: August 13, 1990

GLP STATEMENT: Not GLP, "report does not contain stability or characterization data for the test article/carrier mixture."

COMPOUND & LOT: tramadol hydrochloride, batch number 11

DOSE(S): μg/ml

preliminary toxicity: 50, 150, 300, 625, 1250, 2500, 3000, 3994

-(S-9) Test 1 and 2: 2500, 3000, 3500, 4000, 4500, 5000

+(S-9) Test 1: 2500, 3000, 3500, 4000, 4500, 5000

Test 2: 500, 1000, 2000, 3000, 5000

POSITIVE CONTROLS: ethyl methane sulfonate (EMS), 250 μg/ml, in -(S-9) and 20-Methylcholanthrene (20-MC), 5 μg/ml, in +(S-9).

VEHICLE: Sterile water for tramadol and EMS, DMSO for 20-MC

CELLS: CHO-K1-BH_4, originally derived from ovaries of adult Chinese hamster.

RESULTS:
No dose of tramadol induced increased rates of mutagenicity in either the absence or presence of the S-9 activator. The positive controls, EMS and 20-MC, did significantly increase the mutation rate-(S-9) and +(S-9) conditions, respectively.

4. ASSESSMENT OF MUTAGENIC POTENTIAL OF TRAMADOL HYDROCHLORIDE USING THE MOUSE LYMPHOMA TK LOCUS

STUDY SITE:

REPORT #: Accession No. 500,483
(V059/NDA:P63)

DATE: June 1989

GLP STATEMENT: Not GLP, variations from GLP's: "1) report does not

contain stability or characterization data for the test article/carrier mixture. 2) QA statement does not indicate study inspections or date report audit findings were reported to study director and management."

COMPOUND & LOT: tramadol hydrochloride lot# 114.

DOSE(S): µg/ml:
preliminary toxicity: 10, 100, 312.5, 625, 1250, 3750, 5000

-(S-9) Test 1: 250, 500, 750, 1000, 1250, 1500, 2000, 2500, 3000
Test 2: 125, 250, 500, 1000, 1250, 1500, 2000, 2500

+(S-9) Test 1: 10, 50, 100, 200, 300, 400, 500, 625, 750
Test 2: 10, 100, 200, 300, 400, 500, 625, 750
Test 3: 10, 50, 100, 200, 300, 400, 500, 625, 750

POSITIVE CONTROLS: ethyl methane sulfonate (EMS), 500 µg/ml, in -(S-9) and 20-Methylcholanthrene (20-MC), 2.5 µg/ml, in +(S-9).

Results:

tramadol µg/ml	Suspension Growth	
	% control	mean % control
0	100	100
10	109	
	100	105
50*	73	
	90	82
100*	78	
	46	62
200	34	
	38	36
300	25	
	29	27
400	20	
	16	18
500*	19	
	36	28
625	12	
	8	10
750*	4	
	4	4
20-MC (2.5 µg/ml)	35	
		37

* "Cultures discarded in favor of cultures with more acceptable levels of toxicity"

Viability and mutation of L5178Y cells after treatment with Tramadol in the presence of S9 mixture

Tramadol concentation µg/ml	Mean % Survival			Mean Mutant Frequency ($x10^{-6}$)		
	Test			Test		
	1	2	3	1	2	3
0	100	100	100	118	84	120
10	73	93	85	150	96	75
50			70			122
100		21			221**	
200	28	19	29	248**	190*	264**
300	23	12	20	222**	134	332**
400	12	6		253**	295**	
625	6			318***		
20-MC	16	6	19	582***	781**	720***

*p<.05 **p<.01 ***p<.001

DISCUSSION:

The three tests presented in the table above demonstrate that there is mutagenic activity of tramadol hydrochloride in a mammalian cell line. This was only true in the presence of the activating +S9 mixture. The sponsor suggests that the metabolism could have gone to the formation of formaldehyde, a known mutagen. However, this was not measured and remains only conjecture.

NDA# 20-281

5. <u>IN VIVO MUTAGENICITY TEST</u> - **MICRONUCLEUS TEST IN BONE MARROW OF MALE AND FEMALE MICE, RATS AND HAMSTERS; FOLLOWING ORAL AND INTRAPERITONEAL ADMINISTRATION**

STUDY SITE:

REPORT #: Accession No. 500,487 FO-TX 811
(V059/NDA:P104)

DATE: October 1976

GLP STATEMENT: Not GLP, done prior to regulations, variations from GLP's not stated.

COMPOUND & LOT: tramadol hydrochloride lot# ?.

DOSE(S): (approximately 1/3 or 1/2 the LD_{50} in each species)

Mouse: 90, 175 mg/kg p.o. and 15, 35 mg/kg i.p.
Rat : 57, 144 mg/kg p.o. and 72/143 mg/kg i.p.
Hamster: 200, 400 mg/kg p.o. and 50, 100 i.p.

Two dose administrations separated by 24 hours and final dose was 6 hours prior to sacrifice.

POSITIVE CONTROLS: triaziquone 0.125 mg/kg i.p.

RESULTS:

Mice: No significant increases in the percentage of polychromic erythrocytes with micronuclei was observed.

Rats: The results suggested that tramadol can produce an increase in the number of polychromic erythrocytes with micronuclei. Upon i.p. administration, the highest dose, 143 mg/kg, was lethal to 3 of the 5 ♂ and also ♀ rats. At the lower dose, 73 mg/kg i.p., the percent of micronuclei erythrocytes was increased by 112% in the ♂ and 109% in the ♀, the former was significant at the $p<.05$ level. After oral administration, the increased percentages were evident with both doses, 186% to 288%. Two changes were significant at the $p<.05$ level and one at the $p<.01$ level, the latter

was the limit set by the sponsor but this result was not noted in the report.

This was addressed 11/28/94 and the company agreed that, in the males, tramadol significantly increased micronucleus formation at 57 mg/kg po ($p<0.01$) and 114 mg/kg po (<0.05) and 72 mg/kg ip ($p<0.05$).

There was no positive control for the oral dosing, but Triaziquone i.p. did produce significant elevations of 686% and 767% in the males and females, respectively.

Hamsters: No significant increases in the percentage of polychromic erythrocytes with micronuclei was observed.

DISCUSSION: The micronuclei test in mice and hamsters was negative however, in the rats, tramadol increased significantly the percent of polychromatic erythrocytes with micronuclei in both ♂ and ♀'s. This was evident after oral administration at the sponsor selected limit of $p<0.01$ and in both oral and ip groups at the more common level of $p<0.05$.

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6. CHROMOSOME ABERRATION TEST IN HAMSTER BONE MARROW AFTER SINGLE ADMINISTRATION OF TRAMADOL HYDROCHLORIDE

STUDY SITE:

REPORT #: Accession No. 500,486 FO-TX 812
(V059/NDA:P137)

DATE: August 1984

GLP STATEMENT: Not GLP, variations: 1. report does not contain stability data for the test article. 2. method used to control bias is not addressed. 3. animal acclimation/quarantine not addressed. 4. location of raw data and final report not addressed. 5. no

NDA# 20-281

Quality Assurance Final Report statement.

COMPOUND & LOT: tramadol hydrochloride Batch #1009.

DOSE(S): 10, 30 and 90 mg/kg po.

POSITIVE CONTROLS: cyclophosphamide 200 mg/kg p.o..

RESULTS:

No significant increases in metaphase aberrations were observed in tramadol treated hamsters. However, cyclophosphamide did produce chromosomal changes.

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ADDITIONAL TESTS OF MUTAGENICITY

The sponsor submitted four additional study series of mutagenic tests of tramadol (correspondence date 11/11/94). The three initial studies were done in England by Hazleton Microtest 1991 to 1992. The fourth submission, chromosomal aberrations in rat bone marrow cells, was done in Germany by Cytotest Cell Research GMBH & Company in 1994.

1. ***Escherichia Coli*** ,WP2pKM101, WP2uvrA pKM101 (tryptophan-requiring) and ***Salmonella Typhimurium***, TA98, TA100, TA1536 and TA1537 (histidine requiring).

The strains were tested with tramadol concentrations of 8, 40, 200, 1000 and 5000 µg/plate; with and without S-9 metabolic activator. A second test used doses of 1000, 2000, 3000, 4000 and 5000 µg/plate, with and without S-9, but preincubated with S-9.

No toxicity was observed at any dose tested and no mutation increase was observed in terms of sufficient revertant numbers to be considered a significant mutagenic effect. This was seen in both -S-9 and +S-9 conditions.

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› chromosomal damage in cultured human lymphocytes was :h doses of tramadol from 839 to 5000 μg/ml, with and : S-9 metabolic activator. "It was concluded that tramadol ested in an *in vitro* human peripheral blood lymphocyte assay some borderline activity in inducing structural chromosome s, although it did not fulfill all the criteria to conclude arly clastogenic. Elevated chromosome aberration s were not clearly reproducible, nor were they clearly dose

nuclei test in the polychromatic erythrocytes of CD-1 mice ith tramadol HCl at the dose of 25 mg/kg i.v. for two days. of micronuclei did not differ from controls.

somal aberrations in rat bone marrow cells was done with t 10, 45, and 200 mg/kg p.o.. "No biologically relevant or lly significant increase in the frequency of aberrant cells ed ...."

'S:

lack of consistant mutagenic effects is in agreement with ıted data.

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DOMINANT LETHAL TEST OF TRAMADOL .UTAGENIC EFFECTS IN MALE MICE - AFTER A SINGLE ADMINISTRATION

E:

Accession No. 500,484 FO-TX 838a
(V059/NDA:P151)

NDA# 20-281

DATE: June 1976

GLP STATEMENT: Not GLP, conducted prior to regulations. Also, as stated by the present sponsor, Page 1 has errors in paragraphs three and four, at variance with tabulated data in regard to the positive control, triaziquon (pg 196).

COMPOUND & LOT: tramadol hydrochloride Batch = ?

DOSE(S):

tramadol HCl: 60, 120 and 350 mg/kg po - single dose
11.3,17 and 22.6 mg/kg i.v. - single dose

POSITIVE CONTROLS:

Triaziquon: 0.125 mg/kg i.p. - single dose

PROTOCOL:

In each treatment group, 10 male mice were treated with a dose of tramadol, saline, water or triaziquon. For eight successive weeks, each male mouse was caged with 2 virgin females for 7 nights and the females were sacrificed 13 days later. The ovaries and uteri were examined and the pre- and post-implantation losses were tabulated.

RESULTS:

The single tramadol treatment to the male mice did not change fertility or embryo loss at any time point. The positive control did increase the number of dead embryo and decrease the number of implants at various time intervals. The results are as stated by the report.

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DOMINANT LETHAL TEST OF TRAMADOL MUTAGENIC EFFECTS IN MALE MICE - AFTER FIVE ADMINISTRATIONS

STUDY SITE:

NDA# 20-281

REPORT #: Accession No. 500,485 FO-TX 421a
(V059/NDA:P197)

DATE: December 1976

GLP STATEMENT: Not GLP, conducted prior to regulations. Also, as stated by the present sponsor, one group was described as ip administration in Section 4 and oral in Table 1A.

COMPOUND & LOT: tramadol hydrochloride Batch =?

DOSE(S):

tramadol HCl: 10 and 50 mg/kg p.o. - five doses
10 and 20 mg/kg i.p. - five doses

No statement of when the five doses were given or delays between dosings.

POSITIVE CONTROLS:

Triaziquon: 0.125 mg/kg i.p. - single dose

PROTOCOL:

In each treatment group, 10 male mice were treated five times with a dose of tramadol, saline, water or triaziquon. For eight successive weeks, each male mouse was caged with 3 virgin females for 7 nights and the female were sacrificed 13 days later. The ovaries and uteri were examined and the pre- and post-implantation losses were tabulated.

RESULTS:

There was no statement as to when the five tramadol administrations were made, either in relation to each other or in relation to the mating tests.

The tramadol treatment did not change fertility or embryo loss at any time point. The positive control did increase the number of dead embryo and decrease the number of implants at various time intervals. The tables of data are complex and difficult to decipher. The results are as stated by the report.

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CONCLUSIONS

Tramadol HCl has produced limited mutagenic effects in only two of the ten reported test series. In the Mouse Lymphoma assay, the positive effects could have been due to the formaldehyde produced in metabolism and the positive results in the rat bone marrow Micronuclei test were not confirmed in a chromosomal aberration test done recently in rat bone marrow cells. No mutagenic effects were found in the Dominant Lethal test in mice.

No biologically significant mutagenicity is evident for tramadol HCl in the test series submitted.

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CARCINOGENICITY

TEST FOR CARCINOGENICITY IN NMRI-MICE OF TRAMADOL HYDROCHLORIDE IN THE DRINKING WATER FOR 24 MONTHS

STUDY SITE

REPORT #: DS-90552 Accession No. 500,616
(V036/NDA:P416)

DATE: September 1984 - July, 1986 (dates V036/p416)

GLP STATEMENT: (V041/NDA: p264) The QA Unit of R.W. Johnson PRI reports on study and lists discrepancies from GLP guidelines on pages 264-266/Vol 041. The only significant difference noted was a retrospective stability assessment of the test article and vehicle, rather than measurements during the study. A supplemental

report (V045/p199) indicated six 4th day samples were taken in the middle of the study and were within 10% of the theoretical level.

COMPOUND & LOT: tramadol HCl; batch 143, 148

DOSE(S): 0, 7.5, 15.0 and 30.0 mg/kg/day in the drinking water.

VEHICLE: Distilled water

ANIMALS: NMRI mice(Lippische Versuchtstierzucht Hagemann u. Co.), 5 weeks old, approximately 20g body weight in both ♂ and ♀ at start of study; two control groups and 3 treatment groups, 50 mice/sex/group. An additional group of 20 mice/sex was used for hematology, clinical chemistry and urinalysis.

PROCEDURE: (V036/416):(V039/095)

All animals were observed twice daily or once daily during weekends and holidays. The animals were palpated and weighed weekly. The food consumption was measured 1-3 times weekly to week 55 and generally every 2-4 weeks thereafter. Water consumption was measured four times weekly to week 4, every two weeks to week 55 and generally every four weeks thereafter. Auditory and ophthalmologic examinations were done pretest, after 12 and 18 months and at study termination. The dosing was for 21 months in ♀'s and 24 months in ♂ mice.

The histopathology examination was complete on all control and high dose animals and any in the low and mid-dose groups that died or were killed moribund prior to terminal sacrifice or had abnormalities upon gross observation. The only complete histopathology examinations across all treatment groups were limited to the lungs and livers.

RESULTS:

1. Clinical Observations:

No treatment related effects were observed in the macroscopic examinations of hair and skin changes, grooming behavior or the occasional symptoms such as piloerection, swollen eyelids, diarrhea or

hypothermia. The mean number of palpable masses per animal did not differ significantly between treatment groups.

1.1 BODY WEIGHTS (V040/p329, 345,361 etc: V039/p162,164)

MEAN BODY WEIGHTS AT STUDY COMPLETION (Grams)

Dose mg/kg/day	0	7.5	15	30	0
MALES 104 weeks	48	47 (-2%)	46 (-4%)	46 (-4%)	47 (-2%)
FEMALES 92 weeks	42	42 (±0%)	40 (-5%)	43 (+2%)	43 (+2)

The mean body weights recorded at necropsy were 14 to 19% less but again demonstrated no significant difference between groups (V039/p186). The total number of animals per treatment group were also not identical between the above mentioned sets of tables, but the variation was not extreme. This discrepancy in submitted data will be explained by the sponsor.

1.2 Consumption: No treatment related effects were observed on either food or water consumption.

1.3 Mortality:

SURVIVAL - (groups of 50 mice)
Males = 24 months; Females = 21 months

Dose mg/kg/day	0	7.5	15	30	0
No. MALES	22 [44%]	11 [22%]	17 [34%]	17 [34%]	20 [40%]
No. FEMALES	16 [32%]	17 [34%]	15 [30%]	15 [30%]	9 [18%]

No treatment related effects were observed in body weights, food or water consumption or clinical signs. The survival data indicates treatment related effects are only evident in the low dose males, with no dose-response relationship. Although the statistician confirmed the statistical significance, this probably has no biological significance.

2. Hematology: No treatment related effects.
3. Clinical Chemistry: No treatment related effects.
4. Urinalysis: No treatment related effects.
5. Necropsy: Performed on all animals. No treatment related effects.

6. Histopathology

6.1 Non-Neoplastic changes, irrespective of time of death.
The statistically significant differences from controls, which included the high dose group, were the following, according to sponsors calculations:

In ♂'s:

1. reduced progressive nephropathy in all dose groups
2. reduced incidence of enlarged seminal vesicles in mid and high dose groups
3. increased skin edema in low and high dose groups

In ♀'s:

1. decrease in ovarian cysts in high dose group
2. increased renal arteritis

The decreased pathology was cited by the sponsor as probably attributable to decreased food intake in the treated animals and Other increases occurred in too few incidences to be closely associated with treatment.

However, in the tables of food consumption, in terms of g/20 g body weight /day(V039/p165+), there were only measurements of significant increased consumption in the ♂ treatment group. In the ♀ groups there were 14/52 measurements of significantly reduced intake and 2 increased intake. There was no dose relationship to reduced intake. No significant decreases were evident during the last 11 weeks for treatment in females or in any of the 104 weeks in the males.

6.2 Neoplastic changes, irrespective of time of death.

In ♂'s:

- 1. hepatocellular adenomas significantly increased in the high dose group.

In ♀'s:

1. pulmonary adenomas significantly increased in tramadol treated ♀ subjects.
- 2. histiocytic sarcomas significantly increased in treated females of the high dose group versus the control group.

Tumors per Treatment Group

Dose (mg/kg/day)		0	7.5	15	30
Hepatocellular adenoma	♂	9/100[a] 9%[b]	6/50 12%	9/49 18%	12/50 24%
	♀	0/99 0	1/50 2%	2/50 4%	1/49 2%
Hepatocellular carcinoma	♂	3/100[a] 3%[b]	1/50 2%	0/49 0	2/50 4%
	♀	0/99 0	0/50 0	0/50 0	0/49 0
Pulmonary tumors	♂	34/99 34%	19/50 38%	16/49 33%	17/50 34%
	♀	8/98 8%	12/50 24%	8/50 16%	10/49 20%

Dose (mg/kg/day)		0	7.5	15	30
Histiocytic sarcoma	♂	4/100 4%	2/36 6%	1/32 3%	0/50 0
	♀	0/99 0	0/37 0	1/39 3%	3/49 6%
Harderian gland adenoma	♂	7/96 7%	2/37 6%	2/29 7%	7/46 15%
	♀	9/87 10%	5/34 14%	2/36 6%	5/45 11%
Lymphoma	♂ c	12/100 12%	6/36 17%	2/32 6%	1/50 2%
	♀ c	27/99 27%	15/37 41%	10/39 26%	16/49 33%

[a] occurrence/animals examined [b] percent occurrence

c. - from tabulated data Vol 041/NDA:p302; Vol 02/pg 0065 (9/03/92): V036/NDA:p424)

In the mouse carcinogenicity study, the statistician found significantly increased hepatocellular adenomas in the males, however since adenomas are a common occurrence, this may have limited biological significance. The histiocytic sarcoma incidence was found to be significantly increased (6%) by the statistician in the high dose ♀ group. This may be of some biological significance but is not present in the males in the high dose group.

MAXIMUM TOLERATED DOSE (MTD)

The treatment groups did not have higher mortality than controls, were not significantly different in body weight and did not eat or drink significantly different amounts. This indicates that the MTD was not tested. In reference to this question of MTD determination, the

sponsor supplied a post-hoc study done by R.W. Johnson PRI in Spring House PA from July to October 1992.

The study (June 10, 1994 submission), was a 3-month oral toxicity study in mice. The doses used, 30, 60, 120 and 240 mg/kg/day, were administered in the drinking water. The subjects were 10 ♂ and 10 ♀ per dose and mortality and clinical signs were recorded daily. Body weight, food and water consumption were recorded weekly and gross necropsies were performed on all mice at the end of the three month study. No pathological differences were found between treatment groups and controls.

The only decrease from controls in body weight at the end of the study that exceeded 10 % was in the high dose females, 240 mg/kg/day, and these ♀ were 10.2% less than control animals. In the males the difference was 6.6% in this treatment group. In the four dose groups, with 13 weekly body weight measurements, the treated males were never less than 92.3% of controls and the females were only 10% less than controls in the highest dose group.

The sponsor stated "dosages > 30 mg/kg/day would likely result in marked effects on homeostasis after long-term administration because of decreased water consumption". This is very weakly supported as the variability in the water consumption was very pronounced. i.e. in the male mice, the week 13 measurement was -21% but the week 12 was +4% and the week 11 was +48.1% (120 mg/kg/day). In the females, all treatment groups were about -20% during week 13, [illegible] at 30 and 240 mg/kg/day and -25.5% for the 60 and 120 mg/kg/day. During week 11, only the lowest dose group was [illegible]

The measured water consumption [illegible] into differences in body weight [illegible] difference in body weight [illegible] and [illegible] as the MTD [illegible]

[illegible]

XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

NDA# 20-281

ORAL CARCINOGENICITY STUDY OF TRAMADOL HCL IN WISTAR RATS - 30 MONTHS

STUDY SITE:

REPORT #: DS-91517 Accession No. 500,619
(V045/NDA:p204); FO-TX 921, FO-PT 598A
(V051/NDA:p441)

DATE: February 1984 - September, 1986

GLP STATEMENT: (V051/NDA: p435)(V050/p358) The QA Unit of R.W. Johnson PRI found minor discrepancies from GLP regulations.

COMPOUND & LOT: tramadol HCl - batches #143 and #148

DOSE(S): 0, 7.5, 15.0 and 30.0 mg/kg/day in the drinking water. Stock solution of tramadol HCl and the drinking-water solutions were prepared twice weekly. The stability of tramadol in the drinking water was done retrospectively by analysis of respective concentrations after 7 days of storage at room temperature.

VEHICLE: [illegible] water

ANIMALS: Wistar rats
30-35 days old, [illegible] ♂, [illegible] ♀ at initiation; two control groups and 3 treatment groups for each sex/group. This was normally combined with the 18 month, [illegible] study with an additional 20 animals/sex/group.

PROCEDURES [illegible]
Blood [illegible] was [illegible] weekly [illegible] and weighed weekly. [illegible] and [illegible] weekly to week 61 and [illegible] was monitored [illegible] every two weeks [illegible]

Results:

1. Survival: No treatment related effects.

Survival at 30 Months

Treatment	control	7.5 mg/kg	15 mg/kg	30 mg/kg	control
females	15/50 [30%]	19/50 [38%]	21/50 [42%]	14/50 [28%]	15/50 [30%]
males	22/50 [44%]	19/50 [38%]	18/50 [36%]	18/50 [36%]	16/50 [32%]

2. CLINICAL OBSERVATIONS: No treatment related effects on palpable masses or clinical signs. Ophthalmoscopic, hearing and fecal blood tests did not reveal any treatment related effects.

2.1 *BODY WEIGHTS*
(V048/NDA:p009,012)

NDA# 20-281

Body Weights During the Last Five Weeks of Testing

	Week	Dose (mg/kg)				
		0	7.5	15	30	0
♂	126	454	430 -5%	408* -10%	405* -11%	437 -4%
	127	456	436 -4%	414* -9%	411* -10%	444 -3%
	128	450	436 -3%	413 -8%	409 -9%	442 -2%
	129	442	424 -4%	417 -6%	402 -9%	428 -3%
	130	444	424 -5%	405 -9%	403 -9%	430 -3%
♀	126	282	274 -3%	294 +4%	271 -4%	292 +4%
	127	282	280 -1%	298 +6%	278 -1%	296 +5%
	128	284	279 -2%	299 +5%	277 -2%	291 +2%
	129	278	275 -1%	300 +8%	278 ± 0%	287 +3%
	130	276	277 ± 0%	297 +8%	273 -1%	294 +7%

* Statistically significant according to sponsor ($p<0.01$)

Body weights of both males and females tended to be lower than controls although there were no significant differences between groups during the final three weeks in the males and final 13 weeks in the females. This reviewer and the statistician agree that there is no significant difference in body weights. This is confirmed with the calculation of total weight gain in each group by subtracting the initial group weights from the terminal group weights and expressing

this as percent of control group weight change:

Percent of Control Weight Gain

	Dose (mg/kg)		
	7.5	15	30
Male	96.8	90.9	90.6
Female	96.2	104.8	104.8

2.2 Food and water consumption was occasionally higher in the treatment groups of both sexes.
3. Hematology: No treatment related effects.
4. Clinical Chemistry: No treatment related effects.
5. Urinalysis: No treatment related effects.
6. Necropsy: Performed on all animals. No treatment related effects.
7. Histopathology

TUMOR INCIDENCE (V45/p210)

Tumor type	sex	Dose (mg/kg/day)			
		0	7.5	15	30
Hemangiosarcoma	♂+♀*	2/200 [1%]	2/63 [3%]	1/61 [1.6%]	3/100 [3%]
Renal mesenchymal tumor	♀*	0/100	0/32	0/29	1/50 [2%]
Ovarian thecoma	♀*	0/100	0/34	0/33	2/50 [4%]
Hepatocellular carcinoma	♀*	0/100	1/39 [2.6%]	0/32	2/50 [4%]
Hepatocellular carcinoma	♂	3/100 [3/%]	0/41	0/39	0/50
Thyroid follicular adenoma[a]	♀*	1/100 [1%]	1/32 [3.1%]	1/29 [3.4%]	2/50 [4%]
Thyroid follicular adenoma[a]	♂	6/100 [6%]	3/32 [9.4%]	1/33 [3%]	0/50

No. tumors / No. animals examined [a] benign tumor of thyroid
* statistically significant increasing doses: Peto's Method (V45/p221)

The limited number of tumors does not allow satisfactory assignment of causality. This reviewer agrees with the statistician's findings that no significant increases in tumors were evident. Trend analysis was not possible as only the control and high dose data were submitted. However, the MTD was probably not tested.

MAXIMUM TOLERATED DOSE (MTD)

At the highest dose there was no significant increase in mortality or change in body weight, food or water consumption, or clinical signs. The pharmacokinetics also indicated that the rodents had significantly less exposure than the humans at the clinically relevant dose of 100 mg QID:

Relative AUC Values for Mice, Rats and Man After Repeated Oral Dosing

tramadol	dose (mg/kg)	dose (mg/M^2)	AUC (ng.h/ml)	AUC_{rodent} / AUC_{human}
mouse[a]	30	(x3=) 90	329	0.089
rat[b]	30	(x5.9=) 177	2727	0.741
man[c]	(100/70) 1.43	(x37=) 52.9	3679	-

a. DM-94301 (V1/1:3/30/94:p4-5) NMRI mice 30 mg/kg/day X 14 days [tram(+)+(-)♂+♀/2]
b. wistar rats (v19/19:p0562) DM-92337 [tram(+)+(-)♂+♀/2] - 30 mg/kg/day X 14 days
c. man DM-93314, 100 Q.I.D. for 29 doses (V01/0023)

In AUC values, the rodent exposures were less than the human exposure by factors from 0.089 to 0.579. This is much less than the 25X increase stated as a general guidance.

Humans excrete about 25% of the tramadol unchanged in the urine and mice and rats excrete only about 1% unchanged. This provides the

rationale for AUC comparisons of tramadol rather than the active metabolite M1. A comparison of the M1 AUCs was actually very similar to tramadol in mice (510 ng.hr/ml). In the rat the M1 AUC was 1402 versus 835 ng.hr/ml in humans. A factor of about 2X greater. These values are also far from the 25X ratio desired.

The MTD was not tested in the rat and it is this reviewer's opinion that this is also true for the mouse. The biostatistician also found that the MTD was not tested in the rats (Biostat. Rev. 9/28/93).

METABOLISM:
The metabolic profile is qualitatively similar in rodents and humans, as depicted on the following table(V60/p056) (V61/p25-68,263-284)(V62/p1-26):

Urinary Metabolites as Percent Total Radioactivity

Oral Administration	Mouse	Rat	human	
			A1	A2
DOSE (mg/kg)	34	30	1.25	1.06
No. / group	3	5	1	1
Tramadol	1.1	0.9	25.1	31.7
M1	11.9	9.1	10.4	4.9
M2	10.3	16.9	2.4	31.4
M3	1.2	9.8	na	0.8
M4	1.5	1.7	0.1	0.8
M5	14.6	12.8	12.8	6.0
M1-conjugate	17.3	10.5	15.5	7.6
M4-conjugate	1.5	3.6	0.8	0.2
M5-conjugate	12.7	13.6	15.1	5.8
fraction unknown	28.1	20.2	18	10.7

na = not available (V60/p056).

The metabolism is qualitatively similar in rats, mice and humans and the renal excretion amounts to about 90% in humans and 86% to 100% in other species. As humans excretes about 25% of tramadol unchanged, the comparison of AUC values based on tramadol are the most relevant to the human situation.

Mutagenicity:

Tramadol HCl was found to be negative in two *SALMONELLA* tests (Ames), although the highest dose used, 1000 ug, was less than the 5 mg/plate usually requested. In the **CHO/HGPRT** assay tramadol was negative at the maximum dose of 5000 ug/ml. The **Micronucleus Test** was done in mice, hamsters and rats. Although the results were negative in mice and hamsters, the doses of 73 mg/kg i.p. and 57 and 144 mg/kg po in the rats increased the number of polychromic erythrocytes with micronuclei more than 100%, although none were marked as significant. Using the means and standard deviations supplied, two differences were significant at $p<0.05$ and one at $p<0.01$. This was done using the Student's "t", the cited method of analysis. The company was questioned about the discrepancy, but has not yet responded. This was addressed 11/28/94 and the company agreed that, in the males, tramadol significantly increased micronucleus formation at 57 mg/kg po ($p<0.01$) and 114 mg/kg po (<0.05) and 72 mg/kg ip ($p<0.05$).

In the **Mouse Lymphoma, TK locus**, the significant increases in mutation frequency are shown in the following table.

Viability and Mutation of L5178Y Cells after Treatment with Tramadol in the presence of S9 mixture (V059/p104)

Tramadol µg/ml	Mean % Survival			Mean Mutant Frequency ($x10^{-6}$)		
	Test			Test		
	1	2	3	1	2	3
0	100	100	100	118	84	120
10	73	93	85	150	96	75
50			70			122
100		21			221**	
200	28	19	29	248**	190*	264**
300	23	12	20	222**	134	332**
400	12	6		253**	295**	
625	6			318***		
20-MC	16	6	19	582***	781**	720***

*p<.05 **p<.01 ***p<.001

The three test series presented in the table above demonstrate the mutagenic activity of tramadol hydrochloride in a mammalian cell line. This required the presence of the activating +S9 mixture. The sponsor suggests that the metabolism could have gone to the formation of formaldehyde, a known mutagen. However, this was not measured, remains only conjecture and does not remove the effect.

<u>**Summary and Conclusions**</u>:

MICE

There was a statistically significant increase in male hepatocellular adenomas and female histiocytic sarcomas, although both are of limited biological significance.

However, the MTD was not used, either in terms of survival, body

weight, clinical signs or other homeostatic changes, associated pathologies or AUC values in the pharmacokinetic studies. There were no preliminary tests to determine an MTD and the post-hoc study, which was only submitted upon request, also did not support an MTD of 30 mg/kg.

RATS

In the rat study, no significant increases in tumors or decreases in survival, body weight, clinical signs or increases in associated pathology were reported. Again, the AUC values in the rat were less than the human AUC. These factors indicate that the MTD was not used.

In conclusion, there appear to be no treatment related changes which can justify the use of 30 mg/kg as the high dose in either mouse or rat. As a result, the carcinogenic potential of tramadol, mutagenic in two tests, has not been examined.

xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

The above Carcinogenicity section was submitted to the Carcinogenicity Advisory Committee - Executive Commmittee and the the Final Report is attached as Appendix 1, two Addendums as 2 and 3.

xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

SUMMARY

OF TRAMADOL EFFECTS IN ANIMAL STUDIES

- Analgesic: parent molecule is a weak μ-agonist and principal metabolite, M1, is a strong μ-agonist. Analgesic potency in rats correlates with M1 blood concentrations.

- An inhibitor of serotonin and norepinephrine reuptake, but less than some other opiates. Analgesia is not completely blocked by naloxone. The sponsor cites the monoamine uptake inhibition as contributing factor to analgesia, but no comparative studies done with meperidine or methadone which are 10X as potent as uptake inhibitors.

- Mild tolerance develops in animals and only mild withdrawal symptoms are evoked. Cross-tolerance is variable.

- Will not substitute for morphine, at least in relieving GI withdrawal symptoms.

- Relatively non-toxic, but lethality (often respiratory depression) is not counteracted by naloxone - which may increase convulsions. Convulsions are observed at high doses in rats, mice, rabbits, dogs and monkeys and may develop at lower doses upon chronic treatment.

- Acute toxicity is not organ specific, although convulsions and CNS depression are common symptoms shared with other opiates. The chronic toxicity was also centered on convulsions, without specific organ toxicity except for some hepatic nuclear atrophy at high dose in rats, 60 mg/kg.

- Has no effect on fertility or fetal toxicity or development at doses below maternal toxicity. No teratogenic effects were observed. However, extra supernumerary ribs were observed in F1 mice, rats and rabbits after high maternal doses of tramadol.

- Has very limited mutagenic effects *in vivo* or *in vitro*. Is not considered an actual mutagen.

- Was not carcinogenic in rats at the highest dose of 30 mg/kg/day. In a 52 week study in mice at 30 mg/kg/day, tramadol did increase the incidence of hepatocellular adenomas in male mice and histiocytic sarcoma in the female mice. However, 30 mg/kg/day may not have been the Maximum Tolerable Dose (MTD).

This review of the effects of tramadol HCl in animal studies has provided no pharmacological/toxicological basis to prohibit its use in humans. The application is approvable, based on the preclinical studies.

Harry M. Geyer

Harry M. Geyer, III Ph.D.

In consensus: Almon W Coulter 1/10/95

Peer Leader: William A. Coulter, Ph.D. Date

APPENDIX I

CAC Executive Committee Final Report

Application: NDA 20-281
Division: HFD-007
Date: November 29, 1994
Reviewer: Geyer
Chairperson: Taylor
Members: Contrera, Defelice, Jean
Participants: Farrelly, DeGeorge

The CAC-EC reviewed the carcinogenicity studies in rats and mice for the R.W. Johnson drug tramadol.

Mice
NMRI mice were administered drug in drinking water (0, 7.5, 15, 30 mg/kg/day) for 24 months. Over the course of the study, there were no signs of significant toxicity (e.g. no effect on survival, body weight gain, clinical pathology parameters or histopathology) except: increased skin edema in low and high dose males and increased renal arteritis in females. Statistically significant increases were reported in hepatocellular adenoma in male mice (9/100, 6/50, 9/49, 12/50) and histiocytic sarcoma in female mice (0/99, 0/37, 1/39, 3/49). The Committee agreed that the hepatocellular adenomas in males and histiocytic sarcomas in females were unlikely to be of biological relevance. The hepatocellular adenomas were within the historical incidence of the tumor. The rate of histiocytic sarcomas was low(6%) in females and males showed a reverse trend with 4% incidence in the controls.

When questioned about the adequacy of dose selection for the carcinogenicity study, the Sponsor provided data from a 3 month "exploratory " study in mice dosed at 30, 60, 120 and 240 mg/kg. In this study, apparently drug-related effects were limited to: decreased body weight in males(4-6% at 120-240 mg/kg) and females (10% at 240 mg/kg); and decreases in water consumption (>15% decrease relative to controls for 6 or more weeks of the 13 week study) in high dose males and females at 30, 60 and 240 mg/kg. Because the drug was administered in drinking water, decreases in water consumption would decrease the administered dose and could complicate the interpretation of the study. The Sponsor argued that sustained decreases in water consumption could, over the course of a 2 year study, result in marked affects on homeostasis and therefore, the dose of 30 mg/kg/day represented the MTD for drug administered in drinking water.

The CAC-EC agreed that additional information was needed before a decision could be made concerning the adequacy of dose selection for the mouse study. The Committee recommended that the Sponsor perform complete histopathology on all study animals in the 3 month exploratory study and submit the data for review. (Originally, histology was limited to the liver and kidneys from 5/10 control and high dose animals and gross lesions in all groups.) A final recommendation on the adequacy of dose selection in mice (and validity of the study) will be made after an evaluation of the requested data.

It is noted that the relative AUCs (rodent human) for the parent drug at the high dose of 30 mg/kg tested in the carcinogenicity studies were quite low and less than 1 in mice (0.09) and rats(0.74).

Rat
Tramadol was administered to Wistar rats at 0-30 mg/kg/day for 30 months. There were no treatment-related organ-specific toxicities or evidence on increased tumor incidence in the study. Significant decreases(10-20%) in body weight in males and females over the course of the study was the primary evidence that a maximum tolerated dose had been utilized in the study. The CAC-EC agreed that this study was valid and acceptable.

Recognizing the safe human use of the compound, marketed in foreign countries for many years, and the lack of carcinogenic potential in an acceptable rat study (and marginal mouse study), the CAC-EC recommended that any repeat of the mouse study, if needed, could be performed post-marketing. Some raised concerns about the positive activity of tramadolin the mouse lymphoma assay with activation. However, it appeared that the compounds metabolism to formaldehyde in vitro, was a reasonable explanation for this activity.

cc:
NDA 20-281
HFD-007/div file
/Geyer
/Jean
HFD-502/cac file

APPENDIX II

NDA #20-281

ADDENDUM to Pharmacology Review of November 29,1994

submitted November 29,1994

CORRECTIONS AND ADDITIONS TO THE CAC SUBMISSION

Relative AUC Values for Mice, Rats and Man After Repeated Oral Dosing

tramadol	dose (mg/kg)	dose (mg/M^2)	AUC (ng.h/ml)	AUC_{rodent} / AUC_{human}
mouse[a]	30	(x3=) 90	329 (164)[s]	0.089 (0.06)[sr]
rat[b]	30	(x5.9=) 177	2727 (2118)[s]	0.741 (0.799)[sr]
man[c]	(100/70) 1.43	(x37=) 52.9	3679 (2649)[s]	-

a. DM-94301 (V1/1:3/30/94:p4-5) NMRI mice 30 mg/kg/day X 14 days [tram(+)+(-)♂+♀/2]
b. wistar rats (V19/19:p0562) DM-92337 [tram(+)+(-)♂+♀/2] - 30 mg/kg/day X 14 days
c. man DM-93314, 100 Q.I.D. for 29 doses (V01/0023)
s. single dose of 100 mg (V01/0022) in man and 30 mg/kg in rodents.
sr. single dose ratio

In AUC values, the rodent exposures were less than the human exposure by factors from 0.089 to 0.741. This is much less than the 25X increase stated as a general guidance. The ratio values do not change significantly when single dose values are compared.

The half-life was about 2-3 hrs in the rodents and 6 hrs in man. This indicates that the 28 days of administration to the rodents was probably only representative of multiple doses and not the

steady-state as seen in man.

Harry M. Geyer, III Ph.D.

In concurrence
Peer Reviewer Dou Jean, Ph.D. Dec. 16, 1994
date

cc
Addendum to NDA#20-281
HFD-007/Div. File
HFD-007/HMGeyer
HFD-007/Cmoody
HFD-345
R/D Init by
F/T by HMGeyer
WP#tramaddl.cac

APPENDIX III

NDA #20-281

ADDENDUM to Pharmacology Review of November 29,1994

submitted December 13, 1994
(Carcinogenicity Section)

Additional data from peripheral 1 month mouse dose-ranging study:

There were 4 early deaths, 1 control, one from 60 mg/kg/day and one from 240 mg/kg/day group. Urethral plugs and blood collection trauma were listed as causes of death. No death was considered treatment related.

Five male and female mice per treatment group were necropsied at study completion and the other four or five mice per sex were necropsied two days later. Gross observations were recorded. No histopathological observations were associated with any treatment.

The livers and kidneys of 5 ♂ and 5♀ mice were examined for histopathological changes in the controls and high dose groups (240mg/kg/day). The lesions, mainly mild inflammatory infiltrates of kidney and liver, were considered spontaneous and not treatment related.

Harry M Geyer III
Harry M. Geyer, III Ph.D.

In concurrence:
Peer Reviewer — Hou Jean, Ph.D. — Dec. 16, 1994 — date

cc:
Addendum to NDA#20-281
HFD-007/Div. File
HFD-007/HMGeyer
HFD-007/CMoody
HFD-345
R/D Init by
F/T by HMGeyer
WP#ltrsmaddl...

2025/1

EA

MOODY

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

Date: June 15, 1994

From: Asoke Mukherjee Ph.D., HFD-007/102

Through: Phillip G. Vincent Ph.D., HFD-102

Subject: EA for Tramadol hydrochloride, NDA 20-281

To: Corinne Moody, HFD-007

The initial review for environmental assessment of above mentioned NDA has been completed. Following recommendations and comments have been suggested by the reviewer.

For item #4:

1. Provide types of environment present around the German and Delaware facilities. Also provide EPA certificates for each incineration site. The emission from incinerators should meet local, state and federal standards.

For item #5:

2. Provide list of chemicals used in the synthesis of Tramadol hydrochloride with CAS # and physicochemical properties in this section. Also provide a list of impurities for the synthesis of Tramadol if known.

For item #6:

3. Provide estimated amount of the dust that would be released in the air and that would be washed into the waste water system from each manufacturing site in Germany, Delaware, Pennsylvania and Puerto Rico for the drug substance per year basis for the fifth year of production. If packaging materials containing polyethylene and polypropylene used for packaging, storage of drug products and any other waste are planned to be incinerated, provide the emission of its pyrolysis products per year basis. Provide state, federal and local standards for emission of these products at each incineration site.

Also provide list of chemicals other than the drug substance that would be released in the environment per year from the manufacturing of the drug substance at German and Delaware sites, and manufacturing of the drug product at the Spring House and Puerto Rico sites. Type of control institutionalized to minimize environmental exposure of these chemicals need to be discussed. Provide copy of certificates to substantiate the environmental safety for plant according to the state, local and

federal authorities.

For item #8:

4. Subacute toxicity of tramadol base in earthworm needs to be determined for predicting its impact in soil and terrestrial environment.

For item #9:

5. Provide a list of chemicals and packaging materials to justify that none of these would have any effect on the endangered species.

For item #11:

6. All solid waste and plant washing from the manufacturing of the drug substance and the drug product should be incinerated for avoiding aqueous and terrestrial effect of Tramadol. This recommendation has been made with the consideration that Tramadol would degrade slowly in the environment to generate anisole and other products that may have environmental impact. Beside this possibility, inhibitory effect of Tramadol on microorganisms may be detrimental to the environment.

For item #12:

7. Provide academic qualifications of the preparer in this section also.

For item #15:

8. Identify which charts and appendices would be considered as confidential documents and list them separately in this section.

Endorsements:

HFD-007/102 Asoke Mukherjee, Ph.D.
Pharmacologist

HFD-102/ P.G. Vincent, Ph.D.

JUN 28 1994

C.C Original NDA 20-281
EA file
Divisional file/ HFD-007
Supervisory Chemist/ HFD-007

20281E00.LAM
F/T AM

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-281

ULTRAM® (Tramadol Hydrochloride) Tablets

50 and 100 mg

HFD-007 REVIEW DIVISION

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-102

DATE COMPLETED: December 8, 1994

ENVIRONMENTAL ASSESSMENT

1. **Date:**

NDA submitted:	?
EA review #1:	06/14/1994
Deficiency letter:	08/10/1994
EA revised:	11/02/1994
Consult to HFD-102	11/22/1994
Assigned:	11/30/1994
Telecon:	12/02/1994
Response/Telecon:	12/02/1994

CSO: Corinne Moody

2. **Name of applicant/petitioner:**

The R. W. Johnson Pharmaceutical Research Institute

3. **Address:**

Welsh & McKean Roads
Spring House, PA 19477-0776

RESPONSE TO DEFICIENCY LETTER OF August 10, 1994:

Note: The company has submitted a complete copy of the EA. Only those sections which have been revised have been reviewed as the remaining information was reviewed by Dr. Mukherjee on June 14, 1994.

Note: The environmental assessment has deleted reference to manufacture of the drug product at the Spring House, PA facility. The company states that the NDA was amended on 1/20/1994 to delete this manufacturing facility. this was confirmed by Corinne Moody of HFD-007

For Item #4:

1. Provide types of environments present around the German and Delaware facilities. Also provide EPA certificates for each incineration site. The emission from incinerators should meet local, state and federal standards.

   RESPONSE: The types of environments have been provided for the German and Delaware facilities. The EPA certificates have been provided. Adequate.

For item #5:

2. Provide list of chemicals used in the synthesis of Tramadol Hydrochloride with CAS # and physicochemical properties in this section. Also provide a list of impurities for the synthesis of Tramadol if known.

   RESPONSE: The list of chemicals used in the synthesis with CAS #'s and physicochemical properties are included in Appendix C. Adequate. The impurities with specifications are provided in the non-confidential section. Adequate. This should be redacted from the public EA.

For item #6:

3. (1) Provide estimated amount of the dust that would be released in the air and that would be washed in to the waste water system for each manufacturing site in German, Delaware, Pennsylvania and Puerto Rico for the drug substance per year basis for the fifth year of production. (2) If packaging materials containing polyethylene and polypropylene used for packaging, storage of drug products, and any other waste are planned to be incinerated, provide the emission of its pyrolysis products per year basis. (3) Provide state, federal and local standards for emission of these products at each incineration site.

   (4) Also provide a list of chemicals other than the drug substance that would be released in the environments per year from the manufacturing of the drug substance at German and Delaware sites, and manufacturing of the drug product at the Spring House and Puerto Rico sites. (5) Type of control institutionalized to minimize environmental exposure of these chemicals needs to be discussed. (6) Provide copy of certificates to substantiate the environmental safety for Normaco plant according to the state, local and federal authorities.

RESPONSE:

(1) The quantities are provided. All wastewater is collected and incinerated. No air emissions are expected at the German or Delaware facilities, 1.5 kg/year at Puerto Rico. Adequate.
(2) The kg's of packaging material are provided. They provide information to support that pyrolysis products are not an issue.
(3) Regulations vary from state to state but many require the emissions of par iculates and acid emissions be controlled. A summary of the emission requirements is provided in appendix P. The typical emission controls are stated. All incinerators used meet regulatory requirements. Adequate.
(4) The expected emitted substances are provided. Adequate.
(5) Bag filters, scrubbers or condensers and spill prevention diking are used at the drug substance manufacturing plants. Fabric bag dust collectors and dry clean-up procedures prior to equipment washing limits the emissions at the drug product manufacturing facility.
(6) Current permits for the Normaco facility are provided.

For item #8:

4. Subacute toxicity of tramadol base in earthworm needs to be determined for predicting its impact in soil and terrestrial environment.

RESPONSE: If all Tramadol hydrochloride were to adhere to sludge, the concentration in the sludge would be about and the mg tramadol as the base/kg. The test method followed Toxicity is not indicated. Adequate.

For item #9:

5. Provide a list of chemical and packaging materials to justify that none of these would have any effect on the endangered species.

RESPONSE: The list of chemicals and identification of packaging material is provided. Adequate. The usage and disposal practices will ensure that there will be no impact on endangered species. Adequate.

For item #11:

6. All solid waste and plant washing form the manufacturing of the drug substance and the drug product should be incinerated for avoiding aqueous and terrestrial effect of Tramadol. This recommendation has been made with the consideration that Tramadol would degrade slowly in the environment to generate anisole and other products that may have environmental impact. Beside this possibility, inhibitory effect of Tramadol on microorganisms may be detrimental to the environment.

RESPONSE: The pharmaceutical solid wastes and cleaning residues containing tramadol will be isolated and incinerated, where possible, to avoid environmental impact. Adequate.

For item #12:

7. Provide academic qualifications for the preparer in this section also.

RESPONSE: The information is provided. Adequate.

For item #15:

8. Identify which charts and appendices would be considered as confidential documents and list them separately in this section.

RESPONSE: The confidential appendices have been identified. Appendix B, D, J and K must be non-confidential.

Comments:
On 12/2/1994, Dr. Horowitz was contacted and asked to confirm the locations of use of the product and to label Appendices B, D and J as non-confidential appendices. This information was FAXED on December 2, 1994.

Corinne Moody confirmed receipt of the official copy and also confirmed that the NDA was amended to delete the Spring House PA. Facility on 12/08/1994.

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

ULTRAM®

(Tramadol Hydrochloride Tablets)

50 and 100 mg

NDA 20-281

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-007

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-281

ULTRAM®

(Tramadol Hydrochloride)

Tablets

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and search has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **ULTRAM®**, **R.W. Johnson Pharmaceutical Research Institute** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Tramadol hydrochloride is a synthetic opiate agonist analgesic drug which is administered orally for management of pain in humans. The drug substance will be manufactured at

The drug product will be manufactured by McNeil Pharmaceutical Company, Dorado, Puerto Rico. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Chemical and physical testing results indicate that the product would most likely be restricted to the aquatic environment with no appreciable partitioning into the atmospheric or terrestrial environments. The product does not rapidly biodegrade under aerobic conditions or photodegrade in the aquatic environment.

As Tramadol hydrochloride is expected to persist in the environment for some time, the acute toxicity of the compound was characterized. Acute static toxicity studies in *Daphnia magna* and bluegill sunfish (*Lepomis macrochirus*) and a subacute toxicity study in earthworms (*Lumbricus terrestris*) were conducted. The data indicates that the drug substance is not toxic to the organisms at concentrations of at least 4 orders of magnitude greater than the maximum expected environmental concentration (MEEC).

Microbial inhibition studies indicate that environmental microorganisms are not inhibited at concentrations of at least 4 orders of magnitude greater than the maximum expected environmental concentration (MEEC).

Disposal of the drug substance may result from out of specification lots, production waste, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Pharmaceutical waste generated at and McNeil Pharmaceutical Company will be disposed of by incineration where possible. In the United States, returned or rejected drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. For home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system or in a sanitary landfill while some unused drug may be disposed of in the sewer system.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Grünenthal GmbH has received authorization from the appropriate authorities to operate the plant and has provided certification that operation is in accordance with applicable German environmental regulations.

12/9/94 Nancy B Sager
DATE

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Attachments: Environmental Assessment
FDA Addendum to Environmental Assessment

Data Summary Chart
Material Safety Data Sheet (drug substance)

ENVIRONMENTAL ASSESSMENT

NDA 20-281

ULTRAM® TRAMADOL HYDROCHLORIDE

III. ENVIRONMENTAL ASSESSMENT

LIST OF APPENDICES

LIST OF APPENDICES

Chemistry, Manufacturing, and Controls Information - Environmental Assessment

1.0 DATE

February 1, 1993

(Revised November 2, 1994)

2.0 NAME OF APPLICANT/PETITIONER

The R.W. Johnson Pharmaceutical Research Institute

3.0 ADDRESS

Welsh & McKean Roads
Spring House, PA 19477-0776

4.0 DESCRIPTION OF THE PROPOSED ACTION

4.1 Need for Action

We are requesting the approval of an application for the manufacture of ULTRAM® tramadol hydrochloride 100 mg and 50 mg tablets. Tramadol hydrochloride is a synthetic opiate agonist analgesic to be marketed to the management of pain in humans.

4.2 Manufacturers of Drug Substance

will be preparing drug substance using the same synthetic steps. The addresses of the drug substance manufacturers are provided below.

4.2.

4.2.1.1 Plant Address

4.2.1.2 Administrative Address

4.2.1.3 Grünenthal Drug Master File Information

A complete description of the synthesis of tramadol hydrochloride, along with a certification of compliance with Germany's environmental laws, is provided in Type II Drug Master File (DMF) No. , which was submitted to the FDA on August 5, 1992.

4.2.2

4.2.2.1 Plant Address

4.2.2.2 Administrative Address

Johnson & Johnson
410 George Street
New Brunswick, New Jersey 08901-2023

4.2.2.3 ___ Drug Master File Information

A complete description of the synthesis of tramadol hydrochloride, along with an assessment of environmental impact, as conducted by . is provided in their Type II Drug Master File (DMF) No. , which was submitted to the FDA on August 7, 1992.

4.3 Names and Addresses of Manufacturers of Drug Product

McNeil Pharmaceutical Company
KM 0.8, Route 698
P.C. Box 710
Dor. PR 00646-0710

4.4 Usage and Disposal

Tramadol hydrochloride tablets will be used by individuals throughout the United States.

Returned and rejected tramadol hydrochloride tablets will be sent to incinerators that are designed to treat waste pharmaceuticals. The incinerators used by McNeil Pharmaceutical are operated at temperatures in excess of 1500°F and have gas residence times greater than one second. In addition, the incinerators are equipped with air pollution control scrubbers and bag filter houses. These control equipments remove acid vapors and particulates that may be generated as by-products of incineration. All are permitted by their respective environmental regulatory agencies to treat pharmaceutical wastes, such as tramadol hydrochloride and packaging.

Incinerators used by McNeil Pharmaceutical in the past include ones that are operated by

4.5 Type of Environment Present and Adjacent Manufacturing and Disposal Locations

The Delaware facility is located on the banks of the Christina River, in a light industrial area adjacent to a residential neighborhood, in Wilmington, Delaware, U.S.A. Wilmington is in a coastal area of low rolling hills with a temperate climate.

There are no incinerators at the facility. All hazardous waste sent off-site for incineration is directed to EPA permitted facilities listed below:

Certifications for their operation are provided in **Appendix A**. The incinerators are capable of treating a wide range of hazardous and non-hazardous waste while complying with emission limits set for them in their permits.

The German facility, owned b . is located in the

The production plant for tramadol hydrochloride occupies an area of 391 square meters within a total company area of 120,000 square meters. The topography around the plant is flat to hilly and the climate is temperate.

4.5 Type of Environment Present and Adjacent Manufacturing and Disposal Locations Continued

Three waste streams are generated from manufacturing tramadol hydrochloride:

A) Aqueous waste containing solvents and organic residues

B) Industrial waste water (cooling and/or cleaning water)

C) Pharmaceutical waste

The waste streams A and C are incinerated. Waste stream A is collected in a separate storage tank. Disposal of this waste stream is performed by specialized companies authorized by the local government, the Waste stream C is also disposed by authorized companies with the permission of the local government. The emissions from the incinerators meet federal (German) standards. Waste stream B is collected in a separate basin for industrial waste waters. After neutralization, the industrial waste water stream is combined with sanitary water and released to the local sewage plant. is authorized by the German government to synthesize tramadol hydrochloride and is able to comply with Germany's environmental laws. The certification of compliance is provided in **Appendix B**.

The McNeil Pharmaceutical Company facility in Puerto Rico is located in a commercial and residential area, in a flat to hilly region on the north coast of the island. The climate is tropical.

4.5 Type of Environment Present and Adjacent Manufacturing and Disposal Locations Continued

The incineration facilities that have been used for the disposal of returned or rejected products are located in New Orleans, Ohio, South Carolina and New York. These incineration facilities are usually located in rural or commercial areas. The terrain surrounding these facilities varies from flat to hilly. Certifications for their operation are provided in **Appendix A**.

5.0 IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION

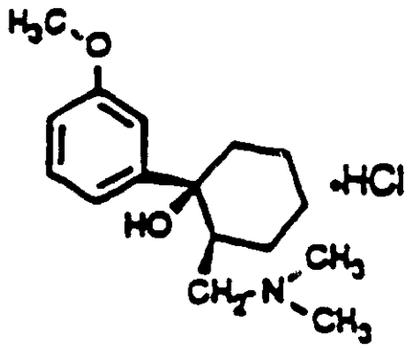
5.1 Active Ingredient

The active ingredient is tramadol hydrochloride (CAS Registry Number: 36282-47-0)

5.1.1 Chemical Name

(+/-)-*cis*-2-[Dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol Hydrochloride

5.1.2 Structural Formula



5.1.3 Molecular Formula

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

5.1.4 Molecular Weight

263.37/299.84

5.1.5 General Properties

A list of chemicals used in the synthesis of tramadol hydrochloride with CAS number and physicochemical properties is provided in **Appendix C.**

The following is a list of known impurities for the synthesis of tramadol with acceptable limits for each:

IMPURITY	LIMIT
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Tramadol hydrochloride drug substance was evaluated for the following physical and chemical properties: organoleptics, crystallinity, thermal properties, hygrodynamics, dissociation (pKa) and partitioning, solubility, and solid state and solution stability.

The results of these evaluations are summarized below and in the Data Summary Chart in **Appendix D.** For a more complete discussion of these results, please refer to **Appendices E, F, G, and H** of this Environmental Assessment. The reports in **Appendices E, F, and G** were also provided in **Attachments 3, 4, and 5** of the Chemistry, Manufacturing and Control (CM&C) Section.

5.1.5.1 Organoleptics

Tramadol hydrochloride is an odorless, bitter-tasting, white crystalline powder.

5.1.5.2 Crystallinity

Tramadol hydrochloride is monotropic.

5.1.5.3 Thermal Properties

The capillary melting range is between 180.2°C and 182.0°C. The heat of melting is between 26.5 and 28.6 cal/g.

5.1.5.4 Hygrodynamics

Tramadol hydrochloride is neither hygroscopic nor deliquescent.

5.1.5.5 Dissociation and Partitioning

The pKa determined by potentiometric titration and regression modeling is 9.41 at 23°C. The n-octanol/water apparent partition (distribution) coefficient at pH ca. 7 is 0.189 at both 23 to 24°C and at 37°C. After correction for dissociation, the calculated true log (P)s are 1.35 at 23 to 24°C and 1.83 at 37°C.

5.1.5.6 Solubility

The solubility of tramadol hydrochloride exceeds 200 mg/mL (expressed as tramadol free base) in water, pH adjusting solutions and aqueous buffers in the pH range 0.86 to 7.72. A solution in water containing 245 mg/mL has a pH of 5.30.

5.1.5.7 Solid-state and Solution Stability

Accelerated degradation studies were conducted with tramadol hydrochloride to determine the solid-state and solution stability of the drug substance and its route of degradation. A detailed report of these studies is provided in **Appendix G**.

Tramadol hydrochloride drug substance in the solid-state demonstrated excellent stability under conditions of extreme stress. No degradation was observed when tramadol hydrochloride solid was irradiated with 300 nm light for two months, nor was any degradation observed when tramadol hydrochloride solid was kept for two months at 100°C and 200 psi oxygen. Photo-degradation of tramadol hydrochloride aqueous solutions occurs after exposure to either high intensity 300 nm light (five hours) or with long exposure (two months) to high intensity visible light. Two products are formed when tramadol hydrochloride is degraded in water by light. These products are anisole and dimethylaminocyclohexanone (DMAC).

5.1.5.7 Solid-state and Solution Stability continued

Aqueous solutions of tramadol hydrochloride were exposed to natural sunlight following the procedures in FDA Technical Assistance Document 3.10. It was determined that sunlight does have a slight degradation effect. With an ambient temperature range between 5.0 and 45.3°C, tramadol hydrochloride has a total sunlight exposure half-life of 227, 329, and 36.2 days at pH 5, 7, and 9, respectively. A detailed report of this study is provided in **Appendix H.**

5.2 Inactive Ingredients

Material Safety Data Sheets for all ingredients are provided in **Appendix I** of this Environmental Assessment.

5.3 Packaging Materials

Opaque high density polyethylene bottles with polypropylene enclosures; Aclar® unit-dose blisters with aluminum foil and paper backing materials; paperboard cartons and corrugated boxes for secondary packaging.

6.0 INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Manufacturing of Drug Substance

As stated in Section 4.0, the drug substance is manufactured at

Both companies will submit assessments of the environmental impact relating to the synthesis of tramadol hydrochloride in their respective Type II Drug Master File (DMF).

Both manufacturing locations are able to maintain compliance with their respective permit standards with the production of tramadol hydrochloride. A compliance statement fron is included in **Appendix J.** **Appendix K** includes a letter from the Aachen to certify tha is permitted to produce tramadol hydrochloride at its facility under the current applicable environmental laws of the Federal Republic of Germany.

6.2 Manufacturing of Drug Product

Tramadol hydrochloride is not listed as a hazardous waste under the EPA Resource Conservation and Recovery Act (RCRA) of May 19, 1980, as amended.

6.2.1 Overview

A flow chart showing the sequence of operations regarding the manufacturing of tramadol hydrochloride tablets is shown in Figure 1 on the following page.

6.2.2 Transportation and Storage

The raw materials for manufacturing the tablets are transported to the site from various suppliers. Materials are transported and stored in polyethylene bags. The polyethylene bags are protected against damage during handling by enclosure in a fiber drum with a metal or plastic cover and lockrim, or a corrugated box, or some other rigid outside protective cover. Storage is in a dry area. No raw material is introduced into the environment during transportation and storage.

Figure 1: Introduction of Substances Into the Environment - Tablet Manufacturing

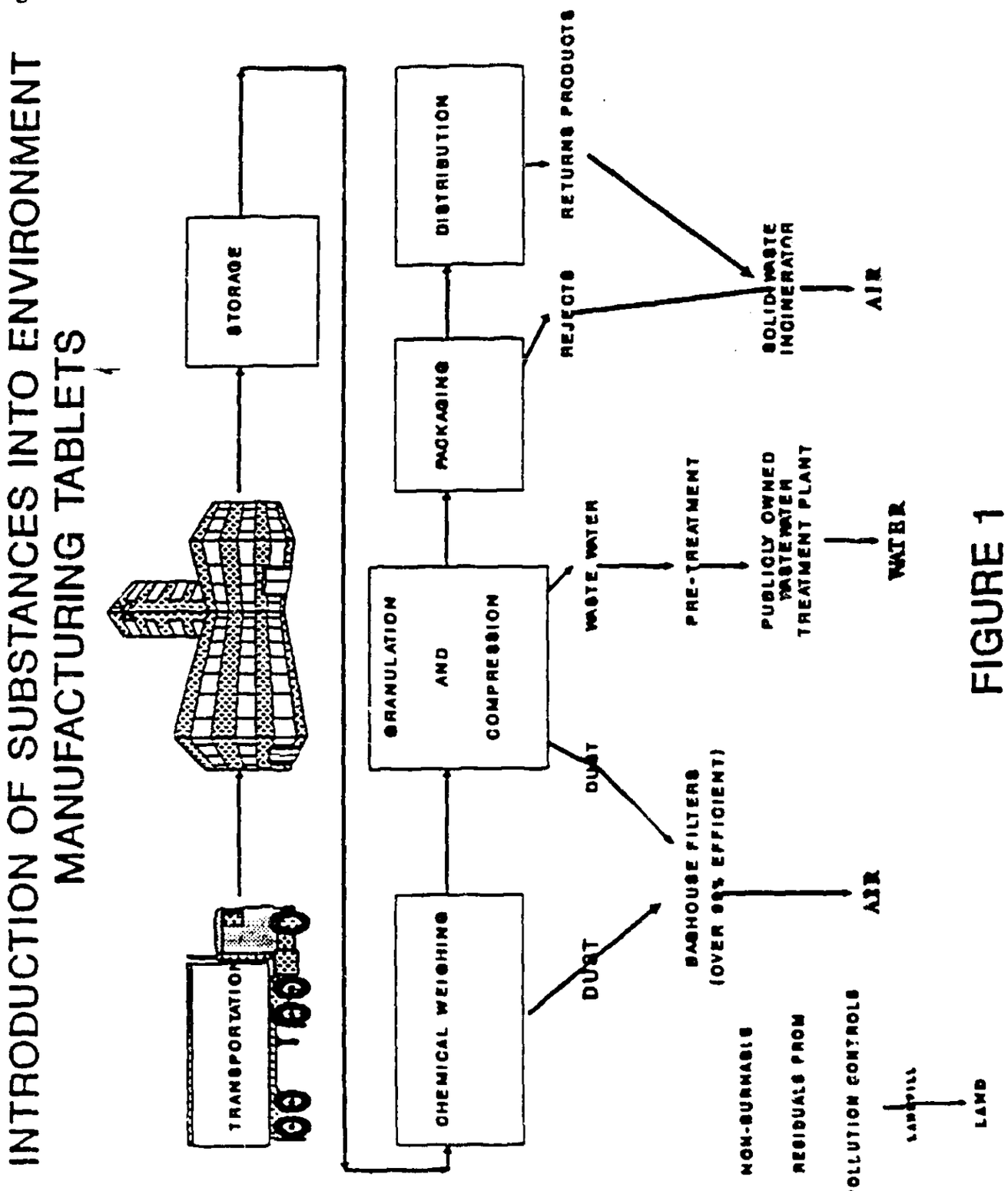


FIGURE 1

6.2.3 Chemical Weighing

All solid materials used in the process are weighed in an enclosed room.

Dust generated in the operation is controlled at the point of generation and collected in fabric bag dust collectors. Such filters have over 99.9% efficiency in removing the entrained dust from the inlet air. The clean air is exhausted into the environment. Fabric filter systems at the McNeil Pharmaceutical facility at Dorado, PR are covered under air discharge permits issued by the appropriate regulatory agencies. Copies of the air permits are provided in **Appendix L** of this environmental assessment. Manufacturing tramadol hydrochloride tablets is allowed under the existing air permit standards.

6.2.4 Granulation, Compression, Coating and Printing

In the granulation, the ingredients are screened, blended, granulated and dried. These batches are tabletted using tablet compression equipment. The tablets are then coated with an aqueous-based coating. The coated tablets are imprinted with the product name and other identification, if applicable.

6.2.4 Granulation, Compression, Coating and Printing continued

The process details are described in **Appendix M** of this environmental assessment. Dust generated from all operations or transfers is captured at the source and is collected in the previously referenced dust collectors and filters. The filters are cleaned, and the waste handled as a non-hazardous waste, based on the EPA Resource Conservation & Recovery Act (RCRA) of 1980 as amended. The solid waste is either landfilled or incinerated in permitted facilities.

Dry-cleanup methods such as vacuuming and wiping are used to minimize any drug materials going to sewer. Wastewater is generated from equipment and facility cleaning. Wastewaters from the production site in Dorado, PR goes to off-site publicly owned wastewater treatment plants. At the Dorado, PR facility, all of the facility's wastewater is neutralized and biologically treated on-site before being discharged to the city of Dorado's wastewater treatment plant. Treated effluent from the treatment plant is discharged into a fresh water river. Copies of the wastewater discharge permit for the Dorado, PR facility are provided in **Appendix N** of this environmental assessment. Manufacturing tramadol hydrochloride tablets is allowed under the existing wastewater permit standards.

6.2.5 Packaging

The drug product many be packaged in unit dose blisters or in opaque high-density polyethylene (HDPE) containers with polypropylene closures.

No drug product is expected to be discharged to air or water as a result of the packaging process. Rejected packaging materials are incinerated or landfilled in permitted facilities. As recyclers of plastics and paper products become available, McNeil Pharmaceutical will seek ways to conserve natural resources by sending rejected packaging materials to approved and permitted recycling facilities.

6.2.6 Warehouse and Distribution

No drug product is expected to be discharged to air or water as a result of the warehouse and distribution process.

Any products returned to the distribution warehouses will be destroyed at permitted incineration facilities.

6.3 Summary - Tramadol Hydrochloride Introduced to the Environment as a Result of Tablet Manufacturing

6.3.1 Production Level Basis

Based on projections kg/year is the maximum annual amount of the active drug to be produced in the first five years following product introduction[1].

To assess the daily emissions, we can assume a maximum of two batches per day. Each batch contains of tramadol hydrochloride. Batch yields are typically greater than 96%[2]. This results in less than of tramadol hydrochloride being lost to the environment from all aspects of the production of each batch.

6.3.2 Air Emissions

Of the estimated of tramadol hydrochloride lost per batch, it is projected that is sent to fabric bag dust collectors.[2] The dust collected is packaged for disposal as a non-hazardous waste. Such dust collectors have over 99% capture efficiencies, meaning that less than 0.005 kg of tramadol hydrochloride is discharged into the air environment per batch produced.

Tramadol hydrochloride is non-volatile. This is confirmed by calculations in **Appendix O** "Vapor Pressure Calculation."

6.3.3 Water Discharges

It is expected that of tramadol hydrochloride per batch would be lost in equipment or lost during material transfer.[2] The material is vacuumed and packaged for disposal. Using dry clean-up techniques, we expect that close to all of the tramadol hydrochloride lost in equipment or lost during material transfer would be captured for disposal as a solid waste. As a worst case scenario for wastewater discharge, we can assume that 1% of the of tramadol hydrochloride or is washed into the sewer during equipment cleaning. At the manufacturing location, the wastewaters flow to publicly owned wastewater treatment works (POTW). The POTW has secondary biological treatment to remove dissolved organics.

6.3.4 Discharge to Land

It is expected that an average of about 2 kg of tramadol hydrochloride per batch would be rejects and would be disposed as solid waste.[2] Total solid waste includes the Kg from dry clean-up, Kg from dust filters, and this from rejects. Therefore, Kg active/batch or abou Kg active/batch would be disposed as solid waste. Solid wastes from manufacturing, returned goods, and reject products are sent to incinerator sites that have been approved by governmental agencies. The residues from the incinerator facilities and any non-burnable materials are landfilled at government approved sites. Normally, no tramadol hydrochloride is released to the land as a result of tablet manufacturing.

6.4 Releases With Use

Tramadol hydrochloride is expected to enter the water environment as a result of use. The maximum expected emitted concentration (MEEC) is calculated below: [3]

Parts per million (ppm) in environment = A·B·C·D·E·F

where:

A = pounds/year product

B = year/365 days

C = day person/150 gallons

D = 1/(246 million persons-population of U.S.)

E = gallons/8.34 pounds

F = one million

Using) tramadol hydrochloride per year, the parts per million in environment is calculated to be 0.0007 ppm. Tramadol hydrochloride will most likely be present in the water, rather than the air or soil environment.

6.5 Concentration of tramadol hydrochloride in the soil and terrestrial environment based on all of the tramadol hydrochloride being in the sewage treatment sludge

Based on the octanol/water coefficient and water solubility, we believe that tramadol hydrochloride will be in the water compartment; however, as a worst case scenario, we will calculate the concentration of tramadol hydrochloride in the soil and terrestrial environment based upon all of the tramadol hydrochloride being in the sewage treatment plant sludge.

6.5 Concentration of tramadol hydrochloride in the soil and terrestrial environment based on all of the tramadol hydrochloride being in the sewage treatment sludge Continued

Assuming that Kg/person/day of wet sludge is produced[4] and using the numbers from Section 6.4, the pound of tramadol per pound of sludge is:

$$\frac{\text{lbs tramadol HCl}}{\text{year}} \times \frac{\text{Year}}{365\ \text{days}} \times \frac{\text{day - person}}{0.44\ \text{Kg sludge}} \times \frac{\text{Kg}}{2.2\ \text{lb}} \times \frac{\text{U.S. population}}{246\times10^{6}\ \text{persons}} \cdot \times 10^{7}\ \frac{\text{tramadol HCl}}{\text{sludge}}$$

In terms of parts per million, this becomes: $\frac{\text{parts tramadol HCl}}{10^{6}\ \text{parts of sludge}}$

Therefore, as a worst case scenario, if all of the tramadol hydrochloride used were to be adhered to sewage treatment plant sludge, the concentration in the sludge is estimated to be about 0.93 parts per million. Because of the high water solubility of tramadol hydrochloride, we do not believe that the 0.93 ppm concentration in the sludge would be reached.

6.6 Estimated amount of dust that would be released into the air and that would be washed into the waste water system from each manufacturing site in Germany, Delaware, Pennsylvania, and Puerto Rico

ANNUAL AMOUNT OF DUST RELEASED IN 5TH YEAR OF PRODUCTION

SITE	AIR	WASTEWATER TREATMENT
Ortho-McNeil Spring House, PA[1]		
Ortho-McNeil Dorado,Puerto Rico		Kg/year - worst case, however, this material will be isolated and incinerated where possible.

[1] The NDA was amended on 1/20/94 to delete Spring House as a manufacturing facility.

6.7 Discussion of Packaging Material Disposal

PACKAGING MATERIALS	ESTIMATED AMOUNT USED IN 5TH YEAR OF PRODUCTION (Kg or pounds)
1)	
2)	
3)	
4)	
5)	

At the manufacturing facilities, paper and cardboard packaging materials are generally sent to recyclers. Recyclers for plastics such as high density polyethylene (HDPE) and polypropylene (PP) are also used when they are available. If the materials were incinerated, the emission products from the combustion process would be mostly water and carbon dioxide. A discussion of incineration is provided below.

The typical commercial incinerators for waste disposal will completely oxidize the waste at temperatures over 1500°F and hold the gases at residence times of 0.5 to 2.0 seconds. The theoretical combustion products are generally estimated as follows[5]:

- All chloride converts to hydrogen chloride, HCl
- All carbon converts to carbon dioxide, CO_2
- All sulfur converts to sulfur dioxide, SO_2
- Alkali metals convert to hydroxides: sodium to sodium hydroxide ($2Na + O_2 + H_2 \rightarrow 2NaOH$) and potassium to potassium hydroxide ($2K + O_2 + H_2 \rightarrow 2KOH$)
- Nonalkali metals convert to oxides : copper to copper oxide ($2Cu + O_2 \rightarrow 2CuO$), iron to iron oxide ($4Fe + 3O_2 \rightarrow 2Fe_2O_3$).
- All nitrogen from the waste, fuel, or air will take the form of a diatomic molecule; i.e., nitrogen is present as N_2.

6.7 Discussion of Packaging Material Disposal Continued

Pyrolysis, the degradation of carbonaceous material in the absence of oxygen, or air, upon the application of heat, is generally not a predominate mechanism used to destroy waste in commercial incinerators. Combustion, the drgradation of materials at greater than the stoichiametric amount of oxygen, is the mechanism which predominates.

Regulations in many states require that the emissions of particulates and acid gases be controlled by incinerator facilities. Particulates are controlled by cyclonic separation, bag filters, and/or wet scrubbers. Acid gases are controlled by wet scrubbers using caustic soda (NaOH) or lime ($Ca(OH)_2$). For example, hydrogen chloride (HCl) scrubbing would yield sodium or calcium salt and water as by-products:

$$HCl + NaOH \rightarrow NaCl + H_2O$$
$$2HCl + Ca(OH)_2 \rightarrow CaCl_2 + 2H_2O$$

The incineration of packaging materials containing polyethylene, polypropylene, paperboard, drug products and other wastes would yield mostly water vapors, carbon dioxide, nitrogen and trace amounts of hydrogen chloride and sulfur dioxide. The hydrogen chloride and sulfur dioxide would be further controlled by wet scrubbers. All incinerators used for the disposal of waste meet regulatory requirements. State standards for incinerators vary from state to state (summary provided in **Appendix P**). Based on the chemical components of the packaging materials and other wastes generated from the manufacturing sites of tramadol hydrochloride, it is not expected that incinerator sites will have any problems in combusting these materials.

6.8 Other Substances Emitted into the Environment

During the manufacturing of the drug substance at the German and Delaware sites, volatile organic compounds and non-volatile dusts may be emitted into the air. The list of compounds are provided in Section 5 and **Appendix C**. It is expected that no more than of volatile substances are volatized per of tramadol hydrochloride produced[6]. Based on projections, Kg/year is the maximum annual amount of tramadol hydrochloride to be produced in the first five years following product introduction. Therefore, about Kg of volatile substances/year will be released into the exhaust air. The exhaust air of the reactors is filtered by scrubbers and/or condensors. Bag filters are used for control of dust and particulate emissions. In the case of the facility, the facility is permitted by the German government to manufacture tramadol hydrochloride. A statement of compliance is provided in **Appendix K**.

At the facility in Delaware, the environmental emissions are controlled by condensors, bag filters, and scrubbers. The emission control equipment and the processed are governed by the Delaware Department of National Resources and Environmental Conservation (DNREC). Copies of the permits for the plant are provided in **Appendix Q** and **Appendix N**.

In addition to the control equipment, both facilities have spill prevention diking to ensure that spills do not contaminate the environment. The production employers are trained at least annually on how to prevent hazardous spills and to reduce the generation of waste.

6.8 Other Substances Emitted into the Environment Continued

During the manufacture of the drug product, inactive ingredients can also be released to the air filters or cleaned to the sewers. These ingredients

It is estimated that less than Kg of inactive ingredients are lost to the environment from all aspects of the production of each batch.

Of the estimated Kg of inactive ingredients lost per batch, it is projected that Kg is sent to fabric bag dust collectors. The dust collected is packaged for disposal as a non-hazardous waste. Such dust collectors have over 99% capture efficiencies, meaning that less than Kg of inactive ingredient is discharged into the air environment per batch produced. On an annual basis, this is approximately Kg.

It is expected that Kg per batch would be lost in equipment or lost during material transfer. Special clean-up practices will be exercised where equipment is cleaned and vacuumed before washed. Since this dry clean-up is effective, we assume that less than 1% of the material lost in equipment or material transfer goes to sewer. Approximately Kg/batch of inactive ingredients is lost to sewer during equipment cleaning. On an annual basis, this is per year. The wastewaters flow to publically owned wastewater treatment works (POTW), where the secondary biological treatment will remove dissolved organics. We expect that the organic inactive ingredients would be biodegraded.

The clean-up residues and rejects from each batch are disposed as solid waste. The amount of inactive ingredients disposed a solid waste is estimated at Kg/batch. On an annual basis, this is Kg. They

6.8 Other Substances Emitted into the Environment Continued

are typically sent to incinerator sites that have been approved by governmental agencies. The air and water permits for the Dorado site are provided in **Appendices L** and **N**, respectively.

7.0 FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The formulation is not volatile. Transfers from dust collectors are carried out in such a manner as to minimize dispersion. Typically, dust is transferred to polyethylene lined fiber drums using collars or sleeves to prevent dispersion to the air. The sealed containers are shipped to a permitted disposal facility. The preferred method of disposal is by incineration.

Material is not released directly to the soil, fresh water, estuarine or marine ecosystems as a result of the manufacturing operation.

Manufacturing operations are conducted according to all applicable Federal, State, and Local regulations, and current Good Manufacturing Practices (21 CFR 210-211), and are carefully monitored to minimize the potential for material losses during processing.

7.1 Fate of Tramadol Hydrochloride

As shown in Sections 5.0 and 6.0 of this environmental assessment, tramadol hydrochloride is extremely soluble in water, very stable as a solid or in solution, and does not have a tendency to bioaccumulate. Therefore, we conclude that tramadol hydrochloride is expected to be in the water ecosystem.

7.1 Fate of Tramadol Hydrochloride (continued)

In the manufacturing process, a small amount (estimated to be less than kg per batch) of tramadol hydrochloride dust is emitted from the air pollution control equipment. A copy of the air permits is attached (**Appendix L**). Normal housekeeping and maintenance procedures call for periodic inspections and cleaning around the air pollution control equipment. It is expected that emitted tramadol hydrochloride would be vacuumed or swept up and disposed as solid waste.

The tramadol hydrochloride generated from the clean-out of air pollution control filters and any rejected materials are packaged and sent to permitted incinerator facilities for treatment. As indicated in Section 6.0 of this environmental assessment, abou kg of tramadol hydrochloride per batch is expected to be disposed of as solid waste. In the incineration process, tramadol hydrochloride would be oxidized to carbon dioxide and water. Any acid vapors produced in the incineration process would be scrubbed and neutralized. A copy of a waste incineration agreement is attached (**Appendix R**).

Wastewater is generated from equipment cleaning. It is estimated that a maximum o kg of tramadol hydrochloride per batch may be washed out from the clean-out.

7.1.1 Fate of Tramadol Hydrochloride Manufactured at Dorado, Puerto Rico

At the Dorado, PR, facility, wastewater is pretreated. Wastewater from the entire facility is generated at a rate between 30,000 and 60,000 gallons per day (gpd).[7] Assuming two batches per day, the concentration of tramadol hydrochloride in the wastewater would be between 0.4 mg/L and 0.9 mg/L. This flow is pumped into an equalization tank to adjust pH, increase dissolved oxygen and add nutrients. The wastewater is then pumped into a aerobic sequential batch biological treatment system to reduce dissolved organics levels and to settle out solids. Wastewater from this pre-treatment process is discharged to the publicly owned treatment works operated by the Puerto Rico Aqueduct and Sewer Authority (PRASA). A copy of the most current PRASA permit is attached (**Appendix N**). This permit is in the process of being renewed.

The PRASA treatment plant in the town of Dorado treats approximately 1.3 million gallons per day (mgd) of wastewater from industrial and residential sources.[8] The plant has primary sedimentation and secondary trickling filters. The treated effluent is discharged into the LaPlata River. The river flows into the Atlantic Ocean one mile downstream of the town of Dorado.

7.2 Results of Wastewater Treatability Testing

Tramadol hydrochloride was tested for acute microbial toxicity, removability in a semi-continuous activated sludge system, and biodegradation under aerobic conditions as indicated in a 28-day CO_2 production test. The test reports are provided in **Appendix S.**

Tramadol hydrochloride exhibited no microbial inhibition at levels as high as 150 mg active used a modification of the standard five day biochemical oxygen demand (BOD) analysis. The test measures the threshold inhibition level of a test compound of a mixed microbial inoculum by measuring the oxidation rate of the inoculum over various concentrations of the test compound and comparing this to the oxidation rate of an easily degradable substance such as glucose. The testing concentration range was 1 to 150 mg active/L.

conducted a Semi-Continuous Activated Sludge (SCAS) Removability Test on tramadol hydrochloride. In this study, activated sludge is exposed to a specific concentration of test substance and the soluble organic carbon is analyzed after a specific time interval to determine the percent soluble carbon remo . Two test units testing tramadol hydrochloride demonstrated % or lower removal. It can be concluded that tramadol hydrochloride was not readily removed in the activated sludge units used in the test.

7.2 Results of Wastewater Treatability Testing continued

conducted a CO_2 Production Test to determine the rate and extent of the ultimate biodegradation of tramadol hydrochloride under aerobic conditions. The results indicate that flasks containing tramadol hydrochloride produced less than 10% of the theoretical CO_2. It can be concluded that tramadol hydrochloride does not readily break down under the conditions of this test.

In summary, it can be concluded that tramadol hydrochloride, at concentrations as high as 150 mg/L, would not inhibit the performance of a biological secondary wastewater treatment plant. The results show that tramadol hydrochloride may pass through a treatment plant and into the receiving stream.

Based on the calculated worst-case concentration at Dorado, PR, (0.9 mg/L maximum), it does not appear that the manufacturing of tramadol hydrochloride would impact the performance of municipal wastewater treatment plant.

7.3 Degradation Mechanism of Tramadol Hydrochloride

Natural sunlight does have a slight degradation effect on tramadol hydrochloride in water. Tramadol hydrochloride has sunlight exposure half-lives of 227, 329, and 36.2 days at pH 5, 7, and 9, respectively. Based on stability studies, tramadol hydrochloride in water degrades with exposure (5 hours) to either high intensity ultraviolet (300 nm) light or with long exposure (2 months) to high intensity visible light. Two products are formed when tramadol hydrochloride is degraded in water by light. These products are anisole and dimethylaminocyclohexanone (DMAC). According to published studies, anisole (methylphenylether) will further decompose by microorganisms in soil or by activated sludge inoculum.[9] Although no degradation data were found for DMAC, the studies indicate that dimethylamine and cyclohexanone can be decomposed by microorganisms.[9]

8.0 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1 Effect on Wastewater Treatment Plant

As provided in Section 7.2, the worst case maximum concentrations of tramadol hydrochloride at wastewater treatment plants serving the site of manufacturing and at the plants serving the users of this product are not expected to have any toxic effect on the treatment plant performance.

8.2 Acute Toxicity

performed a test to determine the acute toxicity of tramadol hydrochloride to Daphnia magna. The protocol from the FDA Technical Assistance Document, Section 4.08, was followed. It is reported that the 48-hour EC_{50} or median effective concentration value is 73 mg tramadol hydrochloride/L. The No Observed Effect Concentration (NOEC) was determined to be 23 mg tramadol hydrochloride/L.

performed a test to determine the acute toxicity of tramadol hydrochloride to bluegill sunfish (lepomis macrochirus). The protocol from the FDA Technical Assistance Document, Section 4.11 was followed. It is reported that the 96-hour LC_{50} or median lethal concentration value is 130 mg tramadol hydrochloride/L. The No Observed Effect Concentration (NOEC) was determined to be 38 mg tramadol hydrochloride/L. The test reports are provided in **Appendix T**.

8.2 Acute Toxicity Continued

also performed a test to determine the subacute toxicity of tramadol hydrochloride in earthworms (L. terrestris). The protocol from the FDA Technical Assistance Document Section 4.12 was followed. It is reported that the LC_{50} or median lethal concentration is greater than Kg. The No Observed Effect Concentration (NOEC) was determined to be mg tramadol hydrochloride/Kg synthetic soil media. Adjusted to a tramadol base, these results are LC_{50} greater than mg/Kg and mg/Kg, respectively. The text report is provided in **Appendix U.**

8.3 Effect at the Dorado, Puerto Rico, Site

In the worst case, if tramadol hydrochloride passes through the PRASA Dorado wastewater treatment plant without removal, the concentration at the treatment plant outfall is calculated to be mg/L. (This is based on the plant's 1.3 million gallons/day of flow, and kg/day of tramadol hydrochloride from Dorado manufacturing.)

Effluent from the treatment plant would be further diluted in the receiving stream, LaPlata River. The LaPlata River flows into the Atlantic Ocean about one mile downstream of the town of Dorado. Using the lowest seven day average flow in the last ten years (7Q10) for LaPlata River, the maximum concentration of tramadol hydrochloride in the stream is calculated to be mg/L.[10]

The expected concentrations are much less than the No Observed Effect Concentrations (NOEC) determined for Daphnia magna (23 mg/L) and for bluegill sunfish (38 mg/L). We expect that tramadol hydrochloride in the water would be degraded with prolonged exposure to strong light. The degradation by-products (Section 7.3) are further degraded in the environment by microbial activities.[9]

8.4 Maximum Expected Emitted Concentration (MEEC)

The MEEC, calculated in Section 6.0 of this assessment, is determined to be mg/L. This is much less than the toxicity levels observed for Daphnia magna and for bluegill sunfish. We expect that tramadol hydrochloride in water would be degraded with prolonged exposure to strong light. The degradation by-products (Section 7.3) are further degraded in the environment by microbial activities.[9]

The high water solubility of tramadol hydrochloride indicates that it would be in the water environment; however, as a worst case scenario, if all of the tramadol hydrochloride used were to be sorbed into sewage treatment plant sludge, the concentration in the sludge is calculated in Section 6.0 to be 0.93 parts per million. This is much less than the toxicity levels observed for earthworms. Tramadol hydrochloride is expected to have no impact on the soil and terrestrial environment.

9.0 USE OF RESOURCES AND ENERGY

Existing facilities are planned to be used for the production of this product. Based on producing 293 batches per year at the Dorado facility (Section 6.3), production of tramadol hydrochloride is estimated to require 21 percent of electricity, other fuels, and water used by the facility. We estimate that this can require an additional 4600 kilowatt hours per day of electricity and 9400 gallons of water per day. These resource usages may even be lower since McNeil Pharmaceutical is implementing conservation measures such as more efficient heating, air conditioning, and lighting at its facility.

It is expected that manufacturing tramadol hydrochloride will produce very little additional solid waste from the Dorado facility. No new facilities nor significant demand on natural resources would be needed for the disposal of additional solid wastes from manufacturing tramadol hydrochloride.

9.0 USE OF RESOURCES AND ENERGY continued

The production of tramadol hydrochloride is not expected to have any effects upon endangered or threatened species, or upon property listed in, or eligible for listing in the National Register of Historical Places. Regulatory agencies in Puerto Rico have determined that the Dorado, PR site is not located where historical and archaeological properties, endangered or threatened species' habitats are present. Documentation is provided in **Appendix V**.

As indicated in Section 5 of this Environmental Impact Analysis Report, the production of the drug substance requires the following chemicals:

9.0 USE OF RESOURCES AND ENERGY continued

The production of the drug product requires:

k

Packaging materials used include: opaque high density polyethylene (HDPE) bottles, polypropylene closures, unit dose blisters with aluminum foil and paper backing materials, paper cartons and corrugated boxes for secondary packaging.

There is no known relationship between these chemicals and packaging materials and any endangered species. The usage and disposal practices outlined in Section 6 of this Environmental Assessment Report will ensure that the production, packaging, distribution, and usage of tramadol hydrochloride would not impact endangered species.

10.0 MITIGATION MEASURES

Processing of this product will be in strict compliance with current Good Manufacturing Practices and Federal, State and Local requirements. The procedures outlined in Section 6.0 are sufficient to avoid any adverse environmental impact. The pharmaceutical solid wastes and cleaning residues containing tramadol will be isolated and incinerated, where possible, to avoid environmental impact. Employees receive training on spill control, emergency response, and waste management. The facilities used have adequate spill control procedures and practices in place.

McNeil Pharmaceutical is pursuing opportunities to reduce solid waste generation, recycle, and conserve energy. Cardboard, office paper, aluminum cans, and clear glass bottles are currently being recycled. Efficient heating and air conditioning controls and upgrades have been installed at some of the facilities.

11.0 ALTERNATIVES TO THE PROPOSED ACTION

Alternatives to the proposed action are not needed, since no potential environmental effects have been noted. Procedures are in place at the manufacturing sites to minimize the introduction of drug substance and other chemicals into the environment. These procedures include the incineration of pharmaceutical waste. The manufacturing, distribution, and usage of tramadol hydrochloride result in concentrations that are far below threshold effect levels for aquatic and terrestrial organisms tested. No impact is expected on endangered or threatened species, or upon properties listed in or eligible for listing in the National Register of Historical Places.

12.0 LIST OF PREPARERS

The environmental assessment was prepared by Sandy Yee who is currently the Manager of Engineering, Facility Services and Environmental Affairs. Mr. Yee holds a B.S. and M.S. in Environmental Engineering from the University of Louisville in Louisville, KY. The curriculum was based on a chemical engineering program with additional courses in wastewater, water, hazardous waste, air quality, and environmental law. Mr. Yee's master's thesis was on the biotoxicity of coal liquefaction waste in activated sludge. He has presented papers on wastewater treatment and waste management.

Mr. Yee's twelve years of environmental experience includes work at U.S. EPA, BFGoodrich Chemical, Procter & Gamble, Pennwalt, and McNeil Pharmaceutical. Some of his past projects included construction of biological wastewater treatment plants, soil and groundwater clean-up, infectious and trash incinerator modifications, dust control filters, catalyst bed incinerators, electrostatic precipitators, river ecosystem surveys, and life-cycle analysis of packaging materials.

12.0 LIST OF PREPARERS Continued

The people listed below were consulted for portions of the environmental assessment. C.V.'s for Mr.Yee, Dr. Fackler, Dr. Mills and Dr. Ramanathan are provided in **Appendix W**.

John Mills, Ph.D.
Research Fellow
R.W. Johnson Pharmaceutical Research Institute
Spring House, PA

13.0 CERTIFICATION

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of McNeil Pharmaceutical for the preparation of the environmental assessment.

MCNEIL PHARMACEUTICAL

BY: N Sjee

N.S. Sandy Yee
Manager
Engineering, Facilit, Services,
and Environmental Affairs

11/2/94
Date

14.0 REFERENCES

1. Tramadol hydrochloride planning projections based on March 5, 1992, conversation with B. J. Sewell, McNeil Pharmaceutical, Spring House, PA.

2. Provided by J. Hoblitzell, Ph.D., The R.W. Johnson Pharmaceutical Research Institute, on March 10, 1992. (Based on mass balance of typical batches).

3. Draft "Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA", Version 5, page 47. (Unpublished) Distributed at Joint Seminar on Environmental Assessments, July 29-30, 1991, Rockville, MD.

4. -

5. Handbook of Incineration Systems, C.R. Brunner. McGraw-Hill 1991.

6. -

7. Flowrates from 1990-1991, monthly reports sent by McNeil Pharmaceutical, Dorado, PR, to PRASA.

8. Provided by Peter Kos, Ph.D., P.E., Malcolm Pirnie, Inc., White Plains, NY.

9. Verschueren, Karel, Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Company, New York, NY, 1977, pages 468, 260, and 207.

10. Flow rate in LaPlata River was obtained from the U.S. Geological Survey in San Juan, Puerto Rico by Dr. Peter Kos of Malcolm Pirnie, Inc. The 7Q10 of the LaPlata River was provided as 8.3 cubic feet per second.

15.0 LIST OF APPENDICES (Confidential appendices are bolded)

Appendix A	Incineration Facility Certifications
Appendix B	
Appendix C	**List of Chemicals Used in the Synthesis of Tramadol Hydrochloride**
Appendix D	**Data Summary Chart** ←
Appendix E	**Research Report No. PD-91310-A, "Physical and Chemical Properties of Tramadol Hydrochloride."**
Appendix F	
Appendix G	**Research Report No. AD-91028, "Degradation of Tramadol Hydrochloride (RWJ-26898) in Solution and in the Solid State."**
Appendix H	**Aqueous Photolysis Study**
Appendix I	Material Safety Data Sheets
Appendix J	**Compliance Statement** ←
Appendix K	**Compliance Certification Letter -**
Appendix L	Air Permit McNeil Pharmaceutical
Appendix M	**Process Information**
Appendix N	Wastewater Discharge Permits
Appendix O	**Vapor Pressure Calculation**
Appendix P	State Incinerator Standards
Appendix Q	Air Permit

15.0 LIST OF APPENDICES (Confidential appendices are bolded) Continued

Appendix R	Waste Incineration Service Agreement
Appendix S	**Microbial Toxicity and Treatability Studies**
Appendix T	**Aquatic Toxicity Studies**
Appendix U	**Subacute Toxicity in Earthworms**
Appendix V	**Endangered Species and Historical/Archaeological Properties**
Appendix W	Curriculum Vitae

FDA ADDENDUM TO THE ENVIRONMENTAL ASSESSMENT FOR NDA 20-281

1. In a separate communication to the agency, The R.W. Johnson Pharmaceutical Research Institute clarified the locations of use of the product and designated appendices B, D and J as non-confidential appendices.

2. FDA has included Appendices B, D, I and J in the public document. The other non-confidential appendices were not included as this information is adequately discussed in the environmental assessment.

3. Impurity information (section 5.1.5) was redacted by the FDA.

4. FDA has included the following clarifications to the data summary chart (Appendix D) based on the information in the test reports:

   a. Solubility was determined at 21-25°C;

   b. The vapor pressure was estimated at $< 10^{-7}$ torr at 30°C (tramadol base);

   c. The length of the aerobic biodegradation study was 28 days.

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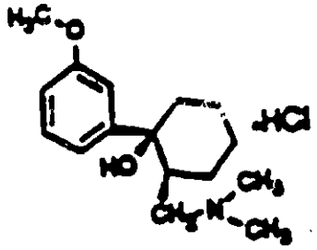
APPENDIX D

Data Summary Chart

DATA SUMMARY CHART

COMPOUND:	Tramadol Hydrochloride CAS Number: 36282-47-0	
STRUCTURAL FORMULA:		
MOLECULAR WEIGHT:	$C_{16}H_{25}NO_2$ • HCl	
ORGANOLEPTICS:	odorless, bitter-tasting white crystalline powder	(APPENDIX E)
CRYSTALLINITY:	monotropic	(APPENDIX F)
THERMAL PROPERTIES:	melting point between 180.2 and 182°C	(APPENDIX E)
HYGRODYNAMICS:	neither hygroscopic nor deliquescent	(APPENDIX E)
DISSOCIATION:	pK_a = 9.41 at 23°C	(APPENDIX E)
N-OCTANOL/WATER PARTITION COEFFICIENT:	log (P) = 1.35 at 23 to 24°C log (P) = 1.83 at 37°C	(APPENDIX E)
SOLUBILITY:	greater than 200 mg/mL in water at pH range from 0.88 to 7.72 @ 21-25 °C	(APPENDIX E)
PHOTODEGRADATION:	photodegradation of aqueous solutions occurs after exposure to either high intensity 300 nm light (five hours) or with exposure (two months) to high intensity visible light.	(APPENDIX G)
	Photodegradation by sunlight halflife of 227 days at pH 5, 329 days at pH 7, 36.2 days at pH 9.	(APPENDIX H)
VAPOR PRESSURE:	~~ln P calculated to be less than -7.008~~ Estimated to be less than 10^{-9} torr @ 30°C (tramadol base)	(APPENDIX O)
MICROBIAL TOXICITY:	threshold inhibition concentration determined to be greater than 150 mg active/L	(APPENDIX S)
ACTIVATED SLUDGE REMOVABILITY:	less than 10% removal	(APPENDIX S)
AEROBIC BIODEGRADATION:	less than 10% theoretical carbon dioxide produced in 28 days	(APPENDIX S)
ACUTE TOXICITY TO DAPHNIDS (Daphnia magna):	48-hour EC_{50} = 73 mg active/L No Observed Effect Concentration = 23 mg active/L	(APPENDIX T)
ACUTE TOXICITY TO BLUEGILL SUNFISH (Lepomic macrochirus):	96-hour LC_{50} = 130 mg active/L No Observed Effect Concentration = 38 mg active/L	(APPENDIX T)
SUBACUTE TOXICITY TO EARTHWORMS (Lumbricus Terrestris):	LC_{50} = greater than 680 mg active/kg No Observed Effect Concentration = 330 mg active/kg	(APPENDIX U)

APPENDIX I

Material Safety Data Sheets

MATERIAL SAFETY DATA SHEET

Chemical: TRAMADOL HYDROCHLORIDE

CAS Number: 0036282470 Issue Date: 1/23/92

SECTION 1 - CHEMICAL IDENTIFICATION

COMPANY: R.W. Johnson PRI
McKean and Welsh Roads
Spring House, PA 19477
Emergency Contact: Donna Kulp Emergency Phone: 215-628-5858

Chemical Family:
Chemical Formula: C16H25NO2.HCL
Molecular Weight: 299.84

Synonyms: MCN-R-1455-11
TRAMALHYDROCHLORIDE

SECTION 2 - CHEMICAL COMPONENTS

Component: TRAMADOL HYDROCHLORIDE
CAS Number: 0036282470 PERCENT OF MIXTURE: 100.0%

OSHA FINAL PEL-TWA:
NOT ESTABLISHED

OSHA FINAL PEL-STEL:
NOT ESTABLISHED

ACGIH TLV:
NOT ESTABLISHED

ACGIH STEL:
NOT ESTABLISHED

SECTION 3 - PHYSICAL DATA

Melting Point (Deg.C): 180 to 182
Specific Gravity: 0.00000
Solubility (H2O): 295 g/l

pH of 5-6 at a Concentration of 10 GRAMS PER

Appearance: White powder

Odor: Odorless

SARA Hazards: Acute: No Chronic: No Fire: No Pressure: No Reactive: No

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SECTION 4 - FIRE FIGHTING & EXPLOSION DATA

Chemical: TRAMADOL HYDROCHLORIDE

CAS Number: 0036782470

Issue Date: 1/23/92

SECTION 4 - FIRE FIGHTING & EXPLOSION DATA

FIRE AND EXPLOSION HAZARDS: UNKNOWN - NONE INDICATED BY THE MANUFACTURER OR AVAILABLE LITERATURE.

EXTINGUISHING MEDIA: USE ANY MEDIA WHICH IS SUITABLE FOR THE SURROUNDING FIRE

SPECIAL FIRE FIGHTING INSTRUCTIONS: SELF-CONTAINED BREATHING APPARATUS MAY BE NECESSARY. USE WATER SPRAY TO COOL FIRE-EXPOSED CONTAINERS.

SECTION 5A - HEALTH HAZARDS & FIRST AID - INHALATION

ROUTES OF EXPOSURE & EFFECTS - INHALATION: UNKNOWN - NONE INDICATED BY THE MANUFACTURER OR AVAILABLE LITERATURE.

FIRST AID - INHALATION: IF INHALED REMOVE FROM EXPOSURE TO FRESH AIR. GET IMMEDIATE MEDICAL ATTENTION.

SECTION 5B - HEALTH HAZARDS & FIRST AID - SKIN

ROUTES OF EXPOSURE & EFFECTS -SKIN: UNKNOWN - NONE INDICATED BY THE MANUFACTURER OR AVAILABLE LITERATURE.

FIRST AID - SKIN: IF SKIN CONTACT OR CONTAMINATION OCCURS WASH CONTAMINATED AREAS THOROUGHLY WITH SOAP AND WATER. CONSULT A PHYSICIAN IF REDNESS OR IRRITATION PERSISTS.

SECTION 5C - HEALTH HAZARDS & FIRST AID - EYES

ROUTES OF EXPOSURE & EFFECTS - EYES: UNKNOWN - NONE INDICATED BY THE MANUFACTURER OR AVAILABLE LITERATURE.

FIRST AID - EYES: IF CONTACT WITH THE EYE(S) OCCURS FLUSH EYES WITH PLENTY OF WATER. GET IMMEDIATE MEDICAL ATTENTION.

SECTION 5D - HEALTH HAZARDS & FIRST AID - INGESTION

ROUTES OF EXPOSURE & EFFECTS - INGESTION: INGESTION OF THIS MATERIAL MAY CAUSE DECREASED SPONTANEOUS MOTOR ACTIVITY, TREMORS, MYDRIASIS AND CONVULSIONS. FURTHER INFORMATION IS AVAILABLE - SEE SECTION 5E

LD50 (RAT) : 225 MG/KG

SECTION 5D - HEALTH HAZARDS & FIRST AID - INGESTION

FIRST AID - INGESTION: IF SWALLOWED GET IMMEDIATE MEDICAL ATTENTION.

SECTION 5E - GENERAL HEALTH EFFECTS - COMMENTS

The clinical signs commonly observed in laboratory animals are: respiratory effects (dyspnea, tachynea, cyanosis); motor activity changes (decreased or increased spontaneous motor activity, decreased preening ataxia, tremors, prostration, unusual locomotion or posture, chewing writhing, somnolence, anesthesia); effects on reflexes (righting, sensitivity to touch); convulsions; piloerection; salivation; muscle tone changes (increased or decreased); gastrointestinal effects (diarrhea, emesis); ocular effects (exophthalmos, mydriasis); straub tail and irritability.
Additional toxicological data:
LD50 s.c. mouse 200 mg/kg; LD50 s.c. rat >400 mg/kg
LD50 oral mouse 350 mg/kg
No teratogenic action has been observed in rats and rabbits.

SECTION 5F - HEALTH CONDITIONS AGGRAVATED BY EXPOSURE

HEALTH CONDITIONS AGGRAVATED BY EXPOSURE: UNKNOWN - NONE INDICATED BY THE MANUFACTURER OR AVAILABLE LITERATURE.

SECTION 6 - REACTIVITY & POLYMERIZATION

Stability: STABLE
Hazardous Decomposition Products:
HYDROGEN CHLORIDE ON COMBUSTION.
Hazardous Polymerization: WILL NOT OCCUR
Conditions to Avoid: THERMAL DECOMPOSITION ABOVE 210 DEGREES C.

SECTION 7 - SPILL, LEAK, & DISPOSAL PROCEDURES

STEPS TO BE TAKEN - SPILLS, LEAKS, OR RELEASE: FOR LARGE LEAKS OR SPILLS - EVACUATE AREA UNTIL DUST SETTLES. CAREFULLY, SWEEP OR VACUUM UP INTO A SEALED WASTE CONTAINER. AVOID CREATING DUSTY CONDITIONS. WEAR SKIN, EYE AND RESPIRATORY PROTECTION - SEE SECTION 8.

WASTE DISPOSAL METHODS: DISPOSE IN ACCORDANCE WITH FEDERAL, STATE AND LOCAL REGULATIONS.

MATERIAL SAFETY DATA SHEET

Chemical: TRAMADOL HYDROCHLORIDE

CAS Number: 0036282470

Issue Date: 1/23/92

SECTION 8 - SPECIAL PROTECTIVE EQUIPMENT

VENTILATION: WHEN HANDLING SMALL AMOUNTS USE: LABORATORY HOOD. WHEN HANDLING LARGE AMOUNTS USE: LOCAL EXHAUST AT CONTAMINANT GENERATION POINTS

PROTECTIVE EQUIPMENT - EYES: SAFETY GLASSES OR GOGGLES RECOMMENDED

PROTECTIVE EQUIPMENT - GLOVES: WHEN HANDLING THE SOLID OR POWDERED MATERIAL WEAR LATEX GLOVES. NEOPRENE OR PVC GLOVES.

PROTECTIVE EQUIPMENT - RESPIRATORS: RESPIRATORY PROTECTION SHOULD BE WORN IN THE ABSENCE OF LOCAL EXHAUST. A RESPIRATOR APPROVED FOR DUSTS, MISTS IS RECOMMENDED.

SECTION 9 - SPECIAL PRECAUTIONS - STORAGE & HANDLING

STORAGE & HANDLING CONDITIONS: PREVENT MOISTURE CONTAMINATION. KEEP CONTAINERS TIGHTLY CLOSED.

SECTION 10A - SHIPPING INFORMATION (49CFR/DOT)

Proper Shipping Name:

SECTION 11 - REFERENCE INFORMATION

NO INFORMATION ON FILE

SECTION 12 - MISCELLANEOUS COMMENTS

NO INFORMATION ON FILE

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